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Targeting Foam Cell Formation in Atherosclerosis: Therapeutic Potential of Natural Products

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Abstract	599
I. Atherosclerosis: An Introduction	599
II. Foam Cell Formation as a Hallmark of Atherosclerosis	600
A. Cholesterol Uptake	600
1. CD36	601
2. Macrophage Scavenger Receptor 1	603
3. Lectin-like Oxidized Low-density Lipoprotein Receptor-1	604
4. Others	605
B. Cholesterol Esterification and Hydrolysis	605
1. Acetyl-CoA Acetyltransferases 1 and Acetyl-CoA Acetyltransferases 2	605
2. Neutral Cholesterol Ester Hydrolase 1	606
3. Lysosomal Acid Lipase (Lipase A) and Hormone-sensitive Lipase 1 (Lipase E)	606
C. Macrophage Cholesterol Efflux	607
1. Aqueous Diffusion Efflux Pathway	607
2. Transporter-Dependent Cholesterol Efflux Pathway	607
a. ATP-binding Cassette Transporter A1	607
b. ATP-binding Cassette Transporter G1	610
c. Scavenger Receptor Class B Type 1	611
3. Acceptors that Mediate Macrophage Cholesterol Efflux	612
a. Apolipoprotein A-1	612
b. High-density Lipoprotein	614
c. Apolipoprotein E	614
III. Models for Studying Foam Cell Formation	615
A. Cellular Models	615
1. Models for Studying Cholesterol Uptake	615
2. Models for Studying Cholesterol Efflux	616
a. Loading cells with labeled lipids to form foam cells	616
b. Inducing cholesterol efflux to extracellular acceptors and quantification	617
B. Animal Models for Studying Foam Cell Formation	618

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IV. Natural Products Targeting Foam Cell Formation in Atherosclerosis.....	619
A. Flavonoids.....	619
1. Alpinetin.....	619
2. Anthocyanin.....	619
3. Baicalin.....	633
4. Chrysin.....	634
5. Cyanidin-3-O- β -glucoside.....	634
6. Daidzein.....	634
7. Ellagic Acid.....	634
8. Hesperetin.....	635
9. Icariin.....	635
10. Iris Isoflavones.....	635
11. Pratensein.....	635
12. Puerarin.....	635
13. Quercetin.....	636
14. Silymarin.....	636
15. Wogonin.....	636
B. Terpenoids.....	636
1. Carotenoids.....	636
a. Astaxanthin.....	636
b. Capsanthin.....	637
c. β -Carotene.....	637
d. Retinoids.....	637
e. Lycopene.....	637
2. Ursolic Acid.....	638
3. Betulinic Acid.....	638
4. Erythrodiol.....	638
5. Ginsenosides.....	638
6. Saikosaponin A.....	639
7. Tanshinone IIA.....	639
8. Tanshindiol C.....	639
9. Zerumbone.....	639

ABBREVIATIONS: ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; AC, anthocyanins; ACAT, acetyl-CoA acetyltransferases; acLDL, acetylated LDL; AMPK, AMP-activated protein kinase; AP-1, activating protein-1; ApoA-1, apolipoprotein A-1; ApoE, apolipoprotein E; APS, astragalus polysaccharides; ATRA, all-trans retinoic acid; BET, extra terminal bromodomains; BMDMs, bone marrow-derived macrophages; BODIPY, dipyrromethene boron difluoride; C3G, cyanidin-3-O-glucoside; CAD, coronary artery disease; CE, cholesterol esters; CETP, cholesteryl ester transfer protein; 9-*cis*- β c, 9-*cis*- β -carotene; CLA-1, clarinet 1; CVD, cardiovascular disease; CXCL16, C-X-C motif chemokine ligand 16; DHA, docosahexaenoic acid; DiI, 1,1'-dioctadecyl-3,3,3',3'-tetra-methylindocyanide perchlorate; EGCG, epigallocatechin gallate; eNOS, endothelial NO synthase; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; FC, free cholesterol; F-Ch, fluorophore Pennsylvania green/*N*-alkyl-3 β -cholesterylamine-derived molecular probe; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; HFD, high fat diet; HMDM, human monocyte-derived macrophages; 12-HODE, 13-hydroxyoctadecadienoic acid; HOTAIR, homeobox protein transcription antisense RNA; hs-CRP, high sensitivity C-reactive protein; HSL, hormone-sensitive lipase; HUVEC, human umbilical vein endothelial cells; ICA, icariin; ICAM1, intercellular adhesion molecule 1; IL, interleukin; JNK, c-Jun N-terminal kinases; LAL, lysosomal acid lipase; LCAT, lecithin cholesterol acyltransferase; LD, lipid droplets; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; LDLR, LDL receptor; lncRNA, long noncoding RNA; LOX-1, lectin-like oxidized LDL receptor 1; LPS, lipopolysaccharide; LXR, liver X receptor; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; MARCO, macrophage receptor with collagenous structure; miRNA, microRNAs; MPM, mouse peritoneal macrophages; NA, nicotinic acid; NCEH, neutral CE hydrolases; ncRNA, noncoding RNAs; Neat1, nuclear paraspeckle assembly transcript 1; NFIA, nuclear factor IA; NF- κ B, nuclear transcription factor- κ B; NHERF, PDZK1/Na⁺/H⁺ exchanger regulatory factor; NO, nitric oxide; NPC1, Niemann-Pick disease, type C1; NPC1L1, NPC1 like intracellular cholesterol transporter 1; Nrf2, nuclear erythroid-related factor 2; oxLDL, oxidized LDL; PCA, protocatechuic acid; PCSK9, proprotein convertase subtilisin/kexin type 9; PEA, pomegranate ellagic acid; PGG, 1,2,3,4,6-penta-O-galloyl- β -D-glucose; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLPEs, phellinus linteus polysaccharide extracts; PNS, panax notoginseng saponins; PON-1, paraoxonase-1; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RCT, reverse cholesterol transport; rHDL, reconstituted HDL; ROS, reactive oxygen species; RXR, retinoid X receptor; Sirt1, sirtuin 1; SR, scavenger receptor; SR-BI, scavenger receptor class B type 1; SREBP, sterol regulatory element-binding proteins; STAT, signal transducer and activator of transcription; TC, total cholesterol; TG, triglycerides; TGF- β , transforming growth factor- β ; TLR, toll-like receptor; TMAO, trimethylamine N-oxide; TMD, transmembrane domains; TNF- α , tumor necrosis factor- α ; trans- β c, trans- β -carotene; UA, ursolic acid; UTR, untranslated regions; VCAM-1, vascular cell adhesion molecule 1; VSMC, vascular smooth muscle cells.

C. Phenolic Compounds	639
1. Gallotannin	639
2. Curcumin	639
3. Danshensu	640
4. 6-Dihydroparadol	640
5. Paeonol	640
6. Polydatin	641
7. Protocatechuic Acid	641
8. Salicylic Acid	641
9. Salvianolic Acid B	642
10. Sesamol	642
11. Resveratrol	642
12. Epigallocatechin Gallate	642
D. Phenylpropanoids	643
1. Lignans	643
a. Arctigenin	643
b. Leoligin	643
c. Sesamin	643
d. Honokiol	643
2. α -Asarone	643
3. Chlorogenic Acid	644
4. Caffeic and Ferulic Acid	644
E. Alkaloids	644
1. Arecoline	644
2. Berberine	644
3. Piperine	645
4. Rutaecarpine	645
5. Evodiamine	645
6. Leonurine	645
F. Steroids	646
1. Diosgenin	646
2. Fucosterol	646
3. Panax Notoginseng Saponins	646
4. Vitamin D	646
G. Fatty Acids	646
1. Docosahexaenoic Acid and Eicosapentaenoic Acid	646
2. 13-Hydroxyoctadecadienoic Acid	647
3. Linoleic Acid	647
H. Amino Acids	647
1. L-(+)-Citrulline	647
2. S-Allyl Cysteine	647
I. Carbohydrates	647
1. Phellinus Linteus Polysaccharides	647
2. Astragalus Polysaccharides	647
J. Others	647
1. Organosulfur Compounds: Allicin	647
2. Pyranone Derivatives: Asperlin	648
3. Anthraquinone Derivatives: Emodin	648
4. Polyacetylene Derivatives: Falcariindiol	648
5. Marine Natural Products	648
V. Clinically Used Drugs that Influence Foam Cell Formation	648
A. Approved Drugs	648
1. Statins	648
2. Nicotinic Acid	649
3. Ezetimibe	649
4. Proprotein Convertase Subtilisin/Kexin Type 9Antibodies	649

B. Drugs in Clinical Trials	649
1. Glucagon-like Peptide-1 Receptor Agonists	649
2. High-density Lipoprotein/Apolipoprotein A-1-raising Agents	649
3. Bempedoic Acid (ETC-1002)	650
VI. The Role of Inhibition of Foam Cell Formation in Antiatherosclerosis Therapy	651
VII. Concluding Remarks and Future Perspectives	652
References	654

Abstract—Foam cell formation and further accumulation in the subendothelial space of the vascular wall is a hallmark of atherosclerotic lesions. Targeting foam cell formation in the atherosclerotic lesions can be a promising approach to treat and prevent atherosclerosis. The formation of foam cells is determined by the balanced effects of three major interrelated biologic processes, including lipid uptake, cholesterol esterification, and cholesterol efflux. Natural products are a promising source for new lead structures. Multiple natural products and pharmaceutical agents can

inhibit foam cell formation and thus exhibit anti-atherosclerotic capacity by suppressing lipid uptake, cholesterol esterification, and/or promoting cholesterol ester hydrolysis and cholesterol efflux. This review summarizes recent findings on these three biologic processes and natural products with demonstrated potential to target such processes. Discussed also are potential future directions for studying the mechanisms of foam cell formation and the development of foam cell-targeted therapeutic strategies.

I. Atherosclerosis: An Introduction

Atherosclerosis is a chronic inflammatory (Ross, 1999; Kasikara et al., 2018), immune (Hansson and Hermansson, 2011), and epigenetic (Xu et al., 2018, 2019) disease characterized by low-density lipoprotein (LDL) retention and defective resolution of vascular inflammation in the vessel wall. It is the major cause of acute cardiovascular events, such as unstable angina pectoris, myocardial infarction, ischemic stroke, and sudden cardiovascular death (Tabas et al., 2015). The pathobiology of atherosclerosis is very complex and involves multiple cell types, such as endothelial cells, monocytes, macrophages, vascular smooth muscle cells (VSMCs), T cells, B cells, mast cells, and dendritic cells (Tabas et al., 2015). Atherosclerosis preferentially develops at arterial branching points and ascending aortic arch, where local disturbance of blood flow occurs. In contrast, regions of high laminar shear stress, such as thoracic aorta, are protected against atherosclerosis (Davies, 2009; Chiu and Chien, 2011; Rezvan et al., 2011; Abe and Berk, 2014; Baeyens et al., 2016; Niu et al., 2019). Shear stress can also regulate atherosclerosis by causing the breach of the intimal layer that leads to increase of inflammation, leukocyte adhesion, and the occurrence of late stage atherothrombotic events (Franck et al., 2019). Therefore, the integrity of the vascular endothelium is critical for maintaining endothelial function, such as regulation of vascular tone, antioxidative response, and antithrombotic effects (Vanhoutte et al., 2017; Nafisa et al., 2018). It has been well established that passive movement of LDL across the compromised endothelial layer instigates atherosclerosis. A recent study has shown that scavenger receptor class B type I (SR-BI)-mediated endothelial LDL transcytosis also promotes LDL entry into the artery wall and promotes atherosclerosis development, raising

a new therapeutic target in combating atherosclerosis (Huang et al., 2019). Dysfunctional properties of endothelial cell cause endothelial dysfunction, which leads to the development of atherosclerosis (Vanhoutte et al., 2017; Nafisa et al., 2018). Under such circumstances, circulating LDLs penetrate into the injured vascular endothelium and accumulate in the subendothelial space, where LDLs are prone to various atherogenic modifications, including oxidation, glycation, enzymatic modification, and carbamylation (Alique et al., 2015). Among these modifications, oxidation is the most common form of atherogenic modification (Quinn et al., 1987). It occurs during increased oxidative stress via cellular sources and enzymatic routes [such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, lipoxygenases, and myeloperoxidases] (Quinn et al., 1987). These types of modified LDL mimic damage- and pathogen-associated molecular patterns, thus serving as the primary sources of cholesterol accumulation and chronic inflammation in atherosclerotic plaques (Tabas et al., 2015). In addition, these modified LDLs can cause oxidative stress, inflammation, NLRP3 inflammasome activation, and immune response, thus amplifying the vicious cycle of atherogenic cellular events (Steinberg and Witztum, 2010; Wang et al., 2017h). In addition to modified LDL, interleukin 1 (IL-1) (IL-1 α and IL-1 β) also drives vascular inflammation, with IL-1 α mainly being involved in arterial remodeling during the early phase of atherosclerosis, whereas IL-1 β drives inflammation and atheroprotection to advanced state of atherosclerosis (Vromman et al., 2019). The recent CANTOS clinical trial has shown that anti-inflammatory effect with canakinumab (a monoclonal antibody targeting IL-1 β) significantly reduces the rate of recurrent cardiovascular events in patients with atherosclerotic diseases without reducing the lipid levels (Ridker et al., 2017). IL-1 β , together with other proatherogenic stimuli

such as modified LDL, can promote endothelial activation and persistent inflammatory responses lead to the proliferation, migration, phenotypic switching of VSMCs, and lipid accumulation in VSMCs [i.e., VSMC-derived foam cell formation (Allahverdian et al., 2012)]. Cholesterol loading (by incubation with cyclodextrin-cholesterol complexes) leads to an inhibited expression of the VSMC marker genes and increased expression of proinflammatory and macrophage marker genes (Rong et al., 2003; Vengrenyuk et al., 2015). These VSMCs could substantially contribute to pooled population of foam cells (Allahverdian et al., 2014). Lineage tracing experiments have shown that VSMC can form foam-like cells, and transcription factor Kruppel-like factor 4 and octamer-binding transcription factor 4 can differentially regulate VSMC-derived foam cell formation in mice (Shankman et al., 2015; Cherepanova et al., 2016). The existence of VSMC-derived foam cells in mouse and human atherosclerotic plaques significantly expand our understanding of the contribution of foam cells and the lipid-deposition theory of atherosclerosis (Allahverdian et al., 2014; Wang et al., 2019b).

Macrophages are heterogeneous immune and metabolic cells that play important roles in the initiation, growth, and ultimate rupture of atherosclerotic plaques (Koelwyn et al., 2018) and serve as an elusive therapeutic target of treating atherosclerosis and designing of novel antiatherosclerotic drugs (Santamarina-Fojo et al., 2000; Tiwari et al., 2008). It has been well recognized that monocytes in the bloodstream are recruited to the atherosclerotic lesion site after endothelial injury and increased vascular permeability. These recruited monocytes then differentiated into mature macrophages (in local prodifferentiation micro-environment), which avidly ingest modified LDL and accumulate lipids, thus giving rise to the formation of “foam cells” stuffed with lipid droplets (LD) (Tabas et al., 2015). Lesional macrophages can also proliferate, self-renew, and accumulate in advanced atherosclerotic lesions in mice. This mechanism represents an important pathway of macrophage build-up and probable macrophage-derived foam cell formation via macrophage replication, in addition to monocyte influx/infiltration (Robbins et al., 2013). The lipid in foam cells (derived from macrophages and VSMCs) represents the major source of plaque lipid content and drives the development of fatty streak and atherosclerotic plaque formation. Macrophages have migratory potential, however, under stimulation with oxidized LDL (oxLDL) the migratory capability has shown to be reduced, leading to macrophages trapping in the arterial wall and athero-progression (Park et al., 2009b). Macrophages regulate in-plaque inflammatory response and oxidative stress by secreting various cytokines and chemokines, as well as generating reactive oxygen species (ROS). In advanced plaques, the death of macrophages drives the enlarged formation of necrotic core. Normally, the necrotic core within the plaque is covered by a “protective” barrier—the

fibrous cap, which serves as an “insulator” between platelets in circulating blood and prothrombotic substances within the lesion (Tabas et al., 2015). The thickness of the fibrous cap is determined by the balanced effects of collagen synthesis by VSMCs and collagen degradation by matrix metalloproteinase 2/9 (MMP-2/9). However, when the necrotic core size is increased (such as under conditions of increased primary necrosis, VSMC apoptosis, defective efferocytosis, and defective inflammation resolution by specialized proresolving mediators) and the fibrous cap gets thinner, the plaques are susceptible to rupture (Tabas et al., 2015; Bennett et al., 2016). The rupture of plaques leads to a vessel occlusion, an arterial thrombosis, and the occurrence of acute cardiovascular events (Arbab-Zadeh et al., 2012; Libby, 2013).

II. Foam Cell Formation as a Hallmark of Atherosclerosis

In the setting of atherosclerosis, lipid uptake and cholesterol esterification are increased, while cholesterol efflux is insufficient. The final outcome is excessive accumulation of cholesterol esters (CE) in macrophages to form foam cells (Yu et al., 2013; Maguire et al., 2019). Therefore, the formation of foam cells is determined by the balanced effects of three major interrelated biologic processes, including lipid uptake, cholesterol esterification, and cholesterol efflux. Each process is regulated by multiple transcription factors, including receptors, enzymes, and transporters, all of which work in concert to regulate lipid homeostasis (Yu et al., 2013; Maguire et al., 2019). Yearly publication counts on “foam cell” have been increasing dramatically (Fig. 1). Multiple natural products and pharmaceutical agents can inhibit foam cell formation and atherosclerosis by affecting one or more of the involved biologic processes. The gene expression of scavenger receptors (SRs) and cholesterol transporters can be regulated through transcriptional, posttranscriptional, translational, and epigenetic mechanisms [such as microRNAs (miRNA) and long noncoding RNAs (lncRNAs)]. Also, macrophage-derived foam cell formation is influenced by multiple cytokines and chemokines (McLaren et al., 2011a). Therefore, targeting the outlined major pathways (uptake, esterification, and efflux) could be effective therapeutic strategies to combat atherosclerosis (Fig. 2).

A. Cholesterol Uptake

Cholesterol uptake is a biologic process by which modified LDLs (such as oxLDL) are taken up by macrophages and VSMCs via SR-mediated pathways, as well as phagocytosis (Schrijvers et al., 2007) and pinocytosis (via receptor-independent endocytic pathway) (Kruth, 2011; Moore et al., 2013). Among these mechanisms, the SR-mediated uptake is the major pathway of cholesterol uptake. The primary functions of SRs are to clear invading pathogens and apoptotic cells as well as modified

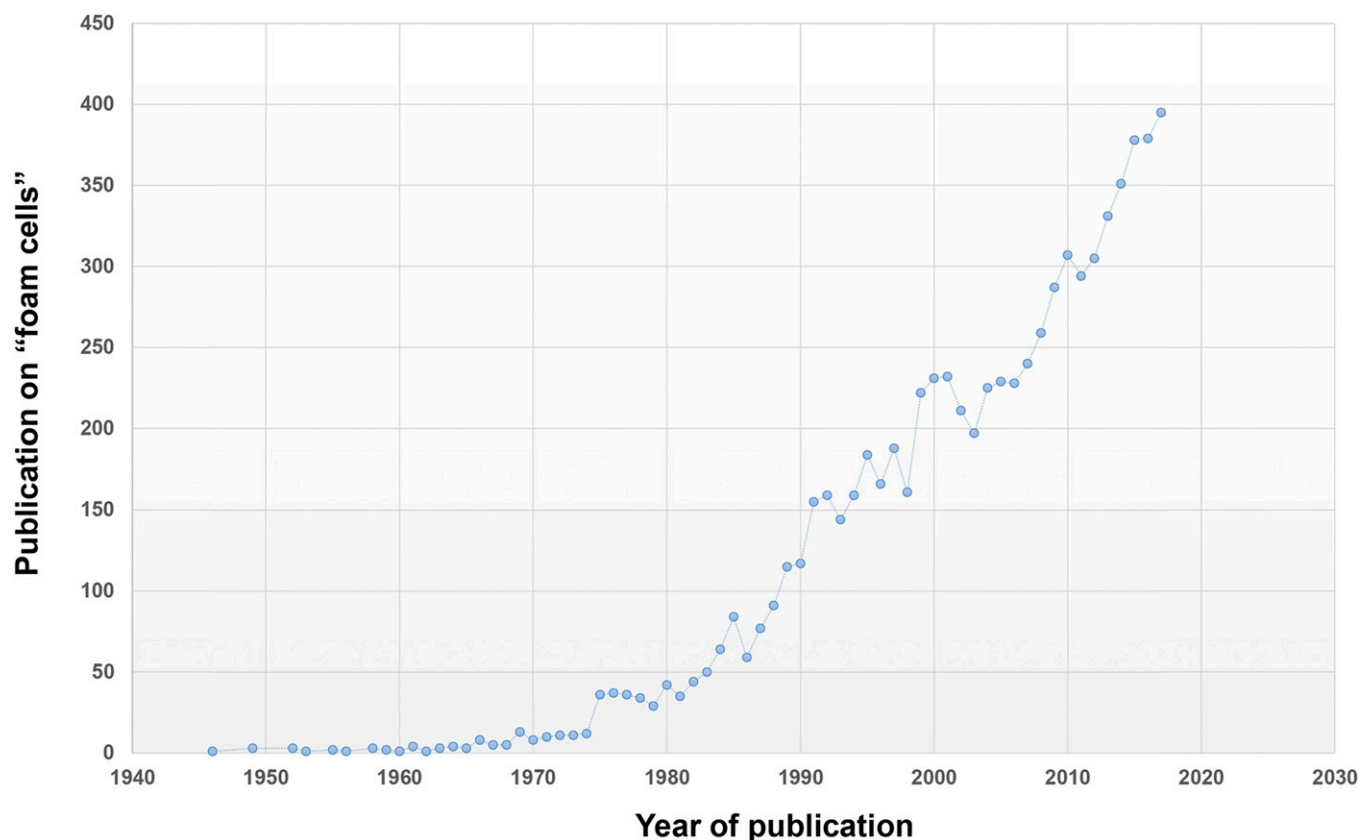


Fig. 1. Yearly publication counts on foam cells for the period 1946–2017. PubMed search was performed on Sep 11, 2018 using the subject term “foam cells.”

lipids. Seminal findings from the Brown and Goldstein laboratories in 1970s (Brown et al., 1979; Goldstein et al., 1979) showed that the uptake of modified LDLs by macrophage “scavenger receptors” is faster than the uptake of native LDL. Since then, burgeoning studies have identified various SRs and elucidated the contribution of SRs to atherosclerosis development in diverse mouse models. Macrophages express several SRs that can bind, internalize, and degrade modified LDL, such as SR-A, CD36, and lectin-like oxLDL receptor-1 (LOX-1) (Xu et al., 2013c). Other SRs include macrosialin/CD68, SR expressed in endothelial cells, macrophage receptor with collagenous structure (MARCO), and C-X-C motif chemokine ligand 16 (CXCL16, also known as SR-PSOX) (Greaves and Gordon, 2005). The different SRs have different binding affinities and preference for various forms of modified LDL. Quantitative analysis in SR-A and CD36 knockout macrophages have shown that SR-A and CD36 account for 75%–90% of oxLDL internalization by macrophages (Kunjathoor et al., 2002; Rahaman et al., 2006). Experiments in LOX-1-deficient macrophages indicated that LOX-1 accounts for 5%–10% of oxLDL uptake by murine macrophages under basal conditions, but in lysophosphatidylcholine-treated macrophages, the contribution of LOX-1 to macrophage oxLDL uptake and lipid accumulation is increased by more than 40% (Schaeffer et al., 2009). Thus, CD36, SR-A,

and LOX-1 are the major SRs responsible for the binding and subsequent uptake of modified LDL by macrophages (Kunjathoor et al., 2002). A detailed description of functions of all SRs in health and disease was reviewed elsewhere (Zani et al., 2015).

1. CD36. CD36 (also known as fatty acid translocase, FAT) belongs to class B of the SR family, representing 88 kDa heavily glycosylated transmembrane platelet glycoprotein III b/IV (Yu et al., 2013). It was first identified in 1993 as a macrophage receptor that binds (with high affinity), internalizes, and degrades oxLDL (Endemann et al., 1993). CD36 has an extracellular domain, two cytoplasmic domains, and two transmembrane domains. CD36 is ubiquitously expressed in multiple cell types, including monocytes/macrophages, endothelial cells, platelets, and many others (Yu et al., 2013). In addition to regulating modified LDL binding, CD36 has other functions as well, such as involvement in inflammatory processes, lipid metabolism, fatty acid transport, and immunity (Febbraio et al., 2001). Another important function of CD36 is to modulate the migration of macrophages upon oxLDL stimulation, which may contribute to macrophage trapping/retention in arterial lesions (Park, 2014). CD36 can also be released to the circulation in patients with atherosclerosis, which leads to the formation of soluble CD36 (Handberg et al., 2008). Thus, soluble CD36 is a promising

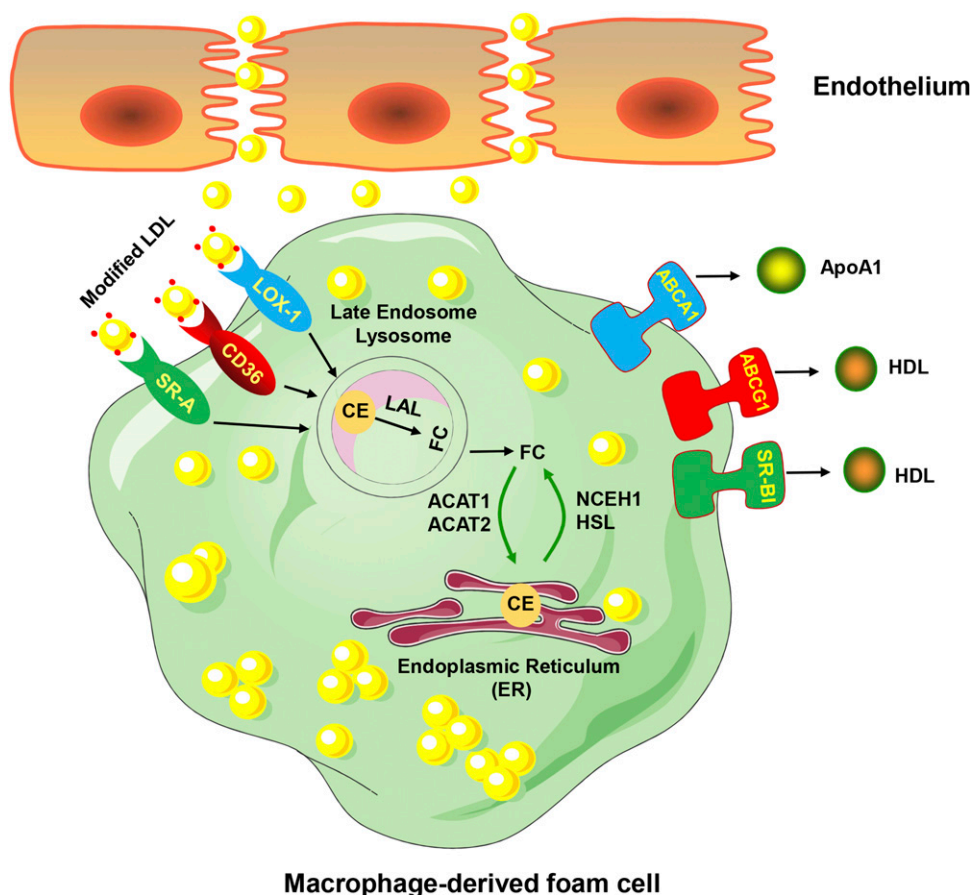


Fig. 2. Therapeutic targets in macrophage-derived foam cell formation. After endothelial injury, LDL penetrates endothelial monolayer, then LDL is modified to form atherogenically modified LDL (such as oxidized LDL). The modified LDL is taken up by multiple scavenger receptors (SRs, such as CD36, SR-A, and LOX-1) on the cell membrane of differentiated macrophages. Then, LDL is delivered to late endosomes/lysosomes, where lysosomal acid lipase (LAL) degrades cholesteryl esters (CE) from the LDL particles to generate free cholesterol (FC) and free fatty acids. The FC can be re-esterified by acyl-coenzyme A: cholesterol acyltransferase-1 and -2 (ACAT1 and ACAT2) in the endoplasmic reticulum (ER), thus contributing to CE accumulation and lipid droplet formation. CE can be hydrolyzed by neutral cholesteryl ester hydrolases (NCEHs), such as NCEH1 and hormone-sensitive lipase (HSL) to liberate FC, which can be reverse transported outside of macrophages by cholesterol efflux transporters, ATP-binding cassette A1 (ABCA1, ApoA-1 as the acceptor) and G1 (ABCG1, HDL as the acceptor), as well as SR-B1 (HDL as the acceptor). Under physiologic conditions, cholesterol homeostasis is fine-tuned by a balance of “input” and “output” of lipids. Under pathologic conditions (such as atherosclerosis), the balance is disrupted, leading to foam cell formation. Therefore, there are three major strategies to reduce foam cell formation, i.e., by 1) reducing the SR-mediated lipid uptake, 2) reducing the ACAT-mediated cholesterol esterification, and 3) promoting the transporter-mediated cholesterol efflux. Other strategies to inhibit foam cell formation include the decrease of LDL modification and inhibition of monocyte to macrophage differentiation.

biomarker of plaque instability and symptomatic carotid atherosclerosis, as well as associated with carotid intima-media thickness (Handberg et al., 2008; Jiang et al., 2017b).

The expression of CD36 in macrophages is upregulated by several proatherogenic stimuli, such as oxLDL (Endemann et al., 1993), palmitate (Kim et al., 2017), and dysfunctional HDL from coronary artery disease (CAD) patients (Sini et al., 2017). The CD36 gene transcription is regulated by peroxisome proliferator-activated receptor- γ (PPAR γ) (Nagy et al., 1998; Tontonoz et al., 1998), nuclear erythroid-related factor 2 (Nrf2) (Ishii et al., 2004; Olganier et al., 2011), as well as by signal transducer and activator of transcription 1 (STAT1) (Kotla et al., 2017) pathways. In addition, CD36 expression can also be regulated by retinol-binding protein 4 (Liu et al., 2017b), protein kinase $C\theta$ (PKC θ)/activating transcription factor 2 (Raghavan et al., 2018), epidermal growth factor receptor (Zeboudj et al., 2018), trimethylamine

N-oxide (Geng et al., 2018), NACHT, LRR, and PYD domains-containing protein 3 inflammasome (Chen et al., 2018b), transient receptor potential vanilloid 4 (TRPV4) (Goswami et al., 2017), cellular communication network factor 3 (Shi et al., 2017), melanocortin 1 receptor (Rinne et al., 2017), cluster of differentiation 146 (CD146) (Luo et al., 2017), triggering receptor expressed on myeloid cells (Joffre et al., 2016), cyclophilin A (Ramachandran et al., 2016), and many others. Furthermore, CD36-mediated foam cell formation and atherosclerosis were negatively regulated by C1q/tumor necrosis factor-related protein 13 via autophagy/lysosome-dependent degradation of CD36 (Wang et al., 2019a).

Recently, noncoding RNAs (ncRNA), such as miRNAs and lncRNAs, were proposed as a new layer of gene regulation in cardiovascular biology. A few miRNAs have been shown to regulate the CD36 expression, thus influencing foam cell formation and lipid accumulation in macrophages (Dai et al., 2016), including miRNA-155

(Huang et al., 2010). The CD36 expression is also regulated by lncRNAs. For example, lncRNA RP5-833A20.1 interacted with miRNA-382-5p to suppress nuclear factor I A (NFIA), thus increasing the expression of nuclear transcription factor- κ B (NF- κ B), SR-A, and CD36, leading to increased cholesterol accumulation and higher inflammatory response (Hu et al., 2015). lncRNAs nuclear paraspeckle assembly transcript 1 (Neat1), which has two isoforms, Neat1_1 (shorter) and Neat1_2 (longer), regulate the formation of paraspeckles (subnuclear structures). Two recent studies have shown that Neat1 is an oxLDL inducible lncRNA that regulates the macrophage inflammation, oxidative stress, apoptosis, and foam cell formation (Chen et al., 2018a; Huang-Fu et al., 2018). Similarly, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a macrophage-enriched and oxLDL inducible lncRNA, also involves in regulation of oxLDL-induced CD36 expression and oxLDL uptake through activation of β -catenin (a transcriptional factor for CD36) (Huangfu et al., 2018). Despite reduced uptake of oxLDL by MALAT1 deficiency, heterozygous deletion of MALAT1 aggravated atherosclerosis in ApoE-deficient (ApoE^{-/-}) mice by inducing massive immune system dysregulation (Gast et al., 2019). Gain- and loss-of-function assays of homeobox protein transcription antisense RNA (HOTAIR) in oxLDL-stimulated macrophages suggest that HOTAIR controlled CD36 expression, oxLDL uptake, inflammation [interleukin-6 (IL-6), IL-1 β , cyclooxygenase 2 (COX2), and tumor necrosis factor- α (TNF- α)], and macrophage-derived foam cell formation via miRNA-330-5p (Liu et al., 2019). Therefore, ncRNAs present potential targets to fine-tune macrophage function within atherosclerotic lesions. For a detailed review of ncRNAs in regulating SRs, we refer to a recent review (Dai et al., 2016).

Studies performed using CD36^{-/-} mice to dissect the role of CD36 in atherosclerosis have yield controversial results (Collot-Teixeira et al., 2007). For example, targeted disruption of CD36 reduced the oxLDL uptake, foam cell formation, and atherosclerotic plaques in ApoE^{-/-} mice (Febbraio et al., 2000). This was supported by an independent study using shRNA-mediated gene silencing of CD36, which showed that silencing of CD36 in bone marrow-derived cells decreased atherosclerotic plaques (Mäkinen et al., 2010). Another study showed that CD36^{-/-}-deficient male ApoE^{-/-} mice, but not female mice, showed reduced atherosclerotic plaque area after feeding normal diet and Western-type diet; however, this was unexpectedly related to increased aortic sinus lesion areas (Moore et al., 2005). In contrast, a second study observed that CD36 deficiency reduced atherosclerosis in both sexes of ApoE^{-/-} mice (Kuchibhotla et al., 2008). A third study observed increased atherosclerosis only in male CD36^{-/-} and ApoE^{-/-} mice fed a Western-type diet, albeit with reduced foam cell formation in vitro; however, simultaneous deletion of both CD36 and SR-A significantly reduced

atherosclerosis as well as plaque necrosis in ApoE^{-/-} mice without affecting foam cell formation (Manning-Tobin et al., 2009). These discrepancies in phenotypic observations suggest that CD36 in other cell types (such as endothelial cells, VSMCs, monocytes, and dendritic cells) may have lipid uptake-independent functions, and the possible reciprocal interaction network among SRs may be complicatedly regulating lipid metabolism and atherosclerosis (Maguire et al., 2019).

2. Macrophage Scavenger Receptor 1. SR-A (also known as CD204, or macrophage scavenger receptor 1) is a 77-kDa glycoprotein belonging to class A of the SR family. SR-A is the first identified and cloned SR in macrophages (Kodama et al., 1990). Alternative splicing of SR-A leads to the generation of several variants, such as SR-A1/2/3 (human SR-A) and SR-A1/2 (mouse SR-A). SR-A gene is located on chromosome 8 (8p22). SR-A protein has a cysteine-rich C-terminal domain, an extra-cellular domain, and a collagen-like domain (McLaren et al., 2011a). SR-A1/2s are the common functional receptors that mediate the endocytosis of modified LDLs, such as acetylated LDL (acLDL) (Terpstra et al., 1997). The expression of SR-A was upregulated by multiple proatherogenic stimuli [such as acLDL (Terpstra et al., 1997), oxLDL (Terpstra et al., 1997), TNF- α (Hashizume and Mihara, 2012), IL-6 (Hashizume and Mihara, 2012), high glucose (Fukuhara-Takaki et al., 2005), etc.] and downregulated by many plant-derived phytochemicals (Yu et al., 2013). SR-A1 gene transcription is primarily regulated by PU.1 (Horvai et al., 1995), NF- κ B (Hashizume and Mihara, 2012), activating protein-1 (AP-1) (Mietus-Snyder et al., 1998), and CCAAT/enhancer binding protein (C/EBP) (Mietus-Snyder et al., 1998). Several miRNAs were shown to regulate the SR-A expression, such as miRNA-29a (Dai et al., 2016). SR-A1 expression can be upregulated through Orail store-operated calcium channel (Liang et al., 2016), chloride channel ClC₃ (Tao et al., 2015b), and endophilin-A2 (Huang et al., 2016a).

Earlier studies in the 1990s showed that deletion of SR-A can reduce atherosclerosis development in both LDL receptor-deficient (LDLR^{-/-}) mice (Sakaguchi et al., 1998) and ApoE^{-/-} mice (Suzuki et al., 1997). The pathologic role of SR-A is supported by its silencing in LDLR^{-/-} ApoB100 mice. However, simultaneous depletion of SR-A and CD36 did not reduce atherosclerosis, due to reciprocal regulation of both receptors (Mäkinen et al., 2010). Follow up studies suggested the more complex role of SR-A in atherosclerosis. For example, deficiency of either SR-A or CD36 alone had no impact on atherosclerotic development in ApoE^{-/-} mice, although it attenuated foam cell formation (Moore et al., 2005), but SR-A and CD36 double knock-out reduced plaque complexity without significant impact on macrophage-derived foam cell formation. Also, SR-A transgenic in either LDLR^{-/-} mice or ApoE-3 Leiden mice decreased the atherosclerosis development

despite increased foam cell formation in SR-A overexpressed macrophages (De Winther et al., 2000). This discrepancy may be attributed to several factors, including different diet, time of feeding, and different atherosusceptible mouse strain. To avoid the systemic effects caused by global knockout, macrophage-specific overexpression of SR-A was done and unexpectedly led to attenuated atherosclerosis development in LDLR^{-/-} mice (Whitman et al., 2002). Similarly, overexpressing SR-A in LDLR^{-/-} mice (via bone marrow transplantation) does not affect atherosclerotic lesion development despite increased SR activity in vitro (Herijgers et al., 2000). In addition to regulating lipid uptake, SR-A also has other biologic functions, such as regulation of vascular inflammation, host defense, innate immunity, cell fate determination, and ischemic injury, highlighting that SR-A could be a double-edged sword implicated in cardiovascular health as well as in multiple cardiovascular diseases (CVD) (Kelley et al., 2014; Ben et al., 2015).

3. Lectin-like Oxidized Low-density Lipoprotein Receptor-1. LOX-1 (lectin-like oxLDL receptor-1) belongs to the Class E of scavenger receptors located at chromosome 12 (12p13.2). LOX-1 is encoded by the gene-oxLDL receptor 1 (OLR1). LOX-1 was identified in 1997 as a major SR in endothelial cells that binds, internalizes, and degrades oxLDL (Sawamura et al., 1997). Genetic variants of LOX-1 were associated with increased risk of CVD (Chen et al., 2003; Wang et al., 2010c; Morini et al., 2016). The human LOX-1 gene has six exons and five introns, encoding LOX-1 protein, which has 273 amino acid residues. LOX-1 is composed of a C-type lectin-like domain, an extracellular domain, a transmembrane domain, and an N-terminal cytoplasmic domain (Dunn et al., 2008; Ogura et al., 2009). The C-type lectin domain is critical for oxLDL binding. In terms of expression, LOX-1 is ubiquitously expressed in vascular cells, such as endothelial cells (Sawamura et al., 1997), macrophages (Draude et al., 1999), VSMCs (Zhang et al., 2017), cardiomyocytes (Schlüter et al., 2017), and fibroblasts (Liu et al., 2016a). The ubiquitous expression pattern of LOX-1 in cardiovascular cells implicates its important role in regulating cardiovascular pathophysiology. In patients with advanced atherosclerotic plaques, LOX-1 protein expression was markedly increased in lesional macrophages and VSMCs (Kataoka et al., 1999). In addition, LOX-1 is cleaved to form soluble LOX-1, which serves as a diagnostic and prognostic biomarker for CAD (Tian et al., 2019a).

To date, oxLDL is the most common and well-characterized ligand for LOX-1 (Yoshimoto et al., 2011). Other ligands of LOX-1 include carbamylated LDL (Speer et al., 2014; Holy et al., 2016), glycoxidized LDL (Shiu et al., 2009), electronegative LDL fraction L5 (Wang et al., 2018g), and advanced glycation

end-products (Jono et al., 2002). Expression of LOX-1 under basal unstimulated conditions is very low, but LOX-1 expression can be significantly upregulated by several atheroprone stimuli, such as disturbed blood flow (Lee et al., 2018), lipopolysaccharide (LPS) (Zhao et al., 2014), TNF- α (Kume et al., 2000), and high glucose (Li et al., 2003). Dysfunctional HDL from patients with CAD can also cause endothelial dysfunction by reducing endothelial nitric oxide (NO) synthase (eNOS)-dependent NO production, anti-inflammatory responses, and endothelial repair capacity via LOX-1 activation (Besler et al., 2011; Xu et al., 2013b). Similarly, dysfunction of HDL could probably lead to LOX-1-mediated uptake of modified LDL and result in foam cell formation.

LOX-1 gene transcription can be regulated by several transcriptional factors, including NF- κ B, AP-1, and POU-domain transcription factor (Oct-1) in a context-dependent manner (Hermonat et al., 2011). LOX-1 gene expression can be epigenetically mediated by several miRNAs. For example, silencing of miRNA-155 promoted oxLDL-elicited lipid uptake by increasing the expression of LOX-1 (Huang et al., 2010). A recent miRNA transcriptional profiling assay showed that LOX-1 is the target of miRNA-30c-1-3p and miRNA-28a-5p in oxLDL-stimulated RAW264.7 macrophages (Li et al., 2018b). Sirtuin 1 (Sirt1), a class III histone deacetylase, can downregulate LOX-1 expression and LOX-1-mediated foam cell formation, as well as attenuate development of atherosclerosis by deacetylating in macrophages (Stein and Matter, 2011). It remains to be investigated whether there are lncRNAs that can regulate LOX-1 expression and LOX-1-mediated foam cell formation.

LOX-1 transgene accelerates endothelial dysfunction, aortic inflammation, intramyocardial vasculopathy, and atherosclerotic development in ApoE^{-/-} mice (Inoue et al., 2005). Experiments using endothelial cell-specific overexpression of LOX-1 obtained similar phenotype in either ApoE^{-/-} or LDLR^{-/-} mouse background by impairing endothelial function (White et al., 2011; Hofmann et al., 2017). In contrast, LOX-1^{-/-} and LDLR^{-/-} mice show reduced collagen deposition, oxidative stress, and developed fewer atherosclerotic plaques (Mehta et al., 2007; Hu et al., 2008). These series of gain- and loss-of-function studies provide the “proof-of-concept” that LOX-1 is a proatherogenic SR and can serve as a promising therapeutic target for atherosclerosis. The molecular mechanisms of LOX-1 in promoting atherosclerosis include induction of endothelial dysfunction (injury, apoptosis, impaired NO production, and endothelial-mesenchymal transition), the proliferation/migration of VSMCs, macrophage-derived foam cell formation, and platelet activation (Tian et al., 2019a).

For a detailed understanding of the functions and pharmacological modifiers of LOX-1 in atherosclerosis, we refer the readers to a recently published review

(Tian et al., 2019a). More studies are needed to understand the specific role of LOX-1 in macrophage foam cell formation and atherosclerosis (by macrophage-specific knockout mice and/or transgenic mice) (Maguire et al., 2019). Also, LOX-1 was expressed in VSMCs in mice and human atherosclerotic plaques, the potential role of LOX-1 in lipid uptake and foam cell formation in VSMCs remains to be investigated.

4. *Others.* Other SRs that mediate lipid uptake include MARCO (Elomaa et al., 1998), SR expressed in endothelial cells (Adachi et al., 1997), and CXCL16 (Shimaoka et al., 2000). For example, CXCL16 was a SR highly expressed in macrophages (Shimaoka et al., 2000). Knockdown experiments have demonstrated that CXCL16 was important for foam cell formation in human macrophages (Zhang et al., 2008). It is plausible that these less common SRs also contribute to the uptake of modified LDL to certain extent or under specific disease conditions (McLaren et al., 2011a). Further studies are warranted to assess the contribution of these SRs to foam cell formation and atherosclerosis in genetically manipulated mice.

B. Cholesterol Esterification and Hydrolysis

After uptake and internalization by macrophage SRs, modified LDL is transported to the late endosome/lysosomes where the cholesteryl esters (CEs) are further hydrolyzed to free cholesterol (FC) and free fatty acids by lysosomal acid lipase [LAL, also known as lipase A (LIPA)] (Du et al., 2004; Ouimet et al., 2011; Dubland and Francis, 2015; Schlager et al., 2017). To prevent the potential cell toxicity caused by an excessive FC accumulation, FC can be re-esterified by acetyl-CoA acetyltransferases (ACAT) at the endoplasmic reticulum (ER) to form CE, which is stored in cytoplasm in the form of lipid droplets (LD). Optimal cholesterol esterification is regarded as a protective self-defense mechanism to avoid the excessive accumulation of cytotoxic FC. The excessive accumulation of CE in macrophages and VSMCs leads to the formation of foam cells, which represents a major hallmark for the development of atherosclerosis. The accumulated CE within the cells can be hydrolyzed by two neutral CE hydrolases (NCEH), termed NCEH1 (also known as KIAA1362) (Okazaki et al., 2008; Sekiya et al., 2009) and hormone-sensitive lipase (HSL, also known as lipase E) (Escary et al., 1998, 1999; Okazaki et al., 2002; Yeaman, 2004). The result is the release of FC for transporters-mediated efflux. Therefore, preventing cholesterol esterification and stimulating CE hydrolysis are crucial for maintaining cholesterol homeostasis, and therefore, represent novel therapeutic modalities of atherosclerosis.

1. *Acetyl-CoA Acetyltransferases 1 and Acetyl-CoA Acetyltransferases 2.* ACAT has two isoforms: ACAT1 (which is expressed in macrophages, VSMCs, and other cell types) and ACAT2 (mainly expressed in the intestinal enterocytes, macrophages, and hepatocytes).

ACAT2 has 44% sequence similarity with ACAT1 (Cases et al., 1998; Lee et al., 2000b; Sakashita et al., 2003; Allahverdian et al., 2012). ACAT1 was first identified in 1993 by Chang et al. (1993) and is the well-studied ACAT isoform in mediating CE synthesis. ACAT1 is located in chromosome 11 (11q22.3). Human ACAT1 gene spans 27 kb and has 12 exons and 11 introns. ACAT1 gene encodes a 45.1-kDa product, which is composed of 427 amino acids. ACAT1 was predominantly expressed in plaque macrophages in human patients, and its expression was significantly increased during monocyte differentiation to macrophages (Miyazaki et al., 1998). Moreover, several proatherogenic stimuli, including interferon- γ (Panousis and Zuckerman, 2000b), oxLDL (Wang et al., 2016b), TNF- α (Lei et al., 2009), insulin (O'Rourke et al., 2002), leptin (O'Rourke et al., 2002), *Chlamydia pneumoniae* infection (Liu et al., 2010a), and asymmetric dimethylarginine (Zhu et al., 2010), upregulated the expression/activity of ACAT1 in macrophages. Furthermore, cholesterol loading of aortic VSMCs also leads to increase in ACAT1 activity, while ACAT2 was not expressed by arterial VSMCs (Rong et al., 2005). Also, oxLDL increases the ACAT1-dependent foam cell formation in VSMCs via toll-like receptor 4 (TLR4)/MyD88/NF- κ B-mediated proinflammatory pathways (Yin et al., 2014). In contrast, the ACAT1 expression in macrophages can be decreased by ghrelin [via growth hormone secretagogue receptor (Wan et al., 2009)], incretins [via cyclic AMP (cAMP) activation (Nagashima et al., 2011)], and the vasoprotective gasotransmitter hydrogen sulfide (H₂S) [via K_{ATP}/ERK1/2 pathway (Zhao et al., 2011)]. The expression of ACAT1 can be regulated by a few miRNAs, including miRNA-9 (Xu et al., 2013a), miRNA-27a/b (Zhang et al., 2014), and miRNA-467b (Wang et al., 2017a), all of which reduced the macrophage-derived foam cell formation. Clinically relevant, two genetic variants of ACAT1 gene (such as rs1154556 and rs10913733) were associated with an increased risk of CAD in Chinese population (Wang et al., 2017i).

A large part of the scientific knowledge about ACAT1 and ACAT2 has been gained from genetically engineered mice by breeding with atherosusceptible mouse strains. Total deficiency or liver-specific deletion (by administering antisense oligonucleotide targeting ACAT2) of ACAT2 has consistently reduced atherosclerosis in mice (Willner et al., 2003; Bell et al., 2006, 2007), whereas the outcome of deletion/pharmacological inhibition of ACAT1 in experimental atherosclerosis is controversial (Rudel et al., 2005; Farese, 2006). On the one hand, global deletion of ACAT1 in either ApoE^{-/-} or LDLR^{-/-} mice show reduced CE accumulation and atherosclerosis development, but caused cutaneous xanthomatosis and dry eye in mice, probably due to an excessive FC accumulation (Yagyu et al., 2000). Similarly, myeloid-specific ACAT1 deficiency (by breeding with LyzM-Cre mice) reduces the content of CE and

leukocyte adhesion to activated endothelium, lesional macrophage content, and atherosclerosis plaque area in ApoE^{-/-} mice, without causing common side effects caused by the ACAT1 total deficiency (Huang et al., 2016b). Myeloid-specific ACAT1 ablation also reduces macrophage inflammation and prevents diet-induced obesity (Huang et al., 2018). On the other hand, myeloid cell-specific deletion of ACAT1 (by bone marrow transplantation) unexpectedly show accelerated atherosclerosis in both ApoE^{-/-} (Su et al., 2005) and LDLR^{-/-} mice (Fazio et al., 2001). Pharmacological inhibition of ACAT by inhibitors increases atherosclerotic lesion area in ApoE^{-/-} mouse and rabbit models of atherogenesis (Perrey et al., 2001). These unexpected findings are probably due to a FC-induced cytotoxicity and an impairment of cholesterol efflux (Fazio and Linton, 2006).

Diverse pharmacological inhibitors of ACAT have been explored as effective therapeutic strategies to assess the therapeutic potential of ACAT inhibition in atherosclerosis. Most of these inhibitors have shown promising results in ameliorating atherosclerosis development in animal models. For example, ACAT inhibitors, such as avasimibe (Nicolosi et al., 1998; Delsing et al., 2001; Kharbanda et al., 2005), CS-505 (Terasaka et al., 2007), T-2591 (Yasuhara et al., 1997), HL-004 (Ishii et al., 1998), K604 (Yoshinaka et al., 2010), F1394 (Rong et al., 2013), and tomatidine (Fujiwara et al., 2012), have been reported to inhibit foam cell formation and atherosclerosis in hyperlipidemic mice. Some ACAT inhibitors, like avasimibe, have been shown to reduce the systemic inflammation and improve the endothelial functions in patients with hypercholesterolemia (Kharbanda et al., 2005). Most of these inhibitors partially inhibited the ACAT activity and both isoforms of ACAT. Recently, Shibuya et al. (2018) identified a highly potent ACAT1 inhibitor (IC₅₀ = 4.0 nM), which reduced lipid-accumulation in the aortic arch of hamsters fed with an atherogenic diet, raising the therapeutic potential of this compound to attenuate atherosclerosis in other experimental animal models and human patients with atherosclerosis. Other recent studies have shown that other treatment options, such as losartan (Rafatian et al., 2013) or inhibition of the NLRP3 inflammasome (by compound MCC950) (Chen et al., 2018b), inhibit the ACAT activity, CE accumulation, and foam cell formation. However, three randomized, double-blind, placebo-controlled trials failed to observe significant differences in carotid as well as coronary atherosclerosis between treatment with ACAT inhibitors (by pactimibe and avasimibe) and placebo (Tardif et al., 2004; Nissen et al., 2006; Meuwese et al., 2009). The evidence indicates that selective ACAT inhibition might be desired and should be used in combination with therapies that increase cholesterol acceptors (such as HDL or ApoA-1 targeted therapies), driving out excessive FC of the plaques (Fazio and Linton, 2006).

2. Neutral Cholesterol Ester Hydrolase 1. NCEH1 gene is located at chromosome 3 (3q26.31) in the ER. Compared with HSL, NCEH1 contributes more to CE hydrolysis in macrophages (Sakai et al., 2014). NCEH1 gene yields four isoforms that result from differences in mRNA cleaving. Structurally, NCEH1 is a membrane protein consisting of an N-terminal transmembrane domain, a catalytic domain, and C-terminal lipid-binding domains (Okazaki et al., 2008). The N-terminal domain has an ER-anchoring sequence. NCEH1 gene was first cloned and biologically characterized in macrophages (Ghosh, 2000; Okazaki et al., 2008). It was recently shown that estrogen significantly increases the activity of NCEH1 in mouse macrophages, suggesting the possibility of resulting sex difference of atherosclerosis development (Chiba et al., 2011).

To dissect the role of NCEH1 in foam cell formation and atherosclerosis, Igarashi et al. (2010) showed that NCEH overexpression enhanced the CE hydrolysis and promoted cholesterol efflux from macrophages. In contrast, the NCEH1 depletion promoted foam cell formation, indicating the critical role of NCEH1 in maintaining cholesterol homeostasis (Okazaki et al., 2008). In vivo, NCEH1 deletion accelerated foam cell formation and increased atherosclerotic plaque area in ApoE^{-/-} mice without impacting lipid profile. NCEH1 and HSL1 have comparable NCEH activity in macrophages despite one contradictory report (Bucheberner et al., 2010), which showed that HSL deficiency, but not NCEH1 deficiency, abolished the NCEH activity. Mice with deficiency of both NCEH1 and HSL1 showed exaggerated atherosclerotic plaque increase in an additive manner (Sekiya et al., 2009). In contrast, mice overproducing both NCEH and ApoA4 (as cholesterol acceptor) showed decreased atherosclerosis development (Choy et al., 2003). Also, macrophage-specific overexpression of NCEH1 reduced atherosclerotic lesion area and plaque necrosis in LDLR^{-/-} mice due to enhanced FC efflux and reverse cholesterol transport (RCT) (Zhao et al., 2007). Excessive accumulation of FC or oxysterols induces macrophage apoptosis and atherosclerosis. NCEH1-deficient, but not HSL-deficient, macrophages were more sensitive to 25-hydroxycholesterol-induced apoptosis (Sekiya et al., 2014). Therefore, NCEH1 not only reduced the CE content in foam cells, but also prevented the oxysterols-induced apoptosis in atherosclerosis (Sekiya et al., 2014). Overall, these results highlight NCEH1 as a promising target for treating atherosclerosis.

3. Lysosomal Acid Lipase (Lipase A) and Hormone-sensitive Lipase 1 (Lipase E). In addition to NCEH1, LAL is also a principal lipase that hydrolyzes lysosomal CE derived from LDL and modified LDL (Dubland and Francis, 2015). Genome-wide association studies identified several genetic variants of LAL gene, which was associated with increased risk for CAD (Morris et al., 2017). In mice, intravenous administration of recombinant

LAL reduced coronary and aortic atheromatous lesions in LDLR^{-/-} mice fed an atherogenic diet (Du et al., 2004). A recent study has shown that LAL promotes RCT in cultured macrophages and in mice by increasing the expression of ABCA1 and ABCG1 (Bowden et al., 2018).

Unlike LAL, HSL is a neutral lipase expressed in macrophages. Macrophage-specific HSL-transgenic mice show enlarged aortic lesions and increased lipid accumulation in coronary arteries (Escary et al., 1999). However, the overexpression of cholesterol acceptors (ApoA4) reduces atherosclerosis in HSL-transgenic mice (Choy et al., 2003). Studies using macrophages and LDLR^{-/-} mice have indicated that HSL has comparable neutral CE hydrolase activity to those of NCEH1. The deletion of bone marrow-derived HSL increased a diet-induced atherosclerosis (Sekiya et al., 2009).

To date, pharmacological activators of LAL and HSL1 are not available. The specific role of LAL and HSL in foam cell formation of macrophages and VSMCs, as well as eventual effect on atherosclerosis remains to be investigated in future studies.

C. Macrophage Cholesterol Efflux

To maintain intracellular cholesterol homeostasis, excessive cholesterol is removed from cells through multiple pathways, with the cholesterol export process being termed “macrophage cholesterol efflux.” The CE stored in the LD can be hydrolyzed to FC by CE hydrolase (Hopkins, 2013). Then, FC could be outflowed from macrophages by aqueous diffusion and by ATP-binding cassette (ABC) transporters ABCA1, ABCG1, and SR-BI (Rosenson et al., 2012; Chistiakov et al., 2016a). Caveolins (Murata et al., 1995) and sterol 27-hydroxylase (CYP27A1) (Escher et al., 2003) are also known as contributors to cholesterol efflux. ABCA1 promotes FC efflux to lipid-poor apolipoprotein A-1 (ApoA-1) (often referred to as pre- β HDL) or apolipoprotein E (ApoE). ABCG1 can promote FC efflux to mature HDL (HDL2 and HDL3) particles (Hopkins, 2013). ABCA1 and ABCG1 expression are positively regulated by the nuclear receptor liver X receptor (LXR), which forms a heterodimer by binding with the retinoid X receptor (RXR), and acts as a transcription factor. The expression of ABCA1, ABCG1, SR-BI, and LXR can also be induced by activation of PPAR γ (Lusis, 2000; Hopkins, 2013). If cholesterol cannot be exported from cells to a sufficient extent, macrophages are transformed into foam cells (Hansson, 2005; Hansson et al., 2006).

1. Aqueous Diffusion Efflux Pathway. Aqueous diffusion efflux pathway recently was reviewed elsewhere (Phillips, 2014). This pathway involves a simple diffusion process, representing in this way the nonprotein-mediated cholesterol efflux pathway. It was shown that it is one major contributor to cholesterol efflux particularly in normal mouse peritoneal macrophages

(MPMs) (~80%) (Adorni et al., 2007). However, in cholesterol-loaded MPMs, aqueous diffusion was not changed and its contribution to cholesterol efflux became smaller (Adorni et al., 2007). In addition, the major variations in cellular cholesterol efflux rates are not due to aqueous diffusion efflux pathway, but to membrane transporters-mediated cholesterol efflux pathways (Phillips, 2014).

2. Transporter-Dependent Cholesterol Efflux Pathway. A significant pathway for cholesterol efflux from macrophages involves the interaction between transporters (ABCA1 and ABCG1), SR-BI, and acceptors (ApoA-1, HDL, and ApoE) (Brunham et al., 2006; Rosenson et al., 2011). It is proposed that ABCA1 and ABCG1 can act in a sequential way, in which ABCA1 generates nascent HDL, which then further promotes cholesterol efflux via ABCG1 (Gelissen et al., 2006). Genetic knockdown studies indicate that ABCG1 and ABCA1 account for about 20% and 50% of the net cholesterol efflux from cholesterol-enriched MPMs, respectively (Adorni et al., 2007). Furthermore, both ABCA1 and ABCG1 together account for about 60%–70% of the net cholesterol efflux to serum or HDL from LXR-activated macrophages loaded with cholesterol (Yvan-Charvet et al., 2007a). This part of the review will focus on current understanding of the function and regulation of these transporters (ABCA1 and ABCG1), SR-BI, and the acceptors (ApoA-1, HDL, and ApoE), which are related to cholesterol efflux from macrophages.

a. ATP-binding Cassette Transporter A1. ABCA1 is a member of the ABC transporter superfamily that utilizes ATP as a source of energy to transport various substrates across cellular membranes (Dean et al., 2001). ABCA1, originally named as ABC1, was identified by a PCR-based approach and cloned in 1994 (Luciani et al., 1994). The ABCA1 gene consists of 50 exons spanning 149 kb and encodes a 2261 amino acid integral membrane protein, consisting of two transmembrane domains (TMDs) with six helices each and two nucleotide-binding domains (NBDs) (Santamarina-Fojo et al., 2000; Wang and Smith, 2014). The NBDs exhibit a nucleotide-free state, while the two TMDs link each other via a narrow interface in the membrane. Additionally, two extracellular domains of ABCA1 form an elongated hydrophobic tunnel. There are two large extracellular loops that are linked by a disulfide linkage (Fitzgerald et al., 2002; Qian et al., 2017).

It was not until 1999 that mutations of ABCA1 gene were identified as underlying the etiology of Tangier disease (Rust et al., 1999), which is characterized in the homozygous state by an HDL deficiency, frequently premature CAD, extremely enlarged yellow tonsils, and clouding of the cornea (Bale et al., 1971; Serfaty-Lacroisniere et al., 1994; Rust et al., 1999). Further studies indicate that ABCA1 plays a major role in HDL biosynthesis by mediating FC and phospholipid efflux to lipid-poor ApoA-1, thereby producing nascent HDL

particles in the liver (Yokoyama, 2006; Phillips, 2014). Fibroblasts from subjects with Tangier disease are deficient in cholesterol efflux to ApoA-1 (Remaley et al., 1997), indicating that ABCA1 is an important transporter mediating the cholesterol efflux. Details about the interaction of the ABCA1 protein with ApoA-1 in mediation of the cholesterol efflux were reviewed recently (Wang and Smith, 2014; Phillips, 2018). To date, there is no clear consensus regarding the process by which the ABCA1 protein regulates the transport of cholesterol and lipoprotein from the plasma membrane to the acceptor ApoA-1.

Consistent with the proposed function of ABCA1 in nascent HDL formation, ABCA1-deficient mice have almost undetectable levels of HDL, with a significant decrease in total plasma cholesterol and phospholipids (McNeish et al., 2000; Ors   et al., 2000). Overexpression of ABCA1 in mice led to increased HDL-cholesterol (HDL-C) and ApoA-1 levels, facilitating hepatic RCT and biliary cholesterol excretion (Singaraja et al., 2001; Vaisman et al., 2001). However, the studies in vivo from some groups have led to opposite results about the role of ABCA1 expression in atherosclerosis development. Complete ABCA1 deficiency in wild-type, LDLR^{-/-}, and ApoE^{-/-} mice did not alter progression of atherosclerosis (McNeish et al., 2000), but repopulation of ABCA1^{-/-} mice with wild-type macrophages (McNeish et al., 2000) or macrophages from ABCA1-overexpressing mice (McNeish et al., 2000) led to a significant decrease of atherosclerotic lesion in mice. In addition to lipid regulation, ABCA1 protein is also involved in the regulation of apoptosis and inflammation (Soumian et al., 2005). ABCA1 executes its anti-inflammatory effects by modifying cell membrane lipid rafts and directly activating signaling pathways, including Janus kinase 2/STAT3, protein kinase A (PKA), Rho family G protein CDC42, and PKC (Liu and Tang, 2012).

ABCA1 protein plays a critically important role in cholesterol homeostasis and may be viewed as a protector against atherosclerosis, thus there are many studies to decipher how its expression is regulated at both transcriptional and posttranscriptional levels (Schmitz and Langmann, 2005; Zarubica et al., 2007) (Fig. 3). ABCA1 expression is regulated in a tight pathway with a short protein half-life (1 to 2 hours) (Yokoyama et al., 2012) and rapid turnover in macrophages (Soumian et al., 2005). ABCA1 protein expression is highly regulated by a variety of molecules, including secondary messengers (e.g., cAMP), nuclear receptors [e.g., LXR, RXR, PPAR, pregnane X receptor (PXR)], and cytokines [e.g., TNF- α , transforming growth factor- β (TGF- β), interleukin-1 β (IL-1 β)] (Zarubica et al., 2007). cAMP upregulates the expression of ABCA1 protein by acting at both the transcriptional and translational levels (Haidar et al., 2002; Denis et al., 2003). Nuclear receptors are ligand-dependent transcriptional factors that mediate the expression of their target genes

(Beaven and Tontonoz, 2006). The activation of LXR and RXR by physiologically occurring oxysterols (e.g., 27-hydroxycholesterol), retinoids, or synthetic agonists stimulates the transcription of ABCA1 via the DR4 element in the ABCA1 promoter (Zarubica et al., 2007). PPAR upregulates ABCA1 expression and RCT indirectly via enhancement of the transcription of LXR α (Chinetti et al., 2001). PXR, regulated by many compounds including both natural and synthetic steroids, downregulate the ABCA1 gene transcription (Sporstol et al., 2005). Cytokines were shown to exhibit pleiotropic and contradictory effects on ABCA1 expression by cross-talks between the cellular process of cholesterol and inflammatory reactions (Zarubica et al., 2007). TNF- α , IL-1 β , and interferon- γ downregulate the LXR-mediated increase of ABCA1 protein expression (Lusis, 2000; Panousis and Zuckerman, 2000a), whereas TGF- β positively regulates the ABCA1 expression (Panousis et al., 2001). Posttranscriptional regulation also plays a critical role in the regulation of ABCA1 protein levels by adjusting either protein stability or its transporter activity (Llaverias et al., 2005). It was reported that the protein stability of ABCA1 is regulated by the proteasomal, lysosomal, and calpain systems (Ogura et al., 2011; Yokoyama et al., 2012; Aleidi et al., 2015), whereas its activity is under the fine control of diverse protein kinases, such as PKA and protein kinase CK2 (Haidar et al., 2004; Roosbeek et al., 2004). It was shown that a proline, glutamic acid, serine, and threonine sequence in ABCA1 is very important for its degradation by calpain protease, since deletion of this motif leads to increase ABCA1 protein levels by four- to fivefold (Wang et al., 2003).

The regulation of ABCA1 protein expression by miRNA was recently investigated. miRNAs, are a class of ncRNAs that are predominantly posttranscriptional regulators of gene expression (Ambros, 2004; Bartel, 2009). To date, miRNA-10b (Wang et al., 2012a), miRNA-23a-5p, miRNA-33 (Rayner et al., 2010), miRNA-106b (Kim et al., 2012), miRNA-128-2 (Adlakha et al., 2013), miRNA-148a (Goedeke et al., 2015), miRNA-183 (Sarver et al., 2010), and miRNA-758 (Ramirez et al., 2011) have been reported to regulate the ABCA1 protein expression. MiRNA-10b directly repressed ABCA1 expression and also suppressed cholesterol efflux from both murine and human macrophages (Wang et al., 2012a). Transfection of miRNA-23a-5p inhibitor enhanced cholesterol efflux and decreased foam cell formation through upregulating the ABCA1 expression levels. miRNA-23a-5p reduced ABCA1 expression via repressing the 3'-untranslated regions (UTR) activity of the ABCA1 transcripts. Long-term in vivo systemically delivered miRNA-23a-5p antagomir significantly increased ABCA1 expression, reduced atherosclerosis development, and promoted plaque stability in the aorta of ApoE^{-/-} mice (Yang et al., 2018a). miRNA-33, located within the gene encoding

sterol regulatory element-binding factor-2, inhibited ABCA1 expression, thus resulting in the decreased cholesterol efflux (Rayner et al., 2010). miRNA-128-2 inhibited the ABCA1 expression directly via binding to its 3'-UTR. The administration of miRNA-128-2 led to the decrease both protein and mRNA levels of ABCA1 (Adlakha et al., 2013). miRNA-148a decreased expression of ABCA1 and circulating HDL-C levels in vivo (Goedeke et al., 2015). miRNA-758 directly targeted the 3'-UTR of ABCA1, repressed the expression of ABCA1, and reduced cellular cholesterol efflux to ApoA-1. Conversely, the application of anti-miRNA-758 increased ABCA1 expression (Ramirez et al., 2011). miRNA-106b significantly decreased the ABCA1 levels and the cholesterol efflux in neuronal cells (Kim et al., 2012). miRNA-183 targeted the 3'-UTR of ABCA1 mRNA to degrade ABCA1 mRNA in the colon cancer cells and other tumor cells (Sarver et al., 2010). There has been no further study to investigate the effect of miRNA-106b and miRNA-183 on macrophages and liver cells so far.

Recent studies also showed that lncRNA, a large subgroup of RNAs that are >200 nucleotides. Although most lncRNAs do not have apparent protein coding potential, lncRNAs also play a very important role in

modulating ABCA1 protein expression. lncRNAs can regulate the ABCA1 expression at both transcriptional and posttranscriptional levels. It was reported that lncRNA macrophage-expressed LXR-induced sequence (MeXis) increased the ABCA1 protein expression at the transcriptional level by interacting with and guiding promoter to bind to the transcriptional coactivator DDX17 in macrophages (Sallam et al., 2018). Furthermore, the loss of MeXis in mouse bone marrow cells impaired the cellular reaction to cholesterol overload and accelerated the atherosclerotic development (Sallam et al., 2018). Increased long intervening non-coding RNA-DYNLRB2-2 expression promoted the ABCA1-mediated cholesterol efflux by upregulation of the ABCA1 expression through the glucagon-like peptide-1 (GLP-1) receptor signaling pathway (Hu et al., 2014) and decrease of TLR2 expression (Li et al., 2018c) in macrophages. A newly identified lncRNA named lnc-HC, which interacts with hnRNP A2B1 to form an lnc-HC-hnRNP A2B1 complex, decreased the ABCA1 expression at the posttranscriptional level within hepatocytes (Lan et al., 2016). However, the effect of lnc-HC on ABCA1 expression in macrophages remains to be examined. On the contrary, another lncRNA, RP5-833A20.1, attenuated the ABCA1 levels, thus reducing

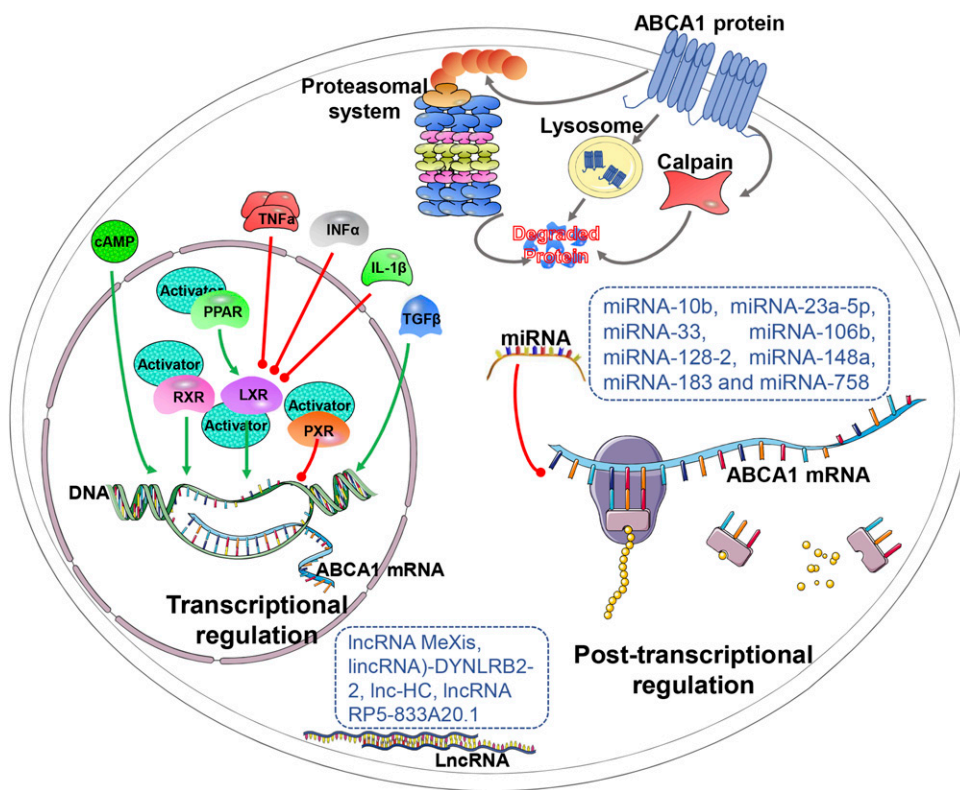


Fig. 3. Regulation of ABCA1 expression at both transcriptional and post-transcriptional levels. At the transcriptional level, ABCA1 protein expression is highly regulated by a variety of molecules, including secondary messengers [e.g., cyclic AMP (cAMP)], nuclear receptors (e.g., LXR, RXR, PPAR, and PXR), and cytokines [e.g., TNF- α , transforming growth factor- β (TGF- β), interleukin-1 β (IL-1 β)]. At the post-transcriptional level, the protein stability of ABCA1 is governed by the proteasomal, lysosomal, and calpain systems. Also, miRNA-10b, miRNA-23a-5p, miRNA-33, miRNA-106b, miRNA-128-2, miRNA-148a, miRNA-183, and miRNA-758 have been reported to regulate ABCA1 protein expression. The long noncoding RNAs (lncRNAs), including lncRNA MeXis, long intervening lncRNA-DYNLRB2-2, lnc-HC, and lncRNA RP5-833A20.1, have also been involved in the regulation of ABCA1 expression (green arrows: upregulation; red lines: downregulation).

the cholesterol efflux via the miRNA-382-mediated NFIA pathway (Hu et al., 2015).

b. ATP-binding Cassette Transporter G1. ABCG1 is another member of the ABC superfamily of transporters (Tarr et al., 2009; Tarling and Edwards, 2012). ABCG1 is a half transporter that contains a single ABC and a single TMD/6 transmembrane α -helice on one polypeptide chain (Tarling, 2013). The half transporter ABCG1 is generally considered to function by forming homodimers (ABCG1:ABCG1) to transport substrates across the cell membrane (Tarling and Edwards, 2011). ABCG1 was first described and cloned in 1996 as the human homolog of the *Drosophila white* gene (Chen et al., 1996). After that, it took around 4 years until ABCG1 again received intensive attention because it is similar to ABCA1 in the expression pattern in monocytes (Schmitz et al., 2001). ABCG1 is involved in regulation of intracellular cholesterol homeostasis and cholesterol efflux from cells to HDL particles for RCT (Rosenson et al., 2012). ABCG1 also effluxes cholesterol to LDL, liposomes, and cyclodextrin (Wang et al., 2004; Kennedy et al., 2005) and it exports sphingomyelin, phosphatidylcholine, and oxysterols to HDL and albumin (Kobayashi et al., 2006; Xu et al., 2009). In addition to regulation of cholesterol efflux from cells, ABCG1 protein exhibits other physiologic functions as well (Sano et al., 2014). For example, ABCG1 is involved in cell proliferation, apoptosis, and immune response (Sano et al., 2014). It has been shown that ABCG1 suppresses the proliferation of T cells by LXR signaling (Bensinger et al., 2008). ABCG1 also induced the apoptosis of cultured cells (Seres et al., 2008), but inhibited the apoptosis of macrophages and prostate cancer cells by decreasing signaling of TLR4 and NADPH oxidase 2 (Yvan-Charvet et al., 2010a) and downregulating Akt signaling (Yvan-Charvet et al., 2010a), respectively.

Consistent with the function of ABCG1 in regulation of macrophage cholesterol efflux from cultured macrophages, ABCG1-deficient mice, first described in 2005, when fed a Western-type diet, displayed excessive lipid accumulation in macrophages within multiple organs, particularly in the lung (Kennedy et al., 2005). Unexpectedly, whole body loss of ABCG1 or overexpression of human ABCG1 had no influence on plasma lipid or lipoprotein levels (Kennedy et al., 2005; Burgess et al., 2008), which are in stark contrast to loss of ABCA1. Deeper insights about the coordinated participation of ABCA1 and ABCG1 in regulation of cholesterol efflux from macrophage have been obtained from animal studies (Rosenson et al., 2012). The combined deficiency of ABCA1 and ABCG1 resulted in markedly accelerated atherosclerotic lesion development in mice compared with the deficiency of either ABCA1 or ABCG1 (Yvan-Charvet et al., 2007b; Out et al., 2008). ABCA1 and ABCG1 double knockout macrophages showed apparently defective cholesterol efflux to HDL and ApoA-1 compared with either ABCA1 or ABCG1 knockout

macrophages (Yvan-Charvet et al., 2007b; Out et al., 2008).

ABCG1 protein expression is mediated at both the transcriptional and posttranscriptional levels (Fig. 4). At the transcriptional level, ABCG1 shares the common regulatory pathways of gene expression with ABCA1. The ABCG1 expression is upregulated by the nuclear receptors LXR, RXR, and PPAR activated by their agonists (oxysterols, retinoids, fatty acids, or synthetic agonists) (Venkateswaran et al., 2000; Hardy et al., 2017). Upregulation of ABCG1 expression mediated by LXR agonists probably involves the presence of multiple LXR responsive elements by the ABCG1 gene promoter and likely only requires the isoform LXR α in human macrophages (Sabol et al., 2005; Ishibashi et al., 2013). Further study suggests that LXR recruitment at the human ABCG1 locus is promoted by the G protein pathway suppressor 2 (Jakobsson et al., 2009). ABCG1 in macrophages is also transcriptionally regulated by the PPAR γ -LXR pathway (Li et al., 2004a). Retinoic acid receptor/RXR heterodimer can bind LXR responsive elements in ABCG1 promoters and transactivates ABCG1 in macrophages as well (Ayaori et al., 2012).

Other mechanisms also contribute to the stability and activity of human ABCG1. Compared with ABCA1, there is limited evidence concerning the posttranscriptional regulation of ABCG1 or protein-protein interactions involving ABCG1. It was reported that calpain facilitated ABCG1 degradation by slicing ABCG1 on the cell surface (Adlakha et al., 2013). The proteasomal inhibition prevented degradation of ABCG1 and led to the accumulation of phosphorylated ABCG1 (Nagelin et al., 2009). Degradation of ABCG1 is suggested to be mediated via the ubiquitin-proteasome system-mediated non-lysosomal pathways (Nakaya et al., 2017) by the NEDD4-1 (neural precursor cell-expressed developmentally downregulated gene 4) and E3 ubiquitin ligases HUWE1 (HECT, UBA, and WWE domain containing 1 E3 ubiquitin protein ligase) (Aleidi et al., 2015). ABCG1 ubiquitination and its proteasomal degradation can be inhibited by cholesterol through interplay with a cholesterol recognition/interaction amino acid consensus (CRAC) motif located in the ABCG1 transmembrane domain (Hsieh et al., 2014; Sharpe et al., 2015).

ABCG1 protein expression was also recently investigated in relation to regulation by miRNAs. The miRNAs implicated in ABCG1 protein regulation include miRNA-10b (Wang et al., 2012a), miRNA-23a-5p, miRNA-33, miRNA-128-2, miRNA-146a-5p, and miRNA-378. The inhibition of miRNA-23a-5p enhanced cholesterol efflux and decreased foam cell formation through upregulating ABCG1 expression levels. miRNA-10b repressed ABCA1 expression and downregulated cholesterol efflux from murine or human macrophages (Wang et al., 2012a). Long-term in vivo systemically delivered miRNA-23a-5p antagomir significantly increased the ABCG1 expression in the aorta of ApoE^{-/-} mice (Yang et al., 2018a).

miRNA-33 inhibited ABCG1 expression, thus resulting in decreasing cholesterol efflux (Rayner et al., 2010). Upregulation of miRNA-33a-5p stimulated by inflammatory cytokines (i.e., IL-6, TNF- α) inhibited the ABCG1-mediated cholesterol efflux from THP-1 macrophages (Mao et al., 2014). miRNA-128-2 inhibited the expression of ABCG1 directly. The administration of miRNA-128-2 led to decrease in the mRNA and protein levels of ABCG1 in mice (Adlakha et al., 2013). Elevated miRNA-146a-5p antagonized the increase of ABCG1 in low-dose LPS-tolerized cells (Li et al., 2015b). The decrease of miRNA-378 level enhanced ABCG1-mediated macrophage cholesterol efflux to HDL by inducing ABCG1 protein expression (Wang et al., 2014a).

c. Scavenger Receptor Class B Type 1. SR-BI is an 82-kDa integral membrane protein, which (together with lysosomal integral membrane protein-2) is a member of the CD36 superfamily of scavenger receptor proteins (Phillips, 2014). SR-BI has a hairpin-looped structure with two short N- and C-terminal transmembrane domains, two cytoplasmic tails, and a large extracellular domain (Williams et al., 1999; Meyer et al., 2013). In 1996, it was identified that SR-BI is an HDL receptor that regulates cholesterol uptake into liver cells (Acton et al., 1996). This process selectively transports the CE from mature HDL into cells without endocytosis and degradation of the HDL particles

(Acton et al., 1996). This receptor is expressed primarily in liver, where it acts in the RCT pathway (Zannis et al., 2006). In addition to promotion of delivery of HDL-C to cells, SR-BI increases the efflux of cellular cholesterol to HDL (Ji et al., 1997; Jian et al., 1998). When incubated with synthetic cholesterol-free HDL, SR-BI-transfected Chinese hamster ovary cells increased initial rates of efflux by approximately threefold compared with control cells, suggesting that SR-BI expression enhanced net cholesterol efflux regulated by HDL (Ji et al., 1997). However, compared with ABCA1 and ABCG1, the contribution of SR-BI to efflux from macrophages is small (Adorni et al., 2007). The performed studies indicated that the SR-BI is a multifunctional receptor that regulates bidirectional flux of lipids, which might be dependent on the content of cholesterol in cells (Rosenson et al., 2012).

In addition to regulating lipid metabolism, SR-BI can also mediate inflammatory responses. SR-BI interaction with HDL reduced the inflammatory response to LPS in human macrophages by markedly reducing NF- κ B activation (Song et al., 2015). Furthermore, recent studies have shown that the interaction of macrophage SR-BI with apoptotic cells activated phosphoinositide 3-kinase (PI3K)/Akt signaling and induced the expression of anti-inflammatory cytokines (Tao et al., 2015a). HDL activated PI3K/Akt signaling in macrophages,

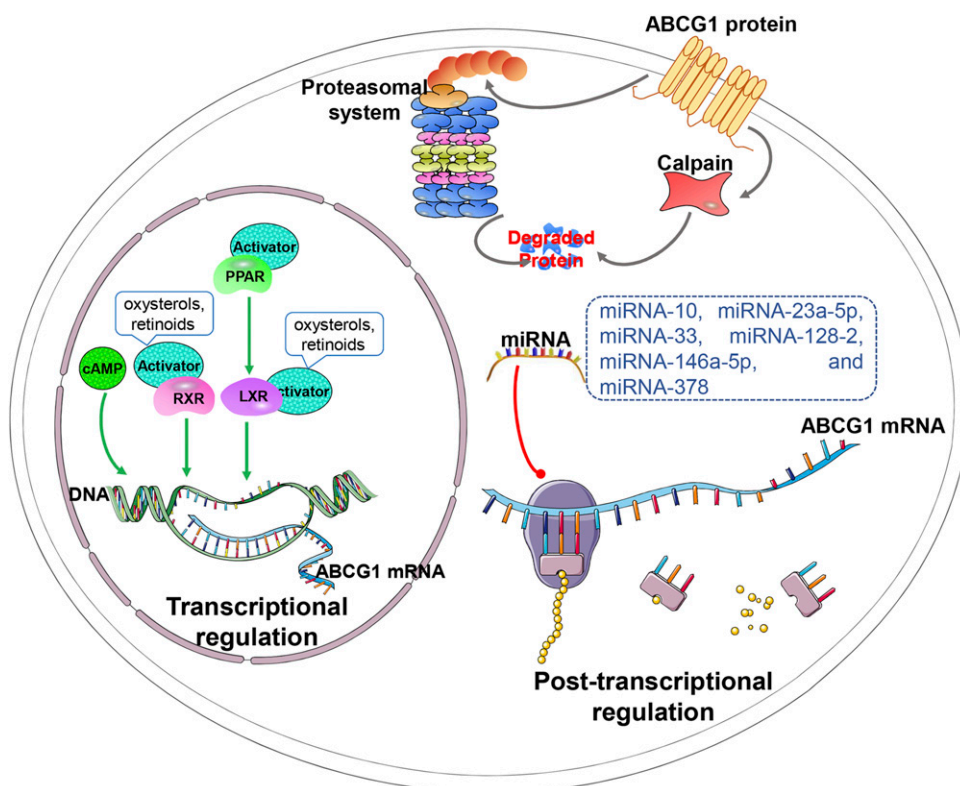


Fig. 4. Regulation of ABCG1 expression at both transcriptional and post-transcriptional levels. At the transcriptional level, ABCG1 shares common gene expression regulatory pathways with ABCA1. The ABCG1 expression is upregulated by the nuclear receptors LXR, RXR, and PPAR activated by their agonists (oxysterols, retinoids, fatty acids, or diverse synthetic agonists). At the post-transcriptional level, the protein stability of ABCA1 is governed by the proteasomal and calpain systems. Also, miRNA-10b, miRNA-23a-5p, miRNA-33, miRNA-128-2, miRNA-146a-5p, and miRNA-378 are involved in the regulation of ABCG1 protein (green arrows: upregulation; red lines: downregulation).

which is mediated by SR-BI and involves interaction with its adaptor protein PDZK1 (PDZ domain-containing 1) and activation of sphingosine 1-phosphate receptor 1 signaling (Al-Jarallah et al., 2014). SR-BI interaction with HDL also prevents endothelial cell inflammation reaction by regulating eNOS activation and expression of the antioxidant enzyme 3-beta-hydroxysteroid-delta 24-reductase (Yuhanna et al., 2001; McGrath et al., 2009). SR-BI-mediated production of NO and 3-beta-hydroxysteroid-delta 24-reductase lead to alleviation of TNF- α -stimulated NF- κ B activation, resulting in the reduced expression of inflammatory monocyte adherence proteins and chemokines in endothelial cells, thereby reducing monocyte recruitment into the intima (Bess et al., 2011). Additionally, a major portion of the endothelial cell-mediated transcytosis of HDL from the apical to the basolateral side is mediated by SR-BI, suggesting that SR-BI regulated HDL transport to the subendothelium, increasing cholesterol efflux from macrophages (Rohrer et al., 2009; Vaisman et al., 2015).

In vivo studies showed that SR-BI deficiency in the bone marrow led to an accelerated atherosclerosis despite increased plasma HDL-C level, which indicated that it played a critical role in the HDL metabolism and exhibited atheroprotective effects in mice (Covey et al., 2003; Rigotti et al., 2003; Van Eck et al., 2004; Brundert et al., 2006). SR-BI overexpression in bone marrow-derived cells protected against atherosclerosis in LDLR^{-/-} mice, as well as in ApoE^{-/-} mice (Covey et al., 2003; Zhang et al., 2003a). However, the physiologic effect of SR-BI-mediated arterial macrophage-specific cholesterol efflux in vivo is not clear (Brundert et al., 2006; Burgess et al., 2008; Yvan-Charvet et al., 2008). Some studies showed that a selective uptake of HDL-CE and the cholesterol efflux from MPMs are independent of SR-BI (Brundert et al., 2006). SR-BI in primary macrophages, although increasing cholesterol efflux in vitro, did not contribute to macrophage RCT in vivo (Wang et al., 2007a). Hepatic SR-BI modulates the changes in the composition and structure of HDL (El Bouhassani et al., 2011). It was indicated that SR-BI polymorphisms contributed to the functional potential of the cholesterol disposition pathway (Vergeer et al., 2011), suggesting that this receptor is involved in RCT and atherosclerosis. Human studies show that carriers of the mutation of SR-BI in humans (P297S mutation) had higher HDL-C levels, but decreased the potential for cholesterol efflux from macrophages without aggravation of atherosclerosis (Alam et al., 2001). In addition, a recent study has shown that endothelial SR-BI promoted LDL transcytosis via dedicator of cytokinesis (DOCK4) and ensuing circulating LDL entry into and retention in the artery wall to instigate atherosclerosis (Huang et al., 2019). The differential functions of SR-BI in macrophage and endothelial cells suggest the necessity to target SR-BI in a specific cell type to achieve atheroprotection.

SR-BI expression is mediated by both transcriptional and posttranscriptional mechanisms (Fig. 5).

Many molecules have been proposed to be involved in the regulation of SR-BI expression at the transcriptional level, including nuclear transcription factors [i.e., PPAR (Straus and Glass, 2007), LXR (Malerød et al., 2002), RXR, farnesoid X receptor (Malerød et al., 2005), PXR (Sporstol et al., 2005), estrogen receptors (Stangl et al., 2002), sterol regulatory element-binding proteins (SREBPs) (Lopez and McLean, 1999)] and some endogenous factors [e.g., IGF-1 (Cao et al., 2004), p38-mitogen-activated protein kinase (MAPK) cascade (Murao et al., 2008; Leiva et al., 2011)]. Recent progress toward understanding the mechanisms of regulating the SR-BI expression at the transcriptional level was summarized in several reviews (Leiva et al., 2011; Shen et al., 2018a,b).

SR-BI can also be regulated posttranscriptionally, for example, by hormones such as estrogens (Zhang et al., 2007), triiodothyronine and thyromimetics (Johansson et al., 2005; Tancevski et al., 2010), insulin (Shetty et al., 2006), as well as glucagon (Nakamura et al., 2005). One important component of the posttranscriptional regulation of SR-BI is the scaffolding protein PDZK1, which regulates the SR-BI protein stability (Nakamura et al., 2005). The exact mechanisms by which the PDZK1 regulates SR-BI membrane expression remain unknown (Leiva et al., 2011). PDZK1/Na⁺/H⁺ exchanger regulatory factor 3 (NHERF3), NHERF1, and NHERF2 were shown to regulate hepatic SR-BI stability (Kocher et al., 2003; Hu et al., 2013b). The mechanisms involved in regulation of the SR-BI expression at the posttranscriptional level were also summarized in recently published works (Leiva et al., 2011; Shen et al., 2018a,b).

Recently, ncRNAs were also investigated in the regulation of SR-BI expression. The miRNAs, which regulate the SB-BI expression, include miRNA-96, miRNA-125a, miRNA-185, miRNA-455, and miRNA-223 (Wang et al., 2013). It was shown that miRNA-96, miRNA-185, and miRNA-223 directly bound the 3'-UTR of SR-BI mRNA to repress the level of SR-BI expression and the uptake of HDL. Furthermore, the decrease of miRNA-185 and miRNA-96 is related to the increase of SR-BI in the livers of ApoE^{-/-} mice with a high-fat diet (HFD) (Wang et al., 2013). Another study reported that miRNA-125a and miRNA-455 negatively regulated the SR-BI expression by binding to 3'-UTR of SR-BI mRNA (Hu et al., 2012). Recent work also demonstrated that obesity induced miRNA-24 and repressed the SR-BI expression, further influencing HDL uptake, lipid metabolism, and steroid hormone synthesis (Wang et al., 2018d). However, the effect of miRNAs on the SR-BI expression and cholesterol efflux in macrophage remains to be further studied.

3. Acceptors that Mediate Macrophage Cholesterol Efflux.

a. Apolipoprotein A-1. ApoA-1 is a main protein constituent of HDL (~70% of the HDL protein) (Phillips,

2013). Human mature ApoA-1 (molecular weight: 28 kDa) comprises a total of 243 amino acid residues. The C-terminal domain of human ApoA-1 contains 11- and 22-amino acid tandem repeats (Li et al., 1988). Each repeat has an amphipathic α -helix, which is crucial for its efficient interaction with lipids in an exchangeable manner (Segrest et al., 1992). The motifs of amphipathic α -helices in ApoA-1 are evolutionally preserved (Bashtovyy et al., 2011). The C-terminal domain takes responsibility for the almost all ApoA-1 lipid-solubilizing property (Tanaka et al., 2008). Furthermore, the C-terminal domain performs as an intact protein, which is able to solubilize phospholipids and facilitate HDL disk formation (Lyssenko et al., 2012). The hydrophobic character of the C-terminal domain and the stability of the N-terminal helix bundle are the major factors for lipid-solubilizing and lipid-binding properties of ApoA-1 (Chistiakov et al., 2016b).

ApoA-1 regulates RCT through mediating cholesterol efflux from foam cells by interaction with the transporter ABCA1 (Mukhamedova et al., 2008). Lipidation of ApoA-1 by cooperation with ABCA1 generates discoidal nascent HDL particles (Wang and Smith, 2014).

Since ApoA-1 is directly involved in lipid metabolism, it is considered as one of the key molecular players in the pathogenesis of atherosclerosis (Chistiakov et al., 2016b). In plasma, ApoA-1 is also involved in the esterification of FC in serum lipoproteins by stimulation of lecithin cholesterol acyltransferase (LCAT), an enzyme secreted by the liver (Zannis et al., 2006). The effect of ApoA-1 in the protection against atherosclerosis has been examined in some in vivo studies. In LDLR^{-/-} mice, ApoA-1 deficiency resulted in aggravating atherosclerosis (Moore et al., 2003). On the contrary, human ApoA-1 overexpression and ApoA-1 infusions in mice mitigated atherosclerotic lesion formation in animal models of atherosclerosis (Duverger et al., 1996). Furthermore, mutations of ApoA-1 enhance CVD risk in humans. Most of the carriers of mutations in the ApoA-1 gene have a lower level of HDL-C and a higher risk of CVD compared with those who do not carry the mutation (Hovingh et al., 2004). Thus, ApoA-1 is widely believed as a promising target for treatment of CVD (Stoekenbroek et al., 2015). There have been some therapies to mimic ApoA-1, including full-length ApoA-1, mutated variants of ApoA-1, and ApoA-1 mimetic peptides,

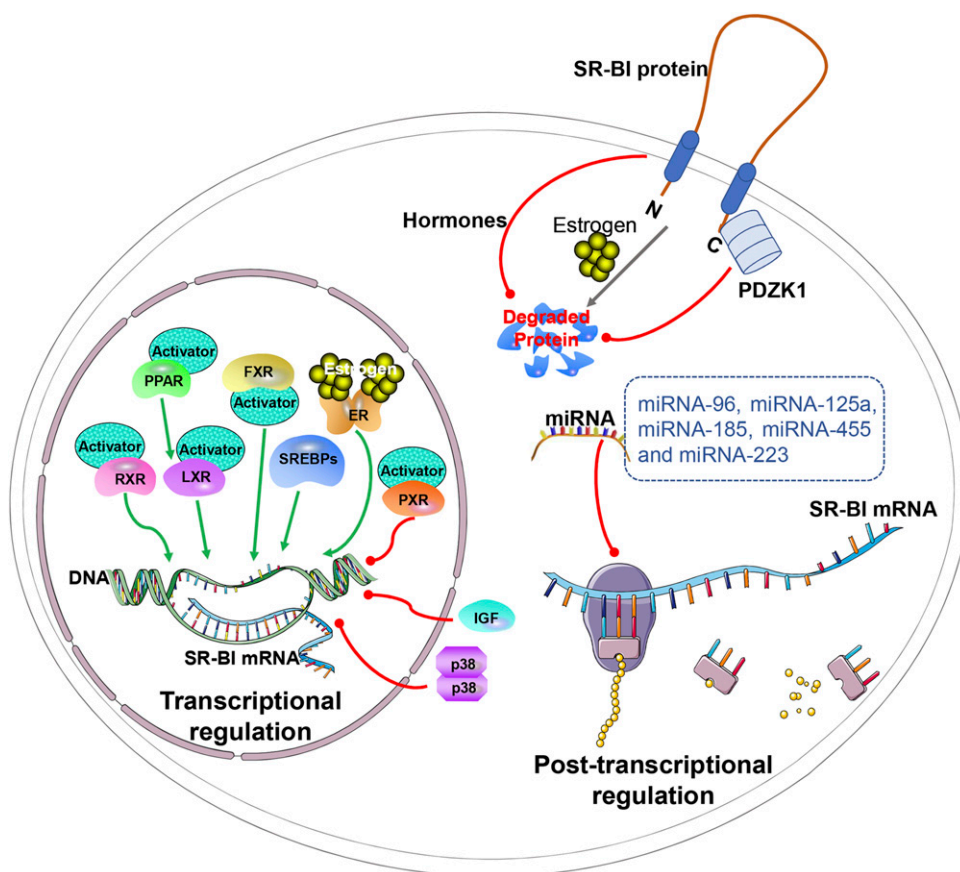


Fig. 5. Regulation of SR-BI expression at both transcriptional and post-transcriptional levels. At the transcriptional level, SR-BI protein expression is regulated by a variety of molecules, including nuclear transcription factors [such as the heterodimeric nuclear receptors PPAR, LXR, RXR, FXR (farnesoid X receptor), and PXR], estrogen receptors, sterol regulatory element-binding proteins (SREBPs), and other endogenous signaling factors (e.g., IGF-1 and p38-MAPK cascade). At the post-transcriptional level, SR-BI can be regulated by estrogens insulin and glucagon as well as other hormones [e.g., triiodothyronine (T3) and thyromimetics]. In addition, miRNA-96, miRNA-125a, miRNA-185, miRNA-455, and miRNA-223 are involved in SR-BI protein regulation. (green arrows: upregulation; red lines: downregulation).

that were well described in several reviews (Millar and Cuchel, 2015; Stoekenbroek et al., 2015). The ApoA-1-mimetic peptides (e.g., 4F, 6F, FX-5A, ATI-5261, and ETC-642) (Garber et al., 1992; Wool et al., 2008; Stoekenbroek et al., 2015) and modified ApoA-1 (Graversen et al., 2008) strongly induced the macrophage cholesterol efflux and exhibited antiatherogenic properties. In the “ApoA-1 Milano Trial,” plaque thickness was significantly decreased in patients treated with ApoA-1_{Milano} compared with the control group (Nissen et al., 2003; Nicholls et al., 2006). However, additional well-designed clinical trials are required to address the therapeutic role of ApoA-1 mimetics on CVD (Stoekenbroek et al., 2015). In addition, it remains a challenge whether increase of the ApoA-1 production or infusion can be performed effectively and safely.

The studies of regulation of ApoA-1 showed that PPAR α was able to regulate ApoA-1 transcription. Activators of PPAR α (e.g., fibrates) increased HDL-C levels by promoting ApoA-1 transcription in preclinical studies (Singh et al., 2005; Fruchart, 2013). However, treatment with a PPAR α agonist LY518674 did not remarkably alter HDL-C levels in humans (Nissen et al., 2007). The mechanisms of the regulation of ApoA-1 expression remain to be further studied.

b. High-density Lipoprotein. In 1929, HDL was firstly discovered as a protein-rich, lipid-poor complex, which was isolated from equine serum (Kingwell et al., 2014). Later in the 1950s, HDL was also extracted from human serum as a chemical entity by ultracentrifugation (Barr et al., 1951). Among lipoprotein particles, HDL are the smaller (7–12 nm in diameter) but denser (1.063–1.21 g/ml) particle due to the higher protein ratio (50% of the content is protein) (Phillips, 2013). HDL is mainly produced by liver and intestine (Nofer et al., 2002). Nascent HDL (discoidal HDL) is formed through lipidation of ApoA-1. Discoidal HDL particles were shown to contain two ApoA-1 molecules and 140 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine molecules (Davidson and Thompson, 2007). During more ApoA-1 incorporation to the HDL particles, conformational changes increase the α -helix content by 40% (Koppaka et al., 1999). In human blood, the circulating HDL is predominantly presented in the form of HDL spheres. The spherical HDL particles are formed from free cholesterol-containing discoidal HDL particles by converting FC into CE, which can then be internalized into the core of the HDL particles (Ferretti et al., 2006; Kuai et al., 2016). In spherical HDL, ApoA-1 plays the major role in stabilizing HDL structure and shape (Hewing et al., 2014). Spherical HDL can further internalize cholesterol from cells (which is mediated by ABCG1 and SR-BI) to form more mature and larger spherical HDL (Kennedy et al., 2005). Mature HDL transports the lipids to liver via an SR-BI-mediated endocytosis to be further metabolized (Kingwell et al., 2014).

Today, it is verified that HDL plays an important role in the lipid [cholesterol and triglycerides (TG)] transport

and metabolism (Wang and Briggs, 2004). HDL particles induce the efflux of excessive lipids from cells, thus being involved in RCT from macrophages (Lund-Katz and Phillips, 2010). In addition to its role in the HDL-mediated macrophage cholesterol efflux, it also has anti-inflammatory, antiapoptotic, antioxidative, and vasodilatory properties, which are also protective in the cardiovascular system (Besler et al., 2012). Circulating HDL also delivers signaling lipids, vitamins, endogenous proteins, hormones, and miRNA to different organs (Kuai et al., 2016), indicating that HDL plays multiple roles in complicated intercellular communication (Vickers et al., 2011). Treatment with infusions of homologous HDL-VHDL significantly reduced the aortic surface area covered by lipid-rich lesions compared with controls (Stoekenbroek et al., 2015), and decreased the extent of preexisting lesions in a rabbit model (Badimon et al., 1990). However, recent clinical studies show that inhibitors of cholesteryl ester transfer protein (CETP) upregulated the HDL-C levels in subjects with normal or low HDL-C. Nevertheless, reduced risk of atherosclerotic diseases was not demonstrated (Schwartz et al., 2009, 2012).

Some reconstituted HDL (rHDL)-based medicines have been propelled to different stages of clinical trials (Krause and Remaley, 2013). Some rHDL products that have been evaluated in clinical trials include CSL-111, CSL-112, ETC-216, ETC-642, SRC-rHDL, and CER-001 (Kuai et al., 2016). The results of one clinical trial showed that there was no significant difference in the atheroma volume and coronary score between patients treated with rHDL CER-001 and those treated with placebo (Tardif et al., 2014). Some other studies suggest that against a background of statin treatment, there may be no clinical benefit of raising HDL-C (Schwartz et al., 2012; Niesor et al., 2015). On the contrary, preliminary clinical results at the 2013 PACE Snapshot session (ESC, Amsterdam) display that CER-001 increased RCT and might decrease the aortic atheroma volume (Goffinet et al., 2012). A clinical report also showed that most patients with elevated cardiovascular risk were treated with a statin and large meta-analyses suggest low HDL-C still represents a cardiovascular risk factor on a background of statin treatment (Baigent et al., 2005). Overall, further clinical studies are required to confirm the anti-atherosclerotic effect of rHDL.

c. Apolipoprotein E. ApoE is a soluble 34-kDa glycoprotein, coded by three alleles (Mahley, 1988). ApoE is essential for the lipid metabolism (production, conversion, and clearance of lipoproteins) in all tissues and organs (Liehn et al., 2018) and is recognized for its ability to suppress atherosclerosis (Raffai, 2012). Although ApoE is synthesized mainly by liver (Kraft et al., 1989), many other cells or tissues are also able to synthesize ApoE, such as macrophages, adipocytes, smooth muscle cells, brain, and kidney (Driscoll and Getz, 1984; Zechner et al., 1991). The expression of

ApoE in the macrophages has been believed to prevent atherosclerosis by inducing cholesterol efflux from foam cells (Fazio et al., 1997; Curtiss and Boisvert, 2000).

ApoE has been shown to mediate uptake of chylomicrons, very LDL (VLDL) remnants, and ApoE-containing HDL (Liehn et al., 2018), as well as to regulate myelopoiesis (Murphy et al., 2011). ApoE is also known to regulate cellular signaling through the interaction with its receptors and heparin sulfate proteoglycans and to influence several biologic effects, including macrophage plasticity, smooth muscle cell proliferation and endothelial cell activation (Curtiss and Boisvert, 2000). ApoE suppresses NF- κ B-driven inflammation and atherosclerosis by influencing the levels of miRNA-146a in monocytes and macrophages in hyperlipidemic mice (Li et al., 2015a). ApoE inhibited the VSMC proliferation and aortic stiffening by regulating p27 through reducing the levels of miRNA221/222 and increasing the levels of miRNA-145, respectively (Kothapalli et al., 2013). In addition, ApoE stimulated the eNOS activation and exhibited anti-inflammatory property, thus preventing neointima formation by binding to ApoE receptor 2 (ApoER2) (Ulrich et al., 2014). Additionally, there is a tight link between ApoE and neurodegenerative diseases. It was reported that the ApoE4 polymorphism is one main risk factor for the development of Alzheimer disease (AD) (Giau et al., 2015). In animal studies, ApoE^{-/-} mice developed atherosclerotic lesions spontaneously, similar to those observed in humans, and these lesions were exacerbated when mice were fed with a HFD. Therefore, the ApoE^{-/-} mice became one of the main animal models of atherosclerotic plaque initiation and growth in cardiovascular research (Daugherty, 2002). ApoE prevents the formation of foam cells through mediating cholesterol efflux via ABCA1/ABCG1 pathway (Yvan-Charvet et al., 2010b).

ApoE is mediated at both the transcriptional and posttranscriptional levels. A recent review (Kockx et al., 2018) summarized the insights regarding the regulation of ApoE production and secretion by monocytes/macrophages, adipocytes, hepatocytes, and the central nervous system. The regulation of ApoE expression is remarkably cell, differentiation, and tissue specific. At the transcriptional level, cholesterol loading in macrophages increased transcription and secretion of ApoE and thus promoted macrophage cholesterol efflux in vitro (Kockx et al., 2012). ApoE can also be regulated by LXR at the transcriptional level (Kockx et al., 2018). At the posttranscriptional regulation, synthesized ApoE in the ER is moved via the Golgi and trans-Golgi network, during which ApoE is further glycosylated and sialylated (Kockx et al., 2018). Accumulation of excessive FC in the ER prevented the movement of ApoE from the ER to Golgi (Kockx et al., 2012). In macrophages, large ratio of ApoE is degraded after leaving the Golgi. Stimulation by ApoA-1 or HDL can prevent ApoE degradation and increases its secretion (Dory,

1991; Kockx et al., 2004). Adipocytes are induced to express and secrete substantial amounts of ApoE during differentiation (Zechner et al., 1991). PKA and dynamin was reported to mediate ApoE secretion in HepG2 cells (Kockx et al., 2009). The LXR-ABCA1 pathway is a common ApoE-activating pathway in astrocytes (Kockx et al., 2018). ApoE secretion by neurons in the central nervous system depends on calcium and microtubule (Dekroon and Armati, 2002). The mechanisms regulating the ApoE expression and secretion in different cell types and tissues have not been extensively studied yet.

III. Models for Studying Foam Cell Formation

Foam cell formation is a hallmark of atherosclerosis. Thus, numerous studies have used a variety of models to study the process of foam cell formation and to screen promising bioactive compounds targeting foam cell formation. In this section, we will discuss the models widely used for in vitro, ex vivo, and in vivo studies on both cholesterol uptake and efflux.

A. Cellular Models

So far, prevention of foam cell formation has mostly been focused on monocytes and macrophages. It was also demonstrated that different cell types present in the artery wall, such as endothelial cells, VSMCs (Maguire et al., 2019), as well as stem cells can exhibit foam cell-like characters and behavior in the growing neointima of atherosclerosis in both human beings (Daub et al., 2006) and mice (Feng et al., 2012). Thus, the cellular models for study on inhibition of foam cell formation include monocytes, macrophages (Hayden et al., 2002), endothelial cells (Constantinescu et al., 2000), VSMCs (Zhang et al., 2016b), and stem/progenitor cells (Zhang et al., 2018). At present, mouse macrophage cell types used for study on inhibition of foam cell formation include J774A.1, RAW264.7 (Li et al., 2013), P388D1 macrophages (Koren et al., 1990), primary MPMs (Sengupta et al., 2013), and bone marrow-derived macrophages (BMDMs). One study has suggested that different types of mouse macrophages might not have significant difference on the cholesterol efflux assays because RAW264.7 and J774A.1 macrophages have highly correlated assay values (Li et al., 2013). Human macrophage cell types used in foam cell formation studies include phorbol 12-myristate 13-acetate (PMA)-stimulated THP-1-derived macrophages, HL-60 cell-derived macrophages and primary human monocyte-derived macrophages (HMDMs) (Kosaka et al., 2001).

1. *Models for Studying Cholesterol Uptake.* Lipid uptake can be assessed by neutral lipid-targeting lysochrome Oil red O staining, Nile red staining, 1,1'-dioctadecyl-3,3,3',3'-tetra-methylindocyanide perchlorate (DiI)-labeled oxLDL (DiI-oxLDL), DiI-LDL, and DiI-acLDL (Xu et al., 2010), NBD-cholesterol, as

well as radiolabeled LDL or derived LDL (e.g., ^{125}I -LDL, ^{131}I -LDL) (Suits et al., 1989).

For Oil red O staining, macrophages are incubated with oxLDL with or without ACAT1 inhibitor in the presence or absence of tested natural products. The cells are then fixed with 4% formaldehyde and stained with Oil red O solution to identify lipid droplets containing CE to assess the amount of lipid inside the cell (lipid uptake) (Kosaka et al., 2001). Lipid accumulation in cells can be assessed by a microscope and separated into different grades according to the intracellular lipid droplet-occupied area. The percentage of foam cells is calculated by counting the total cell and foam cell numbers (Kosaka et al., 2001; Das et al., 2013). Oil red O-stained lipid droplets can also be assessed spectrophotometrically at 518 nm after lysis of the cells (Guo et al., 2006). Nile red, 9-diethylamino-5H-benzo[α]phenoxazine-5-one, is also an important staining method for the determination of intracellular lipid droplets by using fluorescent microscopy and flow cytometry (Greenspan et al., 1985). The increase in fluorescence intensity can be quantitatively determined by the interactive laser cytometer (Koren et al., 1990). Its staining process and application are almost the same with Oil red O for staining lipids. In addition, fluorescent NBD-cholesterol [22-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-23,24-bisnor-5-cholen-3 β -Ol] is also used to assess cholesterol uptake (Frolov et al., 2000; Sengupta et al., 2013). Cells are incubated with NBD-cholesterol and then lysed by adding methanol. Supernatant of cells lysate is used to measure fluorescence intensity by using fluorescence plate reader at emission spectra of 535 nm upon excitation at 475 nm (Frolov et al., 2000; Sengupta et al., 2013).

Staining with Oil Red O requires fixation of cells and staining in the presence of organic solvents (e.g., isopropanol) and is, therefore, limited to the analysis of dead cells (Majka et al., 2014). Water soluble Nile red can be used to stain both live and dead cells. However, its emission maximum at 528 nm may overlap with green (FITC, GFP) and yellow-orange fluorophores in flow cytometry (Majka et al., 2014). In recent years, a big progress has been made to develop new LD-specific probes [e.g., LipidTOX stains (Majka et al., 2014)], which are discussed in a recent review (Fam et al., 2018).

For cellular uptake of DiI-oxLDL, DiI-LDL, or DiI-acLDL, cells are incubated with them and then lysed (Teupser et al., 1996; Xu et al., 2010). Fluorescent intensity of the cell lysates is detected by using a microtiter plate reader with excitation-emission set at 520 and 580 nm, respectively (Teupser et al., 1996). DiI-oxLDL, DiI-LDL, or DiI-acLDL uptake in macrophages can also be evaluated by confocal microscopy and flow cytometry as described previously (Xu et al., 2010). For cellular uptake of radiolabeled LDL or derived LDL, cells are incubated with modified lipoproteins and then

lysed in NaOH (Selmer et al., 1997). Internalized LDL is determined by measuring the NaOH solution in the gamma-counter (Selmer et al., 1997). In addition, foam cell formation can be indirectly evaluated by measuring the total cholesterol (TC) via using cholesterol/CE quantification kit (Das et al., 2013).

2. *Models for Studying Cholesterol Efflux.* One cause for foam cell formation is the inability of cells to export cholesterol to a sufficient extent (Hansson, 2005; Hansson et al., 2006), which can be assessed by quantitating the rate of cholesterol efflux from the cells. Cholesterol efflux assay is usually used to assess the influence of natural products on plasma acceptor-induced cholesterol efflux from cells (Low et al., 2012). Dr. Rothblat's group (Rothblat et al., 1999) pioneered methodologies allowing the assessment of the capacity of human serum- or HDL-induced cholesterol efflux. In general, first of all, cells are loaded with labeled lipids to form foam cells and then incubated in serum-free medium to balance labeled cholesterol in cholesterol pools in cells (de la Llera-Moya et al., 2010; Khera et al., 2011), which can be combined with treatment or stimulation of tested natural products. Then the cells are incubated with acceptors to induce cholesterol efflux. The efflux of labeled lipids from the cells can be quantified (Low et al., 2012). In addition, some studies used ACAT inhibitor to prevent re-esterification of FC to CE (de la Llera-Moya et al., 2010; Khera et al., 2011) when loading lipids to cells or other steps (e.g., equilibration).

a. *Loading cells with labeled lipids to form foam cells.* The conversion of macrophages to foam cells by the accumulation of modified LDL is a critical step in atherosclerosis development. One of the widely used techniques to form the foam cell model is by incubation macrophages with radioactive ^3H -cholesterol-labeled modified LDL, especially acLDL or oxLDL (Asztalos et al., 2005; Singh et al., 2009). This method mimics the critical pathologic step (uptake of modified LDL by macrophages) in the atherosclerosis development. However, the methods of labeling acLDL with radioactive or fluorescent tags have some flaws (Sengupta et al., 2013). For example, LDL is inherently unstable and with limited shelf life, and is easy to be oxidized during the long-lasting isolation processes (Parthasarathy et al., 1999). Isolation and acetylation of LDL can also differ qualitatively between different preparations, which might offer inconsistent information regarding foam cell formation (Sengupta et al., 2013).

In recent time, a novel approach to load lipids to form foam cells has been adopted for high-throughput macrophage cholesterol efflux assay (Khera et al., 2011; Li et al., 2013). Radio-labeled cholesterol (^3H -cholesterol, and ^{14}C -cholesterol) to load macrophages was used to study cholesterol efflux in the presence of serum from human subjects (Khera et al., 2011; Li et al., 2013). For example, J774A.1 cells were plated and labeled with

2 μCi of ^3H -cholesterol per milliliter (Khera et al., 2011). In fact, the basic challenge to incorporate cholesterol in cells is its high hydrophobicity (Sengupta et al., 2013). A recent study reported a biologically relevant detergent compound, lysophosphatidylcholine, form mixed micelles with cholesterol or CE, incubation with which could efficiently generate macrophage foam cells (Sengupta et al., 2013). Further results indicated that such micelles were quite stable at 4°C and maintained the solubilized cholesterol at 4°C for at least 1 month (Sengupta et al., 2013), suggesting this technique could be less time-consuming and thus highly reproducible. It is worth noting that there are some studies using cholesterol-methyl- β -cyclodextrin, which significantly increases cholesterol solubility in water, to load cells with cholesterol to successfully form foam cells (Wang et al., 2018a,b,d). In this method, labeled cholesterol is added to serum-containing media. It is supposed that the labeled cholesterol is incorporated into lipoproteins in serum, which are further taken up by cells. So, it is necessary to allow sufficient time (24–48 hours) for uptake of lipoproteins (Low et al., 2012).

In recent years, fluorescently labeled cholesterol types (e.g., NBD-cholesterol, the fluorophore Pennsylvania green/*N*-alkyl-3 β -cholesterylamine-derived molecular probe [F-Ch], the dipyrromethene boron difluoride (BODIPY)-cholesterol) have become an important tool to study cholesterol metabolism including cholesterol efflux (Frolov et al., 2000; Sankaranarayanan et al., 2011; Zhang et al., 2011), because they closely mimic the properties of cholesterol regarding metabolism and intracellular trafficking (Atshaves et al., 2000). In fact, other studies indicated that NBD-cholesterol has a higher aqueous solubility compared with cholesterol, and might not really represent the uptake and efflux of cholesterol (Atshaves et al., 2000). However, a report showed that the influence of higher solubility of NBD-cholesterol on cholesterol uptake and efflux was ruled out by using ^3H -cholesterol, a common used cholesterol analog (Sengupta et al., 2013). On the contrary, it was reported that the functional property of fluorescent sterol analogs was not closely similar with that of cholesterol (Frolov et al., 2000). F-Ch is also a recently reported fluorescent mimic of cholesterol, which is structurally similar to other cholesterylamine conjugates (Zhang et al., 2011). It was demonstrated that cholesterol efflux of this fluorescent cholesterol mimic is similar compared with ^3H -cholesterol (Zhang et al., 2011). However, the extent of export quantified using F-Ch was somewhat smaller than that of ^3H -cholesterol, which may be due to the molecular weight of F-Ch, which is over twice that of cholesterol, and it accumulates in early endosomes that might affect its rate of export (Zhang et al., 2011). It was demonstrated that BODIPY-cholesterol efflux is significantly associated with ^3H -cholesterol efflux when apoB-depleted sera and pre β 1-HDL were used but not total HDL-C in

J774A.1 macrophages, suggesting that the efflux of BODIPY-cholesterol from cells was regulated primarily by ABCA1 (Sankaranarayanan et al., 2011). It is important to recognize that fluorescent cholesterol cannot completely mimic the behavior of cholesterol, thus one should choose suitable labeled cholesterol according to scientific aims.

b. Inducing cholesterol efflux to extracellular acceptors and quantification. After being loaded with lipids to form foam cells, cells are incubated in serum-free medium to balance labeled cholesterol in cholesterol pools and treated or stimulated by tested natural products. After stimulation of tested natural products, macrophages are exposed to cholesterol acceptors for several hours (2–8 hours), allowing resultant cholesterol efflux from the foam cells (Rothblat et al., 1999). In general, the time of incubation with acceptors should not be very long. Long incubation time (such as 24 hours) would reflect a state of equilibrium and therefore does not reflect the rate of cholesterol efflux (Low et al., 2012). Radioactive and fluorescent cholesterol are quantified by liquid scintillation counting (Khera et al., 2011) and fluorescence, respectively (Atshaves et al., 2000).

Numerous studies have showed that various cholesterol acceptors, ranging from cyclodextrins to serum, stimulate cholesterol efflux from macrophages (Rothblat et al., 1999). The common cholesterol acceptors include cyclodextrin ($\sim 200 \mu\text{g/ml}$), whole serum ($\sim 1\%$ to 2%), plasma ($\sim 1\%$ to 2%), apoB-depleted serum ($\sim 1\%$ to 2%), HDL ($\sim 20 \mu\text{g/ml}$), and ApoA1 ($\sim 10 \mu\text{g/ml}$) (Khera et al., 2011; Li et al., 2013; Wang et al., 2018a). ApoB-depleted serum, also called HDL fraction, can be obtained after removal of ApoB particles using polyethylene glycol (molecular weight 8000) (de la Llera-Moya et al., 2010). It was reported that this method yielded recovery of more than 97% of ApoA1-containing HDL particles and less than 2% of ApoB-containing LDL and VLDL particles (Khera et al., 2011).

For the quantification of exported radioactive cholesterol, the relative cholesterol efflux ratio can be calculated as the radiolabeling counts in the medium divided by total radiolabeling counts (medium and cells) in samples (Li et al., 2013). To validate the methods to measure cholesterol efflux, some additional studies are needed to be considered, such as relationship between cholesterol efflux capacity duplicates and stability of cholesterol efflux assay over time (Khera et al., 2011). Some studies used a pooled serum control to correct for plate to plate and day to day variations by normalizing the data to this pooled value in subsequent analyses (Khera et al., 2011; Li et al., 2013).

For NBD-cholesterol efflux measurement, confocal microscopy can be used to analyze HDL-mediated NBD-cholesterol efflux in living cells as previously described (Atshaves et al., 2000). Briefly, after loading, the cells were placed in serum-free medium with tested natural products and then HDL was added to mediate cholesterol

efflux. A medial section passing through cells was chosen, and the fluorescence intensity of NBD-cholesterol in the total area of each cell was assessed over time and used to calculate NBD-cholesterol efflux from the cells (Atshaves et al., 2000). Since only little (~8%) NBD-cholesterol was esterified at 24 hours (Frolov et al., 2000), the ACAT inhibitor was not applied in the fluorescence experiments. The cholesterol efflux assay has several limitations (Khera and Rader, 2013). The cell-based assays require numerous efforts to standardize and rarely enter clinical studies. In addition, this method evaluates only one step of the RCT pathway.

B. Animal Models for Studying Foam Cell Formation

The knowledge on development of atherosclerosis has been greatly deepened by studies in various animal models, including rodents, rabbits, pigs, and nonhuman primates (Tamminen et al., 1999). Mouse and rabbit models have been most broadly used (Emini Veseli et al., 2017). During the past decades, knowledge about the molecular mechanisms of development of atherogenesis has been largely improved by studies performed on transgenic and gene-targeted mice (Smithies and Maeda, 1995), including ApoE^{-/-}, LDLR^{-/-}, ApoE/LDLR double-knockout, ApoE*3-Leiden, pro-protein convertase subtilisin/kexin type 9 (PCSK9)-adeno associated virus, and ApoE^{-/-} fibrillin-1 mutant (ApoE^{-/-}Fbn1^{C1039G+/-}) mice (Emini Veseli et al., 2017; Maguire et al., 2019). These animal models of atherosclerosis were well detailed by several recent reviews (Getz and Reardon, 2012; Emini Veseli et al., 2017; Lee et al., 2017). It is worth noting that a reliable mouse model for lesion rupture has been developed, ApoE^{-/-}Fbn1^{C1039G+/-} mice (Emini Veseli et al., 2017). All these mouse models, as well as rabbit models, provide a good platform to evaluate the effect of natural products on foam cell formation in vivo and to search for promising drug candidates for treatment of atherosclerosis (Getz and Reardon, 2012; Hilgendorf and Swirski, 2012). However, it should be pointed out that studies in mice have limited suitability because of significant species differences between mice and humans (Lusis, 2000). In addition, these animal models require a genetic variation of the cholesterol processing capacity, which is coupled with extreme changes in diet (e.g., Western-type diet) (Meir and Leitersdorf, 2004; Getz and Reardon, 2012). Moreover, different monocyte biology between humans and mice renders the study on the questions regarding macrophage foam cells to be more difficult (Hilgendorf and Swirski, 2012; Angelovich et al., 2017).

Some studies established the in vivo assay of macrophage RCT, which traced movement of radiolabeled cholesterol or acLDL that originated from peripheral cholesterol-enriched macrophage cells into the blood stream and subsequent fecal elimination (Zhang et al., 2003b; Rothblat and Phillips, 2010; Weibel et al., 2011).

In this method, after treatment with tested natural products, recipient mice were injected with ³H-cholesterol-loaded J774A.1 macrophages intraperitoneally (Zhang et al., 2003b). Transport of ³H-cholesterol from the macrophages into blood, liver, and bile, as well as elimination in the feces, was measured at 48 hours after injection (Zhang et al., 2003b). In this model, overexpression of ApoA1 promoted macrophage RCT compared with control mice (Zhang et al., 2003b). Although this method is believed to be a sensitive approach to monitor cholesterol movement from macrophages in vivo, there are some critical questions (Weibel et al., 2011). For example, it is not possible to monitor cellular cholesterol homeostasis by this method (Weibel et al., 2011). One study developed a novel method employing hollow fibers to re-collect the macrophage-derived foam cells at the end of the in vivo RCT experiments, allowing quantitative analysis of the changes in cholesterol mass in foam cells for the first time (Weibel et al., 2011). Simply, cholesterol-enriched peritoneal macrophages were entrapped in semipermeable hollow fibers and implanted into the peritoneum of mice. Twenty-four hours after implantation, the fibers were removed from the peritoneum, which allowed for complete re-collection of these macrophages for quantification of changes of cellular cholesterol and protein (Weibel et al., 2011). Furthermore, it was demonstrated that the cholesterol content was increased when this experiment was performed in LDLR/apobec double knockout mice (Weibel et al., 2011). So far, this method has not yet been used to evaluate the effect of natural products on changes of cellular cholesterol.

The measurement of foam cell formation is of primary interest as a critical end-point analysis for assessing the influence of natural products on atherosclerosis development in vivo (Xu et al., 2010). Atherosclerotic lesions in in vivo studies are traditionally quantified by staining lesions en face in the whole aorta or aortic cross-section from the proximal aorta and the innominate artery with Oil red O or Sudan IV to identify lipid droplets containing CE (Kobayashi et al., 2004), followed by computer-assisted image analysis (Paigen et al., 1987; Teupser et al., 2003; Xu et al., 2010; Maganto-Garcia et al., 2012). For en face preparations of the aorta, the aortic tree is fixed and opened longitudinally, from the heart to the iliac arteries, while still linked to the heart and main branching arteries in the body, and “pinned out.” After fixation and rinse, the aortas are stained with Oil red O or Sudan IV and photographed for quantification of atherosclerotic lesions (Kobayashi et al., 2004). En face lesion area of the aorta is quantified relative to its surface area. The detailed protocol for this method is reviewed elsewhere (Maganto-Garcia et al., 2012). For cross-sectional analysis of the aorta, sections of the proximal aorta are obtained sequentially, starting at the aortic valve (Kobayashi et al., 2004). Sections are stained with Oil

red O and then counterstained with hematoxylin (Plump et al., 1992). Several sections are used to quantify lesion areas by using appropriate software (e.g., Image Pro Plus) (Kobayashi et al., 2004). It was noted that lesions in innominate artery are normally more advanced and larger than that in other areas (Bentzon et al., 2001; Reardon et al., 2001). For cross-sectional analysis of the innominate artery (also named brachiocephalic artery), the Y-shaped piece of innominate artery is sectioned distally (Teupser et al., 2003). Sections are stained with hematoxylin and eosin and used for quantification of lesion areas (Kobayashi et al., 2004). Atherosclerotic lesions in luminal and the internal elastic lamina are evaluated in equidistant Oil red O-stained sections (Teupser et al., 2003). The detailed protocol for this method is reviewed elsewhere (Maganto-Garcia et al., 2012).

IV. Natural Products Targeting Foam Cell Formation in Atherosclerosis

Natural products from plants, fungi, and marine sources (Dias et al., 2012) represent a rich source for the discovery of new drug leads, since only about 6% of the existing higher plants have been investigated pharmacologically (Cragg and Newman, 2013). In the past several decades, an increasing number of publications have reported that diverse natural products are able to modulate foam cell formation in atherosclerosis, including naturally occurring flavonoids, terpenoids, phenolic compounds, phenylpropanoids, alkaloids, steroids, fatty acids, amino acids, carbohydrates, and among others (Table 1). In this section, we review some important natural products targeting foam cell formation in atherosclerosis.

A. Flavonoids

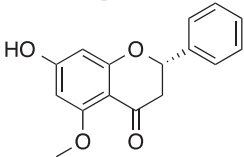
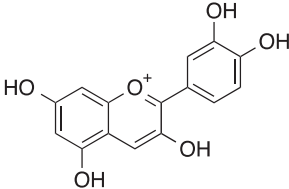
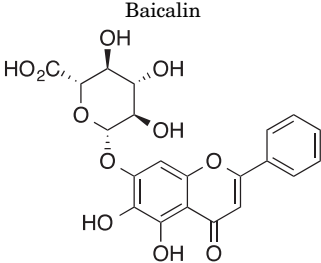
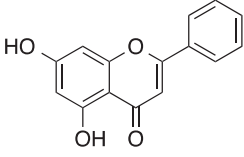
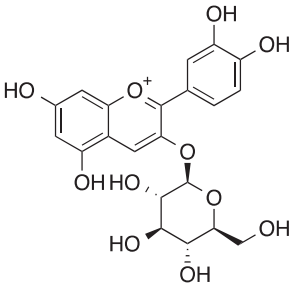
Flavonoids are a class of secondary metabolites from plant and fungus, possessing 15 carbon atoms and divided into 6 major subclasses, namely anthocyanidins, flavans, flavanones, flavononols, anthoxanthins, and isoflavonoids. Flavononols and anthoxanthins (particularly the group of flavones) are the two main classes and most widespread in the human diet. They have been shown to exhibit antiallergic (Yamamoto and Gaynor, 2001), anti-inflammatory (Yamamoto and Gaynor, 2001; Cazarolli et al., 2008), antioxidative (Cazarolli et al., 2008), antibacterial (Cushnie and Lamb, 2011), anticancer (de Sousa et al., 2007), and antiatherosclerotic activities through different mechanisms in vitro and in vivo. The biologic effects of flavonoids appear to be related to their ability to regulate diverse cell-signaling cascades. In this section, we review the studies focusing on natural products belonging to the class of flavonoids, which have displayed influence on macrophage foam cell formation.

1. Alpinetin. Alpinetin (also known as 7-hydroxy-5-methoxyflavanone) is the main bioactive component in the seeds of *Alpinia katsumadai* Hayata. Alpinetin is also present in *Amomum subulatum*, *Scutellaria rivularis*, and plants from the ginger family, such as turmeric and cardamom (He et al., 2005, 2006). Recent studies have shown that alpinetin exerted multiple pharmacological properties, such as antitumor, anti-inflammatory, and antioxidative activities, and inhibition of platelet aggregation (Ramírez-Tortosa et al., 1999; Tang et al., 2012). It was shown that alpinetin (50–150 $\mu\text{g/ml}$) promoted cholesterol efflux and elevated the expression of PPAR γ and LXR α in oxLDL-stimulated THP-1 macrophages and HMDMs. It also inhibited lipid accumulation by enhancing the expression of ABCA1 and ABCG1, suggesting that alpinetin may inhibit foam cell formation by targeting the PPAR γ /LXR α /ABCA1/ABCG1 pathway (Jiang et al., 2015). Furthermore, it is also reported that alpinetin (50–200 $\mu\text{g/ml}$) had an anti-inflammatory effect by inhibiting the TNF- α , IL-6, and IL-1 β expression in LPS-stimulated human macrophages (Hu et al., 2013a). While TNF- α reduced both ABCA1 and LXR α expression and suppressed the cholesterol efflux from monocytes (Voloshyna et al., 2014), it is possible that alpinetin may reverse the suppression of cholesterol efflux proteins ABCA1/ABCG1 and abolish the formation of foam cells by suppressing TNF- α expression.

2. Anthocyanin. Anthocyanins (ACs) are a class of water-soluble natural pigments widely present in dark-colored fruits and foods, such as purple sweet potato, grape, blueberry, black rice, and black soybean. In general, ACs comprise six important types of pigments, including geranium, cyanidin, delphinidin, peony, morning glory, and mallow pigment. Both ACs and anthocyanidins (the sugar-free counterparts of ACs), have shown various biologic activities. For example, ACs regulate blood lipids by decreasing the levels of TG, TC, and LDL-cholesterol (LDL-C), suggesting that ACs may have positive effects on CVD (Wallace et al., 2016). Anthocyanin mixture also inhibited the inflammatory response in hypercholesterolemic patients by decreasing the levels of serum high sensitivity C-reactive protein (hs-CRP) (Zhu et al., 2013).

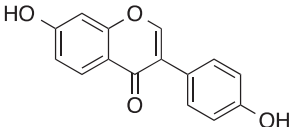
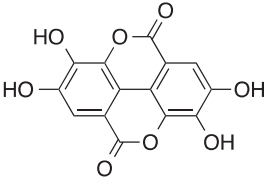
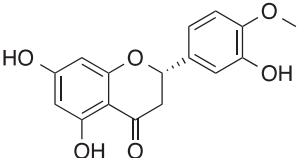
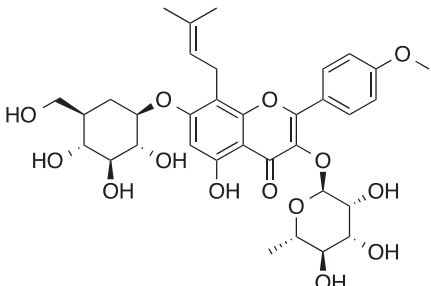
Two bioactive ACs, cyanidin-3-glucoside (10 μM) and peonidin-3-glucoside (100 μM), significantly increased the macrophage cholesterol efflux in MPMs through the PPAR γ -LXR α -ABCA1 pathway (Xia et al., 2005). Moreover, in THP-1-derived macrophages, AC-rich fraction extracted from the wild blueberry (*Vaccinium angustifolium*) powder reduced lipid accumulation (Del Bo' et al., 2016). Another similar observation was recorded in human kidney 2 cells, cyanidin-3-O- β -glucoside chloride, or cyanidin chloride (50 μM) inhibited the high-glucose-induced cholesterol accumulation and inflammation by activating LXR α pathway, and activated the PPAR α -LXR α -ABCA1-dependent cholesterol efflux (Du et al., 2015).

TABLE 1
Natural products targeting foam cell formation in atherosclerosis

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
Flavonoids	<p>Alpinetin</p>  <p>Cyanidin (Anthocyanins)</p> 	<p>Increased the macrophage cholesterol efflux by regulating the PPARγ/LXRα/ABCA1/ABCG1 pathway (Jiang et al., 2015).</p> <p>Cyanidin increased the macrophage cholesterol efflux from mouse peritoneal macrophages (MPMs) through PPARγ-LXRα-ABCA1 pathway (Xia et al., 2005), and activated PPARα-LXRα-ABCA1-dependent cholesterol efflux in human kidney 2 (HK-2) cells (Du et al., 2015).</p>	<p>N.A.</p> <p>The anthocyanin-rich diet reduced the levels of total cholesterol (TC) and low-density lipoprotein (LDL)-cholesterol, while upregulating high-density lipoprotein (HDL)-C in serum, and reduced atherosclerotic plaque formation in rats and ApoE^{-/-} mice (Xia et al., 2006). Anthocyanin mixture reduced the inflammatory response in hypercholesterolemic patients by decreasing the levels of serum high sensitivity C-reactive protein (hs-CRP) (Zhu et al., 2013).</p>
	<p>Baicalin</p> 	<p>Promoted the cholesterol efflux through the PPARγ-LXRα-ABCA1/ABCG1/SR-BI pathway in THP-1 macrophages (He et al., 2016b; Yu et al., 2016).</p>	<p>Decreased atherosclerotic lesion sizes and lipid accumulation in the carotid arteries of atherosclerosis in vivo (He et al., 2016b). Baicalin reduced TC, TG, LDL-C, and hs-CRP in patients with rheumatoid arthritis that have an increased risk of coronary artery disease (Hang et al., 2018).</p>
	<p>Chrysin</p> 	<p>Increased the HDL-mediated macrophage cholesterol efflux by the upregulation of PPARγ, LXRα, ABCA1, and ABCG1 expression (Wang et al., 2015b), and prevented the cholesterol uptake by downregulating the expression of SR-A1 and SR-A2 (Wang et al., 2015b).</p>	<p>Decreased the mean levels of serum TC, triacylglycerol (TG), LDL-C, and very low-density lipoprotein (VLDL)-C significantly in a model of Wistar rats fed with a high-fat diet (HFD) (Anandhi et al., 2014).</p>
	<p>Cyanidin-3-O-β-glucoside</p> 	<p>Upregulated the expression of ABCG1 and ABCA1 in a dose-dependent manner and promoted the cholesterol efflux (Wang et al., 2012c).</p>	<p>Decreased body weight, visceral adiposity, TG, TC, free fatty acids, and atherosclerosis index in a high-fat-induced atherosclerosis rat model (Um et al., 2013). Decreased monocyte infiltration and atherosclerosis in ApoE^{-/-} mice (Wang et al., 2011). A double-blind, randomized, placebo-controlled trial showed that</p>

(continued)

TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
			anthocyanin consumption increased HDL-C, decreased LDL-C, and promoted cellular cholesterol efflux in hyperlipidemia patients. Cyanidin 3- <i>O</i> - β -glucosides revealed to inhibit CETP (Qin et al., 2009).
	<p>Daidzein</p> 	Induced paraoxonase-1 (PON-1) activity, which may regulate cholesterol efflux by stimulating the PPAR γ /LXR α /ABCA1 pathway (Gao et al., 2008; Robb and Stuart, 2014).	Decreased the serum cholesterol, increased triglyceride (TG) level in the male middle-aged rats with HFD (Sosić-Jurjević et al., 2007), reduced plasma VLDL, LDL-C, and TG concentrations, while increased the HDL-C levels in a rheumatoid arthritis rat model (Ahmad et al., 2016). Daidzein was reported to be an inhibitor of HMG-CoA reductase, ACAT1, and ACAT2 (Borradaile et al., 2002; Sung et al., 2004).
	<p>Ellagic acid</p> 	Stimulated cholesterol efflux by promoting the expression of ABCA1 and SR-BI and up-regulating PPAR γ and LXR α (Park et al., 2011), inhibited macrophage lipid accumulation by decreasing the expression of CD36 (Aviram et al., 2008).	Decreased the level of TC and TG and upregulated the expression of LXR α , PPAR α , PPAR γ , and their downstream gene ABCA1 in the high-fat-fed hamster model (Aviram et al., 2008). Reduced atherosclerotic lesions in ApoE $^{-/-}$ mice (Aviram et al., 2008).
	<p>Hesperetin</p> 	Increased activities of ABCA1 promoter and LXR enhancer, the expression of ABCA1, and consequently upregulated the ApoA-1-mediated cholesterol efflux (Iio et al., 2012).	Reduced foam cell formation in plaques by enhancing the expression of ABCA1 (Iio et al., 2012). Reduced plasma TC level, endothelial dysfunction, macrophage infiltration, and atherosclerotic lesion in ApoE $^{-/-}$ mice (Sugasawa et al., 2019).
	<p>Icariin</p> 	Inhibited cholesterol intake and foam cell formation by the reduced expression of CD36 and upregulated SR-BI expression through p38 MAPK pathway (Yang et al., 2015).	Decreased the concentrations of TC, TG, and LDL-C in models of normal rats (Hu et al., 2016b) and ApoE $^{-/-}$ mice with HFD (Xiao et al., 2017).

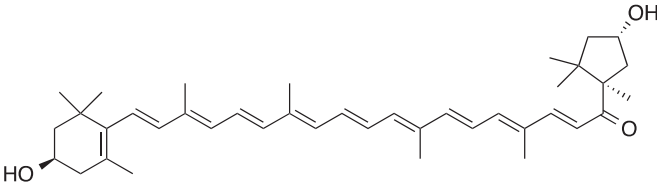
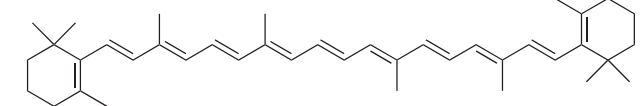
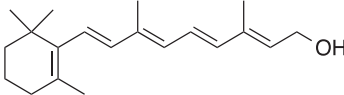
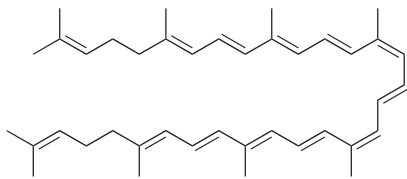
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	Iristectorigenin B	Acted as a novel LXR modulator that increases ABCA1 and ABCG1 expression in RAW 264.7 macrophage (Jun et al., 2012).	N.A.
	Pratensein	Upregulated the CLA-1 expression, a human homolog of SR-BI, may play a potential role in cholesterol efflux to HDL in vitro (Yang et al., 2007, 2009).	One clinical trial showed that red clover isoflavones significantly reduced the incidence of arteriosclerosis (Gordon, 2003).
	Puerarin	Promoted ABCA1-mediated cholesterol efflux through the pathways involving miRNA-7, STK11, and the AMPK/PPAR γ /LXR α /ABCA1 cascade (Li et al., 2017a) suppressed lipid deposition by downregulating the expression of CD36 (Zhang et al., 2015).	Decreased the level of blood sugar, TC, TG, LDL-C, and increased HDL-C level in diabetic animal model (Smith et al., 2006).
	Quercetin	Enhanced ApoA1-mediated cholesterol efflux, induced ABCA1 expression, and increased the expression of PPAR γ in THP-1-derived foam cells (Sun et al., 2015) and LXR α activity (Lee et al., 2013).	Quercetin inhibits atherosclerosis by promoting ABCA1- and ABCG1-dependent reverse cholesterol transport in ApoE $^{-/-}$ mice (Cui et al., 2017).
	Isosilybin A (Silymarin)	Isosilybin A promoted cholesterol efflux from THP-1 macrophages by activating PPAR γ (Wang et al., 2015a).	Supplementation of silybin in food decreased serum level of TC, TG, VLDL-C, LDL-C and increased HDL-C in model of hypercholesterolemic rats (Wang et al., 2005). Furthermore, silybin reduced the formation of atherosclerotic plaque (Gobalakrishnan et al., 2016).
	Wogonin	Enhanced cholesterol efflux through increasing the ABCA1 protein expression (Chen et al., 2011) and decreasing phosphorylated level of ABCA1 protein. Downregulated the expression of SR-A and CD36, which is relevant to uptake of cholesterol in THP-1 macrophages (Yoshida et al., 2010). Promoted ABCA1/G1 expression, resulting in increased ApoA-1/	Wogonin ameliorated hyperglycemia and dyslipidemia in db/db mice via PPAR α activation (Bak et al., 2014).
Terpenoids	Astaxanthin	A randomized, placebo-controlled clinical study in humans with mild hyperlipidemia displayed that astaxanthin administration significantly increased HDL-C (Yoshida et al., 2010). Astaxanthin also	

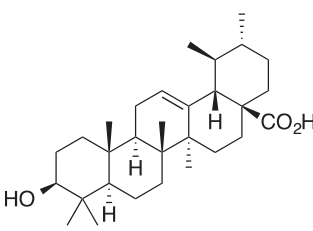
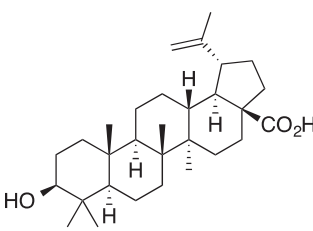
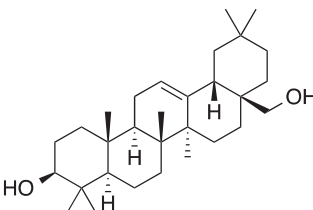
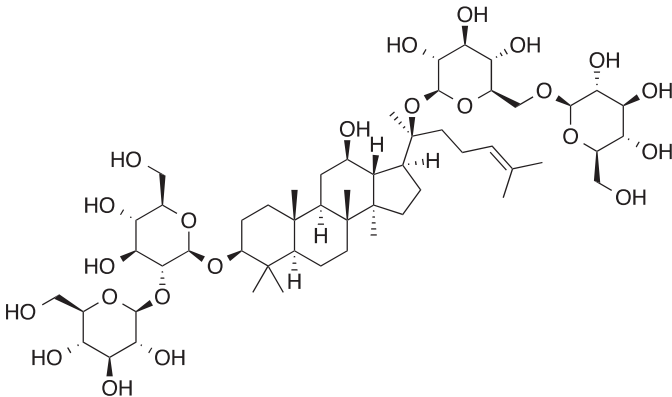
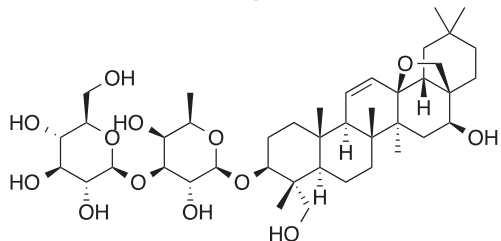
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	Capsanthin	HDL-mediated cholesterol efflux from RAW264.7 cells via an LXR-independent manner (Ramírez-Tortosa et al., 1999; Iizuka et al., 2012).	decreases macrophage infiltration, and plaque vulnerability in hyperlipidemic rabbits (Li et al., 2004c).
		N.A.	An in vivo study showed that male Wistar rats fed with capsanthin exhibited an increase in plasma HDL-C, an upregulation of ApoA-5 and LCAT mRNA expression (Aizawa and Inakuma, 2009).
	β -Carotene (β -carotene isomers all- <i>trans</i> - β -carotene (all- <i>trans</i> - β c), and 9- <i>cis</i> - β -carotene (9- <i>cis</i> - β c))	Suppressed cellular cholesterol synthesis by inhibiting cellular HMG-CoA reductase activity in J774 macrophages (Fuhrman et al., 1997; Relevy et al., 2015).	β -Carotene comprises several isomers (all- <i>trans</i> - β c and 9- <i>cis</i> - β c), which increased plasma HDL-C and attenuated atherosclerosis in LDLR ^{-/-} mice (Harari et al., 2008), ApoE ^{-/-} mice (Harari et al., 2013), and even in fibrate-treated patients (Shaish et al., 2006), which is related with transcriptional induction of ABCA1, ABCG1, and ApoE (Bechor et al., 2016).
		9- <i>cis</i> -RA and ATRA acted as inducers of ABCA1, ABCG1, and ApoE expression in J774 macrophages and THP-1 macrophages (Kiss et al., 2005) and RAW264.7 macrophages (Schwartz et al., 2000), as well as inducers of cholesterol efflux to ApoA-1 in RAW264.7 macrophages (Langmann et al., 2005).	9- <i>cis</i> -RA inhibited foam cell formation and atherosclerosis by activation of LXR α and upregulation of ABCA1 and ABCG1 expression in ApoE ^{-/-} mice fed with HFD (Zhou et al., 2015).
	9- <i>cis</i> retinoic acid (9- <i>cis</i> -RA, Retinoids)		
			
	Lycopene	Decreased cholesterol accumulation through downregulation of SR-A mRNA expression and lipid synthesis in human monocyte-derived macrophages (HMDMs) and THP-1 macrophages (Napolitano et al., 2007). Increased cholesterol efflux possibly through HMG-CoA reductase/RhoA/PPAR γ /LXR α /ABCA1 and caveolin 1 pathway (Palozza et al., 2011).	Clinical investigation reported that dietary supplementation of lycopene reduced plasma LDL-C level (Fuhrman et al., 1997; Sesso et al., 2005; Palozza et al., 2012). Lycopene displays potent hypolipidemic effects via inhibiting PCSK9 and HMG-CoA reductase, thus increasing hepatic LDLR (Sultan Alvi et al., 2017).
			

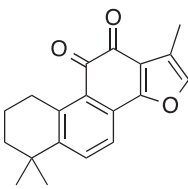
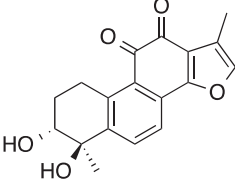
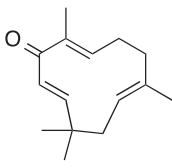
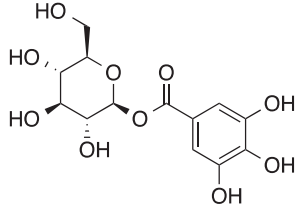
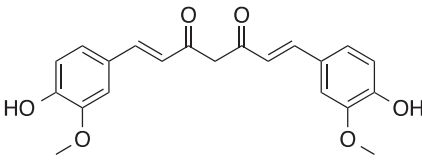
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	<p>Ursolic acid</p> 	Promoted ApoA-1-mediated cholesterol efflux from LDL-loaded macrophages through autophagy (Leng et al., 2016).	Reduced atherosclerotic lesion size, along with an increase of macrophage autophagy in LDLR ^{-/-} mice (Leng et al., 2016). Ursolic acid is a pharmacological inhibitor of ACAT1 and ACAT2 (Lee et al., 2006).
	<p>Betulinic acid</p> 	Induced cholesterol efflux through blocking NF-κB/miRNA-33s/ABCA1 signaling pathway in LPS-treated macrophages (Zhao et al., 2013a) and increased ABCA1/ABCG1-mediated cholesterol efflux in both RAW264.7 and THP-1 cells (Zhao et al., 2013a).	Increased ABCA1 expression and enhanced fecal cholesterol excretion, along with suppressed macrophage positive areas in the aorta of ApoE ^{-/-} mice (Gui et al., 2016). Betulinic acid is a potent pharmacological inhibitor of ACAT1 and ACAT2 (Lee et al., 2006).
	<p>Erythrodiol</p> 	Increased ApoA-1-mediated cholesterol efflux by inhibiting ABCA1 degradation in THP-1 macrophages (Wang et al., 2017f).	N.A.
	<p>Ginsenoside Rb1 (Ginsenosides)</p> 	Ginsenoside Rb1 increased ABCA1 protein expression in macrophage foam cells (Liu et al., 2016c; Qiao et al., 2017). Ginsenoside Rd inhibited SR-A protein expression and oxLDL uptake, thus decreasing intracellular cholesterol content (Li et al., 2011).	Ginsenoside Rb1 treatment reduced lipid metabolism and enhanced atherosclerotic plaque stability via enhancing macrophage autophagy and polarization (Liu et al., 2016c; Qiao et al., 2017). Ginsenoside Rd treatment reduced the oxLDL uptake and atherosclerotic plaque areas in ApoE ^{-/-} mice (Li et al., 2011).
	<p>Saikosaponin A</p> 	Suppressed lipoprotein uptake by diminishing LOX-1 and CD36 expression, as well as stimulated cholesterol efflux through upregulating of ABCA1 and PPAR γ expression (He et al., 2016a).	N.A.

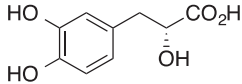
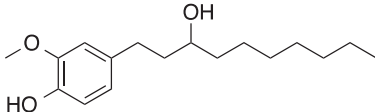
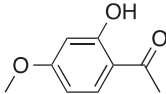
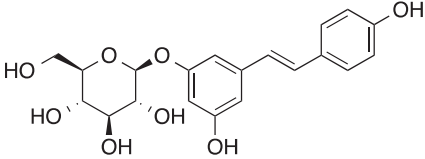
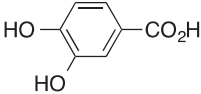
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
Phenols	<p>Tanshinone IIA</p> 	Decreased oxLDL uptake, as well as CD36 expression in mouse macrophages (Tang et al., 2011), increased ABCA1/G1-mediated cholesterol efflux via the ERK/Nrf2/HO-1 loop in THP-1-derived foam cells (Liu et al., 2014c).	Downregulated SR-A expression and ameliorated atherosclerotic lesions in aortas of ApoE ^{-/-} mice (Liu et al., 2014c). Tanshinone IIA promoted ABCA1-dependent cholesterol efflux (Liu et al., 2014c) and upregulated LDLR in hyperlipidemic rats (Jia et al., 2016). A clinical trial has shown that tanshinone IIA reduced hs-CRP in patients with coronary artery disease (Li et al., 2017b).
	<p>Tanshindiol C</p> 	Inhibited oxLDL-induced foam cell formation via activation of Prdx1/ABCA1 signaling pathway (Yang et al., 2018b).	N.A.
	<p>Zerumbone</p> 	Suppressed the SR-A and CD36 expression via regulating AP-1 and NK-κB repression, leading to a blockade of acLDL uptake in THP-1 macrophages (Eguchi et al., 2007). Reduced cholesterol level via upregulation of ABCA1, coupled with the enhanced phosphorylation of ERK1/2 in THP-1 macrophages (Zhu and Liu, 2015).	Prevented the development of atherosclerotic lesions in the cholesterol-fed rabbit model by reducing lipid level and oxidative stress (Hemn et al., 2013, 2015).
	<p>Gallotannin</p> 	Induced cholesterol efflux in oxLDL-stimulated macrophages by increasing SR-BI/ABCA1 expression (Zhao et al., 2015).	N.A.
	<p>Curcumin</p> 	Ameliorated lipid accumulation in macrophages by both decreasing SR-A-dependent oxLDL uptake via ubiquitin/proteasome pathway-reduced SR-A expression, and increasing ABCA1-dependent cholesterol efflux via LXRα-induced ABCA1 protein expression (Kou et al., 2013; Min et al., 2013; Lin et al.,	Protected against atherosclerosis in ApoE ^{-/-} mice (Zhao et al., 2012), and LDLR ^{-/-} mice (Hasan et al., 2014). Curcumin lowers LDL-C, and TG in patients at risk for CVD (Qin et al., 2017). Curcumin functions as an inhibitor of PCSK9 and upregulates hepatic LDLR expression (Tai et al., 2014).

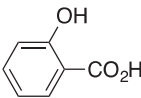
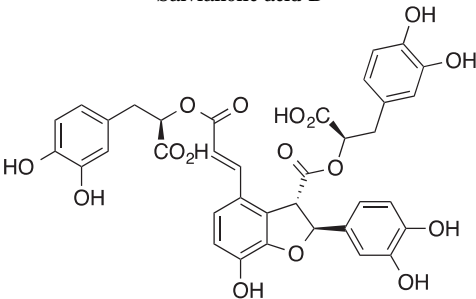
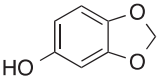
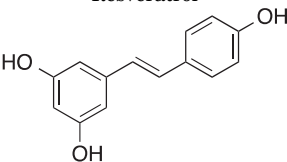
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	<p>Danshensu</p> 	<p>2015c; Soltani et al., 2017). Activation of AMPK/SIRT1/LXRα pathway (Lin et al., 2015c) and Nrf2/HO-1 pathway (Kou et al., 2013), and as well as inhibition of p38 MAPK pathway (Min et al., 2013) may be involved in its effects. Prevented cholesterol accumulation in mouse macrophages by inhibiting CD36-mediated lipid uptake, while enhancing ABCA1/G1-mediated cholesterol efflux (Wang et al., 2010b; Gao et al., 2016).</p>	<p>Attenuated high methionine-rich diet-induced accumulation of foam cells in rat aortic endothelium by attenuating TNF-α and ICAM1 expression (Yang et al., 2010). Danshensu improved dyslipidemia by decreasing LDL-C and fatty acid by inhibiting HMG-CoA reductase and fatty acid synthase expression (Yang et al., 2011).</p>
	<p>6-Dihydroparadol</p> 	<p>Promoted cholesterol efflux from THP-1 macrophages by increasing the expression of ABCA1 and ABCG1 via preventing the proteasome-dependent protein degradation (Wang et al., 2018a).</p>	<p>N.A.</p>
	<p>Paeonol</p> 	<p>Promoted cholesterol efflux via activating LXRα/ABCA1 pathway in macrophages (Zhao et al., 2013b; Li et al., 2015c), inhibited cholesterol uptake through CD36 inhibition (Li et al., 2015c).</p>	<p>Reduced atherosclerotic lesion formation and attenuated systemic inflammation as well as increased ABCA1 expression in ApoE$^{-/-}$ mice (Zhao et al., 2013b). Paeonol reduced the levels of malondialdehyde and oxidized LDL in hyperlipidemia rats (Dai et al., 2000).</p>
	<p>Polydatin</p> 	<p>Activation of PPARγ-dependent ABCA1 upregulation and decrease of CD36 expression (Wu et al., 2015b).</p>	<p>Reduced TC, FC, CE, together with reduction of secretion of TNF-α and IL-1β in oxLDL-stimulated ApoE$^{-/-}$ mouse macrophages (Wu et al., 2015b). Polydatin improved dyslipidemia via suppressing PCSK9 and upregulation of hepatic LDLR expression (Li et al., 2018a).</p>
	<p>Protocatechuic acid</p> 	<p>Promoted cholesterol efflux from macrophages by increasing ABCA1 and ABCG1 expression via reduction of miRNA-10b expression (Wang et al., 2012a).</p>	<p>Reduced the development of atherosclerosis in ApoE$^{-/-}$ mice (Wang et al., 2010a, 2011; Stumpf et al., 2013). Protocatechuic acid could possibly regulate lipid metabolism via</p>

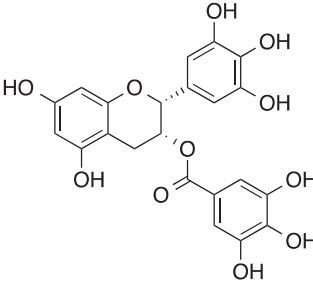
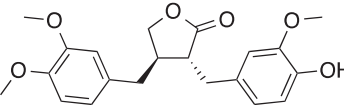
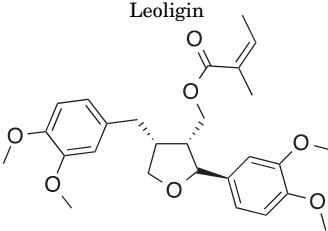
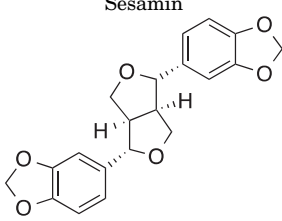
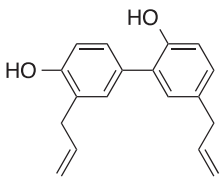
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	<p>Salicylic acid</p>  <p>Salvianolic acid B</p>  <p>Sesamol</p>  <p>Resveratrol</p> 	<p>Upregulated the expression of ABCA1 and SR-BI by AMPK activation or PPARα pathway, thereby stimulating cholesterol efflux from macrophages (Viñals et al., 2005; Lu et al., 2010). Acted as an effective CD36 antagonist that blocks oxLDL uptake in mouse macrophages (Wang et al., 2010b) and THP-1 macrophages (Bao et al., 2012), promoted cholesterol efflux via a PPARγ/LXRα/ABCA1-dependent pathway in THP-1 macrophages (Bao et al., 2012).</p> <p>Decreased the expression of CD36, CD68, SR-A, and LOX-1 (Narasimhulu et al., 2018), and increased the expression/activity of PPARγ and LXRα in macrophages via a MAPK-dependent mechanism (Wu et al., 2015d).</p> <p>Reduced oxLDL uptake (Voloshyna et al., 2013), promoted ApoA-1- and HDL-mediated cholesterol efflux in both mouse and human macrophages by increasing the expression of ABCA1 and ABCG1 via PPARγ/LXRα (Berrougui et al., 2009; Allen and Graham, 2012) and adenosine 2A receptor pathway (Voloshyna et al., 2013).</p>	<p>suppressing the expression of HMG-CoA reductase (Liu et al., 2010b). Aspirin attenuated atherosclerosis in ApoE$^{-/-}$ mice by suppressing systemic inflammation and promoting inflammation resolution (Petri et al., 2017).</p> <p>Exhibited antiatherosclerotic effects in neointimal hyperplasia in rabbits (Yang et al., 2011) and in ApoE$^{-/-}$ mice (Chen et al., 2006; Lin et al., 2007). Salvianolic acid B ameliorated hyperlipidemia via AMPK activation (Cho et al., 2008) and inhibition of LDL oxidation (Yang et al., 2011).</p> <p>Sesamol derivative (INV-403) and sesame oil prevent or regress atherosclerosis in LDLR$^{-/-}$ mice (Narasimhulu et al., 2018) and hyperlipidemic rabbits fed with an atherogenic diet by suppressing NF-κB dependent vascular inflammation (Ying et al., 2011).</p> <p>Exhibited antiatherosclerotic effects in several animal models, including ApoE$^{-/-}$ mice (Do et al., 2008; Chang et al., 2015), APOE*3-Leiden.CETP mice (Bérbé et al., 2013), and ApoE$^{-/-}$/LDLR$^{-/-}$ mice (Fukao et al., 2004). Resveratrol lowered the level of TC and TG in patients with dyslipidemia (Simental-Mendia and Guerrero-Romero, 2019) and regulated lipid metabolism via inhibiting cholesterol-ester-transport protein and HMG-CoA expression/level (Cho et al., 2008).</p>

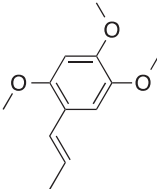
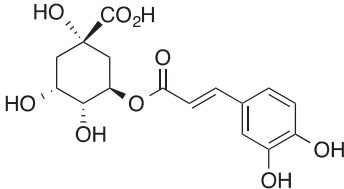
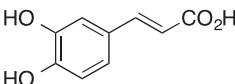
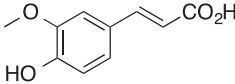
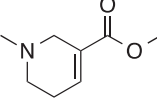
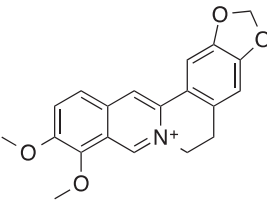
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
Phenylpropanoids	Epigallocatechin gallate (EGCG) 	Reduced cholesterol efflux from macrophages by increasing ABCA1 expression via activating Nrf2-dependent NF-κB inhibitory effects (Jiang et al., 2012) and blocked oxLDL-induced upregulation of SR-A, thus reducing oxLDL uptake (Chen et al., 2017).	Displayed potential antiatherosclerotic and plaque-stabilizing effects in rats, rabbits, and ApoE ^{-/-} mice (Chyu et al., 2004; Xu et al., 2014a; Wang et al., 2018e,f). EGCG prevented hyperlipidemia by increasing the expression and activity of LDLR (Lee et al., 2008).
	(-)-Arctigenin 	Upregulated the expression of ABCA1, ABCG1, and ApoE, resulting in promoting cholesterol efflux in oxLDL-loaded THP-1 macrophages (Xu et al., 2013d).	Decreased cholesterol levels in mice (Huang et al., 2012a) and suppressed lipid accumulation and body weight gain in HFD-induced obese mice (Han et al., 2016).
	Leoligin 	Increased cholesterol efflux from THP-1 macrophages by upregulating the expression of ABCA1 and ABCG1 (Wang et al., 2016a).	Reduced LDL-C level and postprandial serum glucose peaks due to the direct inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and moderate PPARγ agonistic activity; however, no obvious effect on atherosclerotic plaque size was observed (Scharinger et al., 2016).
	Sesamin 	Inhibited oxLDL-induced cholesterol accumulation and enhanced cholesterol efflux from RAW264.7 macrophages via up-regulation of PPARγ, LXRα, and ABCG1 (Liu et al., 2014a).	Prevented fat storage, decreased cholesterol level in serum (Lee et al., 2009c; Rogi et al., 2011). Attenuated atherosclerosis in ApoE ^{-/-} mice by suppressing vascular inflammation (Wu et al., 2010). The lipid-lowering effect of sesamin was exerted through promoting the fecal excretion of sterols and inhibiting HMG-CoA reductase (Liang et al., 2015).
	Honokiol 	Activated the RXR/LXR heterodimer in RAW264.7 cells, resulting in the induction of ABCA1 expression and enhancement of cholesterol efflux from MPMs (Kotani et al., 2010), and increased ABCG1 and ApoE expression in THP-1 macrophages (Jung et al., 2010).	N.A.

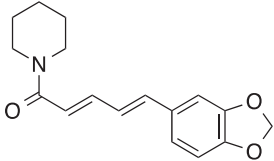
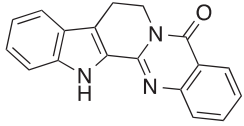
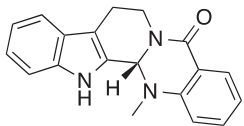
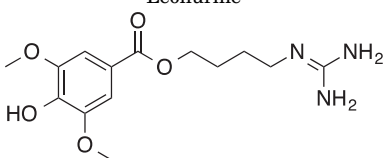
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	<p>α-Asarone</p>  <p>Chlorogenic acid</p>  <p>Caffeic acid</p>  <p>Ferulic acid</p> 	<p>Promoted macrophage cholesterol efflux through the PPARγ-LXRα-ABC transporters pathway (Park et al., 2015).</p> <p>Enhanced HDL-mediated cholesterol efflux from macrophages through increasing the expression of ABCG1 and SR-BI (Uto-Kondo et al., 2010) and enhancement of PPARα ligand binding capacity in vitro (Kim et al., 2014). Decreased oxLDL-elicited neutral lipid and cholesterol accumulation in RAW264.7 macrophages via increasing the transcription of PPARγ, LXRα, ABCA1, and ABCG1 (Wu et al., 2014).</p> <p>Increased the expression of ABCA1 and ABCG1 in macrophage form cells and further promoted cholesterol efflux (Chen and Wang, 2015).</p>	<p>Decreased level of serum cholesterol in hypercholesterolemic rats by inhibition of HMG-CoA reductase (Rodriguez-Paez et al., 2003).</p> <p>Chlorogenic acid prevented atherosclerosis in ApoE$^{-/-}$ mice by inhibiting lipid accumulation and promoting cholesterol efflux via PPARγ/LXRα/ABCA1(G1) pathway (Wu et al., 2014).</p> <p>Reduced the percentage and the total atherosclerotic lesion area as well as promoted vasodilatation in cholesterol-rich diet-fed ApoE$^{-/-}$ mice, and decreased levels of TC, LDL-C and TG in the serum (Wu et al., 2014). Caffeic acid reversed insulin resistance, dyslipidemia, hyperglycemia, inflammation, and oxidative stress in high-fructose diet-induced metabolic syndrome in rats (Ibitoye and Ajiboye, 2018).</p> <p>Ferulic acid suppressed atherosclerosis in ApoE$^{-/-}$ mice by inhibiting the activities of hepatic ACAT and HMG-CoA reductase (Kwon et al., 2010). Ferulic acid also lowered TC, LDL-C, oxLDL, TG, and increased HDL-C in patients with dyslipidemia (Bumrungpert et al., 2018).</p>
	<p>Arecoline</p>  <p>Berberine</p> 	<p>Promoted cholesterol efflux by increasing ABCA1 expression (Ouyang et al., 2012).</p> <p>Inhibited macrophage foam cell formation by promoting LXRα/ABCA1-dependent cholesterol efflux (Lee et al., 2010). Prevented oxLDL-induced upregulation of LOX-1 and downregulation of SR-</p>	<p>Arecoline suppressed atherosclerosis in ApoE$^{-/-}$ mice by inhibiting NF-κB activation (Zhou et al., 2014).</p> <p>Suppressed atherosclerosis development in mice (Feng et al., 2017; Shi et al., 2018; Zhu et al., 2018). One report suggests that berberine promoted atherosclerosis in mice by enhancing</p>

(continued)

TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
		<p>BI in THP-1 macrophages (Guan et al., 2010; Chi et al., 2014a). It was reported to increase foam cell formation in human and mouse macrophages (Li et al., 2009b).</p>	<p>SR-A-mediated oxLDL uptake and foam cell formation (demonstrated in human and mouse macrophages) through suppressing phosphatase and tensin homolog expression, thus promoting the activation of Akt (Li et al., 2009b). In patients with dyslipidemia, berberine reduced TC, LDL-C, TG, and increased HDL-C, partially through inhibiting PCSK9 and increasing LDLR expression/activity (Kong et al., 2004; Cameron et al., 2008; Ju et al., 2018). Regulated lipid metabolism via increasing hepatic LDLR expression through proteolytic activation of SREBPs (Ochiai et al., 2015).</p>
	<p>Piperine</p> 	<p>Promoted ABCA1 protein expression in THP-1-differentiated macrophages by increasing ABCA1 protein stability by preventing calpain-mediated ABCA1 protein degradation (Wang et al., 2017d). Upregulated expression of ABCA1 and SR-BI via LXRα and LXRβ, thereby promoting cholesterol efflux (Xu et al., 2014b).</p>	<p>Reduced atherosclerotic plaque development, as well as macrophage and lipid content in atherosclerotic plaques in ApoE^{-/-} mice (Xu et al., 2014b). Lowered the level of TC, TG, and LDL-C, and hs-CRP in hyperlipidemic and hyperglycemic rats via AMPK activation and NF-κB inhibition (Nie et al., 2016; Tian et al., 2019b).</p>
	<p>Rutaecarpine</p> 		
	<p>Evodiamine</p> 	<p>Increased cholesterol efflux from THP-1-derived macrophages by directly binding to ABCA1 and thereby increasing ABCA1 stability (Wang et al., 2018c).</p>	<p>Decreased the size of atherosclerotic lesions and alleviated the hyperlipidemia, as well as hepatic macrovesicular steatosis in ApoE^{-/-} mice, probably via transient receptor potential vanilloid type 1 (TRPV1) pathway (Su et al., 2014).</p>
	<p>Leonurine</p> 	<p>Promoted ApoA-1- and HDL-mediated cholesterol efflux via the PPARγ/LXRα/ABCA1 and ABCG1 pathway (Jiang et al., 2017a).</p>	<p>Reduced atherosclerotic development in ApoE^{-/-} mice fed with atherogenic diet (Jiang et al., 2017a).</p>

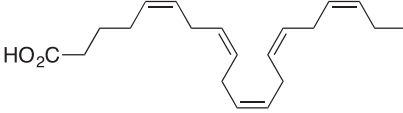
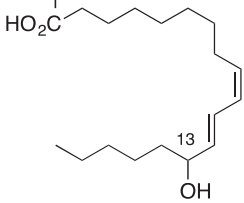
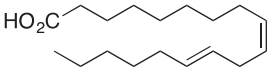
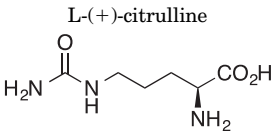
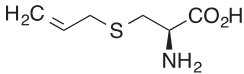
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
Steroids	Diosgenin	Inhibited oxLDL uptake by blocking systemic inflammation and LOX-1/NF- κ B pathway (Wang et al., 2017g). Promoted cholesterol efflux by increasing the ABCA1 expression independent of LXR α (Lv et al., 2015).	Inhibited atherosclerosis in ApoE ^{-/-} mice by reducing TC and CE via promoting ABCA1-dependent cholesterol efflux (Lv et al., 2015).
	Fucosterol	Promoted cholesterol efflux by increasing the efflux transporters ABCA1, ABCG1, and ApoE (Hoang et al., 2012).	Reduced LDL-C, and increased HDL-C (Hoang et al., 2012).
	Ginsenoside Rd (<i>Panax notoginseng</i> saponins (PNS))	Decreased the accumulation of cholesterol esters via increasing ABCA1 expression (Jia et al., 2010).	Inhibited foam cell formation in zymosan A-induced atherosclerosis in rats (Yuan et al., 2011). Prevented atherosclerosis in ApoE ^{-/-} mice by decreasing SR-A-mediated oxLDL uptake and cholesterol accumulation (Li et al., 2011).
	Vitamin D ₃ (Vitamin D)	Vitamin D inhibited CD36 and SR-A-mediated lipid (oxLDL and ac-LDL) uptake (Oh et al., 2009; Yin et al., 2015).	Deficiency of vitamin D receptor (VDR) promoted modified LDL-induced foam cell formation of macrophages from diabetic patients (Oh et al., 2015). Deficiency of macrophage VDR aggravated CD36 and SR-A-mediated lipid uptake (via JNK activation) to increase atherosclerosis in mice (Oh et al., 2015). Vitamin D supplementation improved glycemic control, increased HDL-C and decreased hs-CRP levels in patients with CVD (Ostadmohammadi et al., 2019).
Fatty acids	Docosahexaenoic acid (DHA)	Inhibited the uptake of modified LDL in human macrophages partially through reduction of the expression of CD36 and SR-A (Pietsch et al., 1995), as well as	Reduced atherosclerosis in ApoE ^{-/-} mice by reducing proinflammatory cytokine IL-1 β (Alfaidi et al., 2018). Lowered TG in dyslipidemic

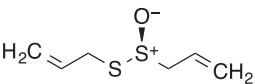
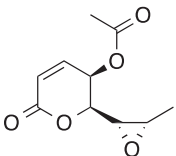
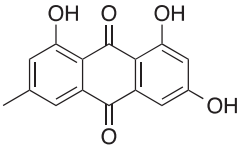
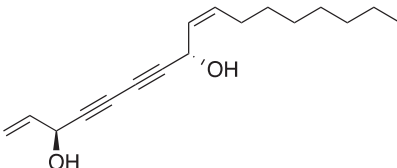
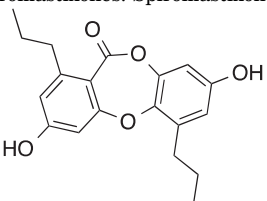
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TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
	Eicosapentaenoic acid (EPA) 	of macropinocytosis and expression of syndecan-4 (McLaren et al., 2011b). Inhibited the uptake of modified LDL in human macrophages partially through reduction of the expression of CD36 and SR-A (Pietsch et al., 1995), as well as of macropinocytosis and expression of syndecan-4 (McLaren et al., 2011b).	patients (Weintraub, 2013). Reduced and stabilized atherosclerotic plaques in ApoE ^{-/-} and LDLR ^{-/-} mice through its anti-inflammatory effects (Ringseis et al., 2006; Laguna-Fernandez et al., 2018). Lowered TG in dyslipidemic patients. EPA served as a substrate for resolvin E1 (RvE1), which promotes inflammation resolution i (Bäck and Hansson, 2019).
	13-Hydroxyoctadecadienoic acid (13-HODE) 	Promoted cholesterol efflux by activating PPAR/LXRα/ABCA1 and ABCG1 pathway (Kämmerer et al., 2011).	N.A.
	Linoleic acid 	Functioned as an endogenous activator of PPARα, PPARγ, and PGC1α, thus stimulating cholesterol efflux (Ringseis et al., 2008).	Induced the regression of pre-established atherosclerotic plaques in ApoE ^{-/-} mice by promoting macrophage polarization toward a M2 anti-inflammatory phenotype (McCarthy et al., 2013). Possibly reduced TC via increasing hepatic LDLR expression and activity (Ringseis et al., 2006).
	L-(-)-citrulline 	Promoted cholesterol efflux by increasing ABCA1 and ABCG1 expression in differentiated THP-1 macrophages (Tsuboi et al., 2018).	Citrulline consumption promoted HDL- and ApoA-1-mediated cholesterol efflux by increasing the expression of both ABCA1 and ABCG1 (Uto-Kondo et al., 2014).
Amino acids	S-allyl cysteine 	Increased ABCA1 expression, thus promoting cholesterol efflux in differentiated THP-1 macrophages (Malekpour-Dehkordi et al., 2013).	N.A.
Carbohydrates	Polysaccharide isolated from <i>Phellinus linteus</i> N.A.	Promoted ApoA-1-mediated cholesterol efflux by activating PPARγ/ABCA1 and ABCG1 pathway (Li et al., 2015d).	N.A.
	<i>Astragalus</i> polysaccharides	Promoted ABCA1 expression in foam cells, thus increasing cholesterol efflux (Wang et al., 2010d).	N.A.

(continued)

TABLE 1—Continued

Chemical class	Natural Compounds	In Vitro Studies	Animal Studies, Clinical Studies, and Targets
Others	<p>Organosulfur compounds: Allicin</p>  <p>Pyranone derivatives: Asperlin</p>  <p>Anthraquinone derivatives: Emodin</p>  <p>Polyacetylene derivatives: Falcarindiol</p>  <p>Spiromastixones: Spiromastixone A</p> 	<p>Upregulated ABCA1-dependent cholesterol efflux via PPARγ/LXRα signaling pathway in THP-1 macrophage-derived foam cells (Lin et al., 2017). Promoted cholesterol efflux from mouse macrophages (Zhou et al., 2017).</p> <p>Promoted ApoA-1-mediated cholesterol efflux from macrophages via PPARγ/LXRα/ABCA1 and ABCG1 pathway (Zhou et al., 2008; Fu et al., 2014)</p> <p>Promoted ApoA-1-mediated cholesterol efflux in macrophages not only by increasing ABCA1 gene expression, but also via preventing cathepsins-dependent ABCA1 protein degradation (Wang et al., 2017e). Inhibited lipid uptake by reducing the expression of CD36. Promoted cholesterol efflux by upregulation of PPARγ/ABCA1 and ABCG1 (Wu et al., 2015a).</p>	<p>Decreased carotid intima/media thickness, decreased homocysteine, TC, and TG in CAD patients with hyperhomocysteinemia (Liu et al., 2017a). Reduced the secretion of proinflammatory cytokines (IL-6, TNFα, MCP-1) and atherosclerosis in ApoE$^{-/-}$ mice (Zhou et al., 2017).</p> <p>Reduced atherosclerosis in ApoE$^{-/-}$ mice (Zhou et al., 2008) and rabbits (Hei et al., 2006). Lowered blood glucose, TC, TG, in diabetic and hyperlipidemic rats (Zhao et al., 2009) by inhibiting SREBP-1 and SREBP-2 (Li et al., 2016).</p> <p>N.A.</p> <p>N.A.</p>

N.A., not available.

Further study indicated that the black rice AC-rich extract (300 mg/kg body weight per day) inhibited the production of oxLDL and reduced the levels of TC and LDL-C, while upregulating the HDL-C level in serum from rats and ApoE $^{-/-}$ mice, and also narrowed the area of atherosclerotic plaque and improved the stability of plaque to prevent the occurrence of embolism (Xia et al., 2006). Moreover, the ACs derived from pomegranate reduced blood lipids and exhibited an anti-inflammatory activity (Wang et al., 2018b). It was reported that pomegranate peel extract containing ACs (1 g/kg diet) has a slight effect on fatty streak formation and lipid metabolism in hypercholesterolemic rabbits (Sharifiyan et al., 2016). These studies indicated that the role of an AC-rich diet on the reduction of the risk of developing CVD might possibly

be due to the ability of these compounds to inhibit lipid accumulation.

3. Baicalin. Baicalin, a glucuronide of baicalein, is a flavone glycoside that is present in the root of *Scutellaria baicalensis* Georgi with content as high as 12.1% (Makino et al., 2008). The latter is a traditional Chinese medicine widely used to treat acute and chronic hepatitis, nephritis, and allergic diseases due to its anti-inflammatory and hypolipidemic effects. One study indicated that baicalin (50 μ M) significantly increased HDL- but not ApoA1-mediated cholesterol efflux and upregulated the expression of SR-BI in a dose- and time-dependent manner (Yu et al., 2016). Another study showed that baicalin (50 and 100 μ M) exerted potentially antiatherosclerotic effects by inhibition of foam cell formation and lipid deposition via promoting cholesterol

efflux through the PPAR γ -LXR α -ABCA1/ABCG1 pathway in THP-1 macrophages (He et al., 2016b).

Baicalin also markedly decreased atherosclerotic lesion size and lipid accumulation in the carotid arteries in an atherosclerotic rabbit model (He et al., 2016b). Furthermore, long-term treatment with baicalin (80 mg/kg body weight) in rats with HFD markedly reduced the rising level of TC, LDL-C, NEFA, insulin, and TNF- α and also significantly ameliorated the fasting serum glucose levels (Guo et al., 2009), which suggests that baicalin may regulate the glucose/lipid metabolic disorders. Baicalin reduces TC, TG, LDL-C, and hs-CRP in patients with rheumatoid arthritis who have an increased risk of CAD (Hang et al., 2018).

4. Chrysin. Chrysin, also called 5,7-dihydroxyflavone, is a flavone present in blue passionflower (*Passiflora caerulea*), *Pelargonium crispum*, and *Oroxylum indicum*. It is one of the main active ingredients of propolis.

In a model of Wistar rats fed with HFD, chrysin (200 mg/kg body weight per day) decreased the mean levels of serum TC, TG, LDL-C, and VLDL-C (Anandhi et al., 2014). A recent report revealed that chrysin activated PPAR γ , the key regulator in lipid metabolism, to exert an anti-inflammatory effect (Feng et al., 2014). This suggested that chrysin might have an antiatherosclerotic effect, possibly by decelerating the formation of foam cells. Additional study displayed that HDL-mediated RAW264.7 macrophages cholesterol efflux was significantly increased after chrysin (10 μ M) treatment by the upregulation of PPAR γ , LXR α , ABCA1, and ABCG1 expression (Wang et al., 2015b). Additionally, chrysin also prevented the transcription of SR-A1 and SR-A2 but had no effect on CD36, suggesting that it may inhibit the cholesterol uptake by downregulating the expression of SR-A1 and SR-A2 (Wang et al., 2015b).

5. Cyanidin-3-O- β -glucoside. As a member of blueberry AC family, cyanidin-3-O- β -glucoside (C3G) is the most widely distributed AC in nature. C3G has anti-inflammatory action, lowers the blood fat, as well as protects cardiovascular health through various mechanisms (Duchnowicz et al., 2012; Luo et al., 2012). It has been reported that C3G (0.5, 5, and 50 μ M) upregulated the expression of ABCG1 and ABCA1 in a dose-dependent manner and promoted the cholesterol efflux in human aortic endothelial cells (Wang et al., 2012c), suggesting a novel mechanism by which C3G reduces oxidative damage on endothelial cells.

The antiatherosclerotic effect of C3G was recently evaluated in an HFD-induced atherosclerosis rat model. The results showed that diet supplementation with C3G (150 mg/kg) markedly decreased body weight, visceral adiposity, TG, TC, free fatty acids, and atherosclerosis index (Um et al., 2013). In ApoE $^{-/-}$ mice, C3G (2 g/kg diet) prevented the hypercholesterolemia-induced endothelial dysfunction and the development of atherosclerosis by inhibiting cholesterol and 7-oxysterol

accumulation in the aorta (Wang et al., 2012b). Interestingly, it was shown that protocatechuic acid, a gut microbiota metabolite of C3G in ApoE $^{-/-}$ mice, displayed a promising antiatherogenic effect at physiologically reachable concentrations (0.25–1 μ M), accelerating the cholesterol efflux in acLDL-loaded MPMs or THP-1 macrophages by interfering with the regulation of miRNA-10b-ABCA1/ABCG1 cascade (Wang et al., 2012a). Therefore, the gut metabolites of AC could also be explored as potential novel molecules for atherosclerotic prevention and treatment. Furthermore, a double-blind, randomized, placebo-controlled trial showed that consumption of anthocyanin increased HDL-C, decreased LDL-C, and promoted cellular cholesterol efflux in hyperlipidemia patients (Qin et al., 2009).

6. Daidzein. Daidzein is a naturally occurring isoflavone found in soybeans and other legumes. Because it is a nonsteroidal compound with estrogen-like biologic activities, daidzein is also regarded as a phytoestrogen. There are many clinical studies that investigated the effects of daidzein on the treatment of hypertension and menopausal syndrome, as well as alcoholism (Liu et al., 2014d,e). Studies conducted over the last several decades showed that it has antiosteoporosis, antioxidative, hypolipidemic, and cardiovascular-protective effects (Robb and Stuart, 2014). Daidzein (25 μ M) induced paraoxonase-1 (PON-1) activity and protected LDL from oxidation in Huh7 cells, thereby displaying an antiatherosclerotic potential (Schrader et al., 2012). It was known that PON-1 may regulate cholesterol efflux by stimulating the PPAR γ -LXR α -ABCA1 pathway (Ikhlef et al., 2016), indicating that daidzein may regulate macrophage cholesterol efflux. Additionally, in another study utilizing cultured HepG2 cells, daidzein (EC $_{50}$ = 3.21 μ M) upregulated the activity of CD36 and lysosomal integral membrane protein-II analogous-1 (CLA-1), which is a homolog of SR-BI, suggesting that daidzein may affect lipid uptake (Yang et al., 2009). Daidzein was also reported to be an inhibitor of HMG-CoA reductase, ACAT1, and ACAT2 (Borradaile et al., 2002; Sung et al., 2004).

In addition, in male middle-aged rats with HFD used to induce atherosclerosis, treatment with daidzein (30 mg/kg body weight) decreased the serum cholesterol and increased TG level (Sosić-Jurjević et al., 2007). In another study using rheumatoid arthritis rat model, it was shown that intragastric administration of daidzein (20 mg/kg body weight) and hesperidin (50 mg/kg body weight) reduced plasma VLDL, LDL-C, and TG concentrations, while increasing HDL-C levels (Ahmad et al., 2016).

7. Ellagic Acid. Ellagic acid, a dilactone of hexahydroxydiphenic acid, is an important antioxidant found in numerous fruits, such as cranberries, raspberries, grapes, pomegranates, as well as in walnuts. Ellagic acid has a wide range of biologic activities, including

antiproliferative and antioxidative properties (Larrosa et al., 2010). One study utilizing J774A.1 murine macrophages suggested that ellagic acid (1 and 5 μM) stimulated cholesterol efflux by promoting the ABCA1 expression and upregulating PPAR γ and LXR α levels (Park et al., 2011). This study also displayed that ellagic acid could modulate the SR-BI expression by counteracting PPAR γ -responsive early signaling. Additionally, it was demonstrated that pomegranate ellagic acid (PEA) (10, 20, and 40 $\mu\text{g/ml}$) regulated the expression of PPAR γ , ABCA1, and cholesterol 7 α -hydroxylase (CYP7A1) in the hepatic cell line L-02, thus regulating cholesterol metabolism (Lv et al., 2016). Also, pomegranate peel polyphenols, especially PEA (25 and 50 $\mu\text{g/ml}$), inhibited macrophage lipid accumulation by decreasing the expression of CD36 and promoted ApoA1-mediated macrophage cholesterol efflux by upregulating ABCA1 and LXR α (Zhao et al., 2016).

In a hamster model with HFD, a high-dose of PEA (177 mg/kg body weight) decreased TC and TG in a dose-dependent manner and upregulated the expression of LXR α , PPAR α , PPAR γ , and their downstream gene ABCA1 (Liu et al., 2015). Moreover, using ApoE $^{-/-}$ mice, it was shown that treatment of pomegranate phenolic compounds (200 $\mu\text{g/mouse}$ per day) for 3 months, mainly including gallic acid and ellagic acid, reduced atherosclerotic lesions (Aviram et al., 2008).

8. Hesperetin. Hesperetin is an aglycone of hesperidin, a natural bioflavonoid that is present in Leguminosae, Dimorphicaceae, Labiatae, and Rutaceae plants. Hesperetin has many biologic and pharmacological activities, such as antioxidative, anti-inflammatory, and antiatherosclerotic effects (Yang et al., 2012; Ren et al., 2016). It was shown that hesperetin (5, 10, and 15 μM) reduced THP-1-derived foam cell formation by enhancing the expression of ABCA1 through increasing the activities of ABCA1 promoter and LXR enhancer, thus upregulating the ApoA1-mediated cholesterol efflux (Iio et al., 2012). Hesperetin (25 μM) may act as an antiatherogenic agent possibly by also inhibiting oxLDL-triggered ROS in human umbilical vein endothelial cells (HUVECs) (Choi et al., 2008), as well as the proliferation and migration of VSMCs (Wei et al., 2016). A recent study showed that hesperetin reduced plasma TC level, endothelial dysfunction, macrophage infiltration, and atherosclerotic lesion in ApoE $^{-/-}$ mice (Sugasawa et al., 2019).

9. Icariin. Icariin (ICA) is present in the traditional Chinese herbal medicine *Epimedium brevicornum* Maxim. In recent years, ICA has been studied for its effect on CVD. It was shown that ICA possessed atheroprotective functions through various mechanisms, including counteracting endothelial dysfunction, suppressing the proliferation and migration of VSMCs, as well as inhibiting foam cell formation and inflammatory responses (Fang and Zhang, 2017). In models of normal rats (Hu et al., 2016b) or ApoE $^{-/-}$ mice with HFD (Xiao et al., 2017), ICA (10–60 mg/kg body weight

per day) significantly decreased the concentrations of TC, TG, and LDL-C. It was demonstrated that the inhibitory effects of ICA (4 μM) on cholesterol intake and foam cell formation were accompanied by a reduced expression of CD36 and an upregulated SR-BI expression through p38 MAPK pathway in THP-1 cells (Yang et al., 2015). Additionally, ICA (5 and 10 μM) lessened RAW264.7 macrophage infiltration at atherosclerosis lesion by blocking the CX3CR1-CX3CL1 interaction, which is highly related to monocyte adhesion and migration (Wang et al., 2016c).

10. Iris Isoflavones. Iris isoflavones (tectorigenin, iristectorigenins, and iristectorins) present in rhizomes of *Iris germanica* L. have many biologic activities, such as antioxidative, anti-inflammatory, and antiangiogenic effects (Jung et al., 2003). Some of these nature products could also regulate the metabolism of blood sugar and cholesterol (Lee et al., 2000a; Jung et al., 2002). It was reported that iristectorigenin B (5 and 10 μM) acted as a novel LXR modulator by regulating the transcriptional activity of LXR α/β in RAW264.7 cells. It also induced the activation of ABCA1 and ABCG1, thus increasing the macrophage cholesterol efflux (Jun et al., 2012).

11. Pratensein. Pratensein is an isoflavone, which is present in *Trifolium pratense* L. (red clover). It was reported that pratensein (10 μM) upregulated ABCA1 protein expression to increase the HDL levels in HepG2 cells (Gao et al., 2008). In the same line, another study indicated that pratensein (EC $_{50}$ = 1.08 μM) upregulated the CLA-1 expression, which is a human homolog of SR-BI, suggesting that it can play a potential role in the process of cholesterol efflux in vitro (Yang et al., 2007, 2009).

12. Puerarin. Puerarin is present in the roots of Pueraria (*Radix puerariae*). Due to positive action on dilating coronary artery, protecting ischemic myocardium, resisting myocardial ischemia and re-injury, and preventing atherosclerosis (Bao et al., 2015), puerarin has been extensively studied for the treatment of CVD. It is demonstrated that puerarin (25, 50, and 100 $\mu\text{g/ml}$) decreased the cellular lipid accumulation in THP-1 macrophages by promoting ABCA1-mediated cholesterol efflux through pathways involving miRNA-7, serine/threonine kinase 11 (STK11), and the AMP-activated protein kinase (AMPK)-PPAR γ -LXR α -ABCA1 cascade (Li et al., 2017a). In the same model, puerarin (50 and 100 $\mu\text{g/ml}$) suppressed lipid deposition and foam cell formation by downregulating the expression of CD36 (She et al., 2014). It (10, 50, and 100 $\mu\text{g/ml}$) also suppressed oxLDL-induced macrophage activation and release of TNF- α and IL1- β by inhibiting the TLR4/NF- κ B pathway. Furthermore, treatment with puerarin (140 and 200 mg/kg body weight per day) decreased the level of blood glucose, TC, TG, LDL-C, and increased the HDL-C level in the streptozotocin-induced diabetic rat model (Smith et al., 2006).

13. Quercetin. Quercetin, a polyhydroxy flavonoid, is one of the most abundant natural polyphenols in different foods, such as onions, apples, broccoli, and ginkgo. It has broad biologic activities, including anti-inflammatory, immunomodulatory, and cardiovascular-protective effects (Rauf et al., 2018). Some studies indicated that quercetin could interfere with foam cell formation (Lara-Guzman et al., 2012). Quercetin (50, 100, and 200 μM) enhanced ApoA1-mediated cholesterol efflux, as well as induced ABCA1 expression and the expression of PPAR γ through activating the PPAR γ signaling in THP-1-derived foam cells (Sun et al., 2015). Another study indicated that quercetin-increased ABCA1 expression possibly due to the p38-dependent pathway (Chang et al., 2012). It was also shown that quercetin-driven ABCA1 upregulation could be mediated by enhancing LXR α activity (Lee et al., 2013). Interestingly, a quercetin metabolite, quercetin-3-glucuronide, inhibited the formation of foam cells at 20 μM by suppressing the expression of SR-A1 and CD36 in RAW264.7 cells (Kawai et al., 2008). Moreover, quercetin was reported to inhibit atherosclerosis by promoting ABCA1- and ABCG1-dependent RCT in ApoE $^{-/-}$ mice (Cui et al., 2017).

14. Silymarin. Silymarin, a mixture of flavonolignans from the medicinal plant *Silybum marianum*, includes silybin (synonymous with silibinin), isosilybin, silydianin, silychristin, and little amounts of other phenolic compounds. Within the last decade, several studies have suggested that, in addition to its use in the treatment of liver diseases, silymarin also has a protective effect on CVD. It was shown that four compounds from silymarin (isosilybin A, silybin B, silychristin, and isosilychristin) induced the expression of ABCA1 protein in THP-1 cells. Especially isosilybin A (10 and 30 μM) promoted cholesterol efflux from THP-1 macrophages due to its PPAR γ -activating properties (Wang et al., 2015a). It is also reported that silymarin not only reduced the LDL and cholesterol levels, but also protected endothelial cells (Skottova and Krecman, 1998).

Furthermore, in the hypercholesterolemic rat model, supplementation of silybin (300 and 600 mg/kg body weight per day) in food significantly decreased serum levels of TC, TG, VLDL-C, LDL-C, and increased HDL-C, as well as reduced the formation of atherosclerotic plaques (Gobalakrishnan et al., 2016).

15. Wogonin. Wogonin, an *O*-methylated flavone, is present in the roots of *Scutellaria baicalensis* Georgi and the rhizomes of *Scutellaria barbata* L. It was shown that wogonin is effective in the treatment of inflammation, cancer, and anxiety (Tai et al., 2005; Li-Weber, 2009). Wogonin (40 μM) attenuated oxLDL-induced cholesterol accumulation in murine J774.A1 macrophages by enhancing cholesterol efflux through increasing the ABCA1 protein expression (Chen et al., 2011). In addition, this flavonoid decreased phosphorylated

levels of ABCA1 protein. Another beneficial effect of wogonin in the context of prevention and therapy of atherosclerosis is to protect physiologic function in vascular endothelial cells and VSMCs (Oche et al., 2016). An in vivo study suggests that wogonin ameliorated hyperglycemia and dyslipidemia in db/db mice via PPAR α activation (Bak et al., 2014).

B. Terpenoids

Terpenoids, also known as isoprenoids, constitute one of the largest families of natural products, which, in contrast to terpenes, contain additional functional groups, mostly oxygen containing. Several bioactive terpenoids have been shown to be promising for therapeutic purposes (Goto et al., 2010). In this section, we focus on the inhibitory effects of terpenoids on foam cell formation and the associated molecular mechanisms of action.

1. Carotenoids. Carotenoids, also called tetraterpenoids, are a complex group of organic pigments with a basic tetraterpene skeleton and a variety of biochemical functions. A number of carotenoids have been reported to be associated with a wide range of bioactivities and potential health benefits (Rao and Rao, 2007; Fiedor and Burda, 2014). Epidemiologic studies, such as research regarding the association between β -carotene and CVD and case-control trials testing the concentration of β -carotene of patients with different CVD events, have demonstrated that the consumption of carotenoids can reduce the risk of CVD (Kohlmeier and Hastings, 1995; Riccioni et al., 2012). Here, the published studies regarding the effect of several main carotenoids, i.e., astaxanthin, β -carotene, capsanthin, retinoids, and lycopene, on cholesterol efflux and foam cells formation are discussed.

a. Astaxanthin. Astaxanthin is a major naturally occurring keto-carotenoid, mainly found in various microorganisms and marine animals and responsible for their pink-red pigmentation. Recently, there is a rapidly growing interest for its application in counteracting foam cell formation and stabilization and/or regression of atherosclerosis. It was shown that THP-1 macrophages incubated in the presence of astaxanthin (5–10 μM) downregulated the SR-A and CD36 mRNA expression (48% and 58%, respectively), which is relevant to cholesterol uptake (Kishimoto et al., 2010). Further studies showed that astaxanthin promotes the ABCA1/G1 expression (up to 2.0- and 3.2-fold in protein level), resulting in increasing the ApoA-1/HDL-mediated cholesterol efflux (116% and 25%, respectively) from RAW264.7 cells via an LXR-independent manner, but only at high concentrations (50 and 100 μM) (Ramírez-Tortosa et al., 1999; Iizuka et al., 2012). In agreement with the in vitro observation, a randomized, placebo-controlled clinical study was conducted in humans (aged 25–60 years) with mild hyperlipidemia (levels of 120–200 mg/dl) for 12-week

astaxanthin administration (at doses of 0, 6, 12, and 18 mg/day). The results showed that 6 and 12 mg/day doses of astaxanthin significantly increased HDL-C in correlation with increased serum adiponectin (Yoshida et al., 2010).

b. Capsanthin. Capsanthin is the main carotenoid in paprika and it does not possess provitamin A activity. There is some scientific evidence supporting the view that capsanthin has the potential to increase cholesterol efflux. An in vivo study showed that male Wistar rats fed with capsanthin (the low dose: 0.16 g/kg, the high dose: 0.32 g/kg) for 2 weeks exhibited an increase in plasma HDL-C and an upregulation of ApoA-5 and LCAT mRNA expression, without significantly influencing mRNA levels of other genes related to cholesterol metabolism (such as ABCA1, ApoA-1, and SR-BI) (Aizawa and Inakuma, 2009). In the same line, it was shown that supplementation of paprika significantly decreased the TC, HDL-C, atherogenic index values in rats fed with a high-cholesterol diet (Park et al., 2010).

c. β -Carotene. β -Carotene is a carotenoid with a hydrocarbon skeleton and high pro-vitamin A activity (Olson, 1989). Several studies provide insights into the effects of β -carotene on the cholesterol metabolism (Fuhrman et al., 1997; Relevy et al., 2015). An in vitro study indicated that treatment with β -carotene (0–10 μ M) results in a dose-dependent suppression of cholesterol synthesis by inhibiting the cellular HMG-CoA reductase activity in J774 macrophages. On the other hand, a study demonstrated that β -carotene (5 μ M) could not significantly upregulate the ABCA1, ABCG1, and ApoE mRNA levels in human monocytes compared with retinoic acid (Langmann et al., 2005).

Natural β -carotene comprises several isomers, including all-*trans*- β -carotene (all-*trans*- β c) and 9-*cis*- β -carotene (9-*cis*- β c). There is a lot of evidence from cellular, animal, and clinical studies supporting the association between the β -carotene isomers and the cholesterol levels. For example, a recent study conducted in RAW264.7 macrophages revealed that all-*trans*- β c and 9-*cis*- β c-regulated cholesterol efflux to HDL was related to transcriptional induction of ABCA1, ABCG1, and ApoE (Bechor et al., 2016). In addition, previous study showed that the alga *Dunaliella bardawil* (containing high levels of all-*trans*- β c and 9-*cis*- β c) increased plasma HDL-C and attenuated atherosclerosis in both ApoE^{-/-} (Harari et al., 2013) and LDLR^{-/-} mice (Harari et al., 2008). A clinical study indicated that 9-*cis*- β c-rich powder of the alga *Dunaliella bardawil* increased plasma HDL-C in fibrate-treated patients (Shaish et al., 2006). It was also reported that 9-*cis*- β c can be cleaved by endogenous β -carotene 15,15'-monooxygenase 1 to form 9-*cis* retinoic acid or other retinoids, subsequently activating the RXR and finally inhibiting foam cell formation and atherosclerosis progress (Zolberg Relevy et al., 2015).

d. Retinoids. Plentiful evidence suggests that retinol (also known as vitamin A₁) and its natural derivatives 9-*cis* retinoic acid (9-*cis*-RA) and all-*trans* retinoic acid (ATRA) can increase macrophage cholesterol efflux and, therefore, are promising therapeutic agents for the prevention of atherosclerosis progression. It was reported that 9-*cis*-RA and ATRA (5 μ M) are potent inducers of ABCA1, ABCG1, and ApoE expression in THP-1 macrophages, as well as exhibited a very strong induction of cholesterol efflux to ApoA-1 in RAW264.7 macrophages (Langmann et al., 2005). Another study revealed that retinoids are able to induce the CYP27 expression, which is likely to act as a modulator of the LXR activation, subsequently mediating cholesterol efflux from macrophages (Szanto et al., 2004). This notion is further underscored by the observation that the cholesterol efflux induced by retinoids involves the activation of steroidogenic acute regulatory protein expression and the upregulation of LXR-targeted genes (SREBP-1c and ABCA1) in mouse macrophages (Manna et al., 2015).

Furthermore, 9-*cis*-RA has been reported to increase ABCA1-mediated cholesterol efflux from J774 macrophages, THP-1-derived macrophages (Kiss et al., 2005), and RAW264.7 macrophages (Schwartz et al., 2000). To further characterize the underlying molecular mechanisms of 9-*cis*-RA on cholesterol efflux, a study using J774A.1 cells and primary peritoneal macrophages showed that 9-*cis*-RA-mediated inhibition of foam cell formation and amelioration of atherosclerosis were regulated by the activation of LXR α and the upregulation of ABCA1 and ABCG1 expression (Zhou et al., 2015). Interestingly, treatment with 9-*cis*-RA (2 mg/kg) can ameliorate the atherosclerosis in ApoE^{-/-} mice fed with HFD (Zhou et al., 2015).

Another study indicated that ATRA-induced upregulation of CD36 mRNA and protein expression were related to the retinoic acid receptor-dependent signaling in THP-1 cells, which may contribute to the foam cell formation and the progress of atherosclerosis (Wuttge et al., 2001). Further work also studied regulatory action of retinoids in this context; ATRA could increase the cholesterol efflux to ApoA-1 and enhance the ABCA1 expression, both at the mRNA and protein level in MPMs and HMDMs, in a dose-dependent manner (0.5–10 μ M). Furthermore, ATRA treatment also increased the ABCG1 and SREBP-1c mRNA expression (Costet et al., 2003). Moreover, ATRA-increased levels of ABCA1 protein and mRNA may partly depend on the induction of LXR in THP-1 cells (Wågsäter et al., 2003).

e. Lycopene. Lycopene is the most abundant carotenoid pigment in tomato and contributes to the red color of tomatoes. It does not have pro-vitamin A activity but has many other biologic effects. Recently, this carotenoid has received marked attention for its potential in preventing CVD and interference with foam cell formation (Mozos et al., 2018). It was shown that lycopene

(10 μ M) decreased cholesterol accumulation through downregulation of the SR-A mRNA expression and lipid synthesis, along with increase in the secretion of IL-10 in HMDMs and THP-1 macrophages (Napolitano et al., 2007). These data are in agreement with another study in THP-1 cells, which showed that lycopene (10 μ M) suppressed the cholesterol synthesis and efflux (Palozza et al., 2011). Furthermore, the potential role of lycopene (0.5–2 μ M) in attenuating foam cell formation through a cascade mechanism may involve HMG-CoA reductase inhibition, RhoA inactivation, subsequent increase in PPAR γ and LXR α activation, and enhancement of ABCA1 and caveolin 1 expression ultimately (Palozza et al., 2011). In this line, there is a known association between the PPAR γ activation and cholesterol efflux from peritoneal macrophages in inflammation (He et al., 2014).

In agreement with these in vitro observations, the studies conducted on animal models (rabbits, rats, and mice) showed that lycopene reduced the serum LDL-C and increased the serum HDL-C levels (Palozza et al., 2012). Mechanistically, lycopene displays potent hypolipidemic effects via inhibiting PCSK9 and HMG-CoA reductase, thus increasing hepatic LDLR (Sultan Alvi et al., 2017). A human intervention trial also suggested that diet with dietary supplementation of lycopene (60 mg/day) in healthy men resulted in a significant decrease (14%) in the LDL-C concentration (Fuhrman et al., 1997). However, another clinical investigation reported that dietary supplementation of lycopene is not associated with a reduced risk of CVD in middle-aged and older men (Sesso et al., 2005).

2. Ursolic Acid. Ursolic acid (UA), a natural ursane-type pentacyclic triterpenoid, is abundantly distributed in the plant kingdom. Recently, one study showed that UA (10 μ M) promoted cholesterol flux from LDL-loaded macrophages to ApoA-1 (not HDL) through autophagy, without altering mRNA or protein levels of ABCA1 and ABCG1 in MPMs (Leng et al., 2016). Furthermore, UA (50 mg/kg) treatment in LDLR $^{-/-}$ mice significantly reduced atherosclerotic lesion size, along with increase of macrophage autophagy (Leng et al., 2016). Taken together, these results provided evidence that UA may have potential to be further studied as an antiatherogenic agent.

3. Betulinic Acid. Betulinic acid, which is derived from the bark of yellow and white birch trees, is a pentacyclic triterpenoid with a wide range of pharmacological properties. One study indicated that betulinic acid may induce cholesterol efflux through blocking the NF- κ B-miRNA-33s-ABCA1 signal pathway in LPS-treated macrophages (Zhao et al., 2013a). Consistently, in both RAW264.7 and THP-1 cells, betulin (a betulinic acid derivative) significantly increased ABCA1/ABCG1-mediated cholesterol efflux via suppressing the expression of SREBPs, which bind to E-box motifs in the ABCA1 promoter (Gui et al., 2016).

Betulinic acid was reported to be a potent pharmacological inhibitor of ACAT1 and ACAT2 (Lee et al., 2006), suggesting its potential utility in reduced CE accumulation. Moreover, an in vivo study was done using ApoE $^{-/-}$ mice in which increased ABCA1 expression and enhanced fecal cholesterol excretion were observed upon long-term administration of betulin (40 mg/kg), along with suppressed macrophage-positive areas in the aortic sinuses (Gui et al., 2016). Another study confirmed that betulinic acid (50 mg/kg) reduced atherosclerotic lesions and reduced TG, TC, and LDL-C levels in ApoE $^{-/-}$ mice (Zhao et al., 2013a).

4. Erythrodiol. Erythrodiol is a pentacyclic triterpenoid present in olive oil. Recently, a study was conducted in THP-1 macrophages to screen the effect of various components of olive oil on foam cell formation. The results showed that among several compounds, only erythrodiol (10 μ M) has a positive effect on ApoA-1-mediated cholesterol efflux by inhibiting ABCA1 degradation (Wang et al., 2017f). Therefore, erythrodiol may serve as a good candidate for further studies related to the prevention of atherosclerosis progression.

5. Ginsenosides. Ginseng, the original sources of which are the roots of the plant species *Panax ginseng*, is therapeutically used throughout the world for its possible curative and health-restorative properties. Most of the pharmacological actions of ginseng are attributed to its major constituents, ginsenosides. There are several types of ginsenosides, including Rb1, Rg1, Rg3, Rh1, Re, and Rd. Numerous studies focused on the potential benefits of the ginseng extract and its purified ginsenoside monomers in the area of CVD (Lee and Kim, 2014). Among these various ginsenosides, ginsenosides Rb1 and Rg1 are regarded as the most abundant active components from ginseng. A study showed that ginsenoside Rb1 (10 μ M) significantly increased cholesterol efflux from foam cells to ApoA-1 by about 21% (Wang et al., 2007b). Similarly, a recent publication indicated that Rb1 (10–80 μ M) treatment showed a significant increase in ABCA1 protein expression in macrophage foam cells, which provided the indirect evidence for a possible effect on the cholesterol efflux. Rb1 treatment also reduced the lipid metabolism and enhanced atherosclerotic plaque stability via enhancing macrophage autophagy in primary peritoneal macrophages isolated from C57BL/6 mice and ApoE $^{-/-}$ mice (Qiao et al., 2017).

Ginsenoside Rd is another important constituent of ginseng. Data obtained from a RAW264.7 cell model revealed that Rd (20 μ M) inhibited SR-A protein expression, followed by the decrease of oxLDL uptake and decreased intracellular cholesterol content, which is probably mediated by the inhibition of Ca $^{2+}$ influx through Ca $^{2+}$ channels (Li et al., 2011). Consistently, an in vivo study indicated that Rd treatment (20 mg/kg per day) reduced the oxLDL uptake and atherosclerotic plaque areas in ApoE $^{-/-}$ mice.

6. *Saikosaponin A*. Saikosaponin A, a triterpenoid glycoside (saponin), is the major bioactive constituent from the Chinese herb *Radix bupleuri*. Saikosaponin A (at concentrations of 0–50 μM) ameliorated oxLDL-induced foam cell formation and suppressed lipoprotein uptake by diminishing LOX-1 and CD36 expression, as well as stimulated cholesterol efflux through upregulating the ABCA1 and PPAR γ expression (He et al., 2016a). Saikosaponin A also regulated the immune inflammatory reaction via PI3K/Akt/NF- κ B/NLRP3 signaling pathway and decreased the diffusion of proinflammatory cytokines (IL-1 β , IL-18, IL-6, TNF- α , and MCP-1), revealing new insight on the potential of saikosaponin A in the context of atherosclerosis (He et al., 2016a).

7. *Tanshinone IIA*. Danshen, the rhizome of *Salvia miltiorrhiza* Bunge, has been widely used to treat various diseases for centuries (Gao et al., 2012). The chemical constituents and biologic activities of Danshen have been extensively studied. Among its constituents, tanshinone IIA is the major bioactive lipophilic compound (Xu and Liu, 2013; Fang et al., 2018). An in vitro study demonstrated that tanshinone IIA (at concentrations of 0.1–10 μM) decreased cellular cholesterol level, oxLDL uptake, as well as CD36 expression at both the mRNA and protein levels in oxLDL-treated MPMs (Tang et al., 2011). Furthermore, tanshinone IIA (1–10 μM) induced the reduction of CD36, which might be related to a PPAR γ antagonism (Tang et al., 2011). Tanshinone IIA also increased the ABCA1- and ABCG1-mediated cholesterol efflux through the ERK/Nrf2/HO-1 loop and decreased the SR-A-mediated oxLDL uptake by inhibition of AP-1, resulting in decreasing cholesterol accumulation in cells (Liu et al., 2014c).

In vivo, tanshinone IIA (at doses of 10–90 mg/kg) also downregulated the SR-A mRNA expression and ameliorated the atherosclerotic lesions in the aortas of ApoE $^{-/-}$ mice (Tang et al., 2011). Consistently, another study also showed that tanshinone IIA (30 mg/kg per day) lessened atherosclerotic plaques in ApoE $^{-/-}$ mice (Liu et al., 2014c). Recently, another study conducted in macrophages from the peritoneal cavity of rats and THP-1-derived macrophages showed that ABCA1 mRNA and protein expression were significantly increased, while CD36 was significantly reduced upon tanshinone IIA treatment, thereby demonstrating simultaneous effects on cholesterol intake and efflux (Jia et al., 2016). In addition, tanshinone IIA was also reported to upregulate LDLR in hyperlipidemic rats (Jia et al., 2016). Furthermore, a clinical trial has shown that tanshinone IIA reduces hs-CRP in patients with CAD (Li et al., 2017b).

8. *Tanshindiol C*. Tanshindiol C is another bioactive compound isolated from Danshen. A recent report showed that tanshindiol C (1, 3, and 10 μM) concentration dependently inhibits oxLDL-induced

foam cell formation via activation of Prdx1/ABCA1 signaling pathway. Also, tanshindiol C treatment-induced Prdx1 transcription was coregulated by Nrf2 and Sirt1 expression (Yang et al., 2018b). Furthermore, tanshindiol C also significantly inhibited the secretion of TNF- α , IL-1 β , and IL-8 (Yang et al., 2018b). These data indicated that the potential therapeutic effects of tanshindiol C on atherosclerosis could be due to the modulation of both foam cell formation and inflammation. However, more conclusive evidence is needed to confirm the significance of tanshindiol C in the context of atherosclerosis in animal models and clinical trials.

9. *Zerumbone*. *Zingiber zerumbet* is a wild ginger commonly found in Asia. It has been used as a traditional herbal medicine to treat various diseases for a long time. A major bioactive component isolated from *Zingiber zerumbet* is zerumbone, which is a natural cyclic sesquiterpene known to possess numerous biologic activities. Zerumbone was reported to have therapeutic potential in the context of atherosclerosis. In vitro experiments showed that zerumbone (5 and 10 μM) suppressed the SR-A and CD36 mRNA expression via regulating AP-1 and NF- κ B repression, leading to a blockade of acLDL uptake in THP-1 macrophages (Eguchi et al., 2007). Furthermore, THP-1 macrophages treated with zerumbone (10–100 μM) showed a significant reduction in the cholesterol levels via upregulation of mRNA and protein levels of ABCA1, but not ABCG1, coupled with the enhanced phosphorylation of ERK1/2 (Zhu and Liu, 2015). The consensus regarding the beneficial effects of zerumbone is strongly supported by experiments conducting in a cholesterol-fed rabbit model, which displayed that zerumbone (8–20 mg/kg) could prevent the development of atherosclerotic lesions (Hemn et al., 2013, 2015).

C. Phenolic Compounds

1. *Gallotannin*. 1,2,3,4,6-Penta-*O*-galloyl- β -D-glucose (PGG) is a prodrug of gallotannin, which is present in diverse medicinal herbs. Zhao et al. (2015) found that PGG (2.5 and 5 μM) induced cholesterol efflux in oxLDL-stimulated J774A.1 and THP-1 macrophages by increasing SR-BI/ABCA1 expression, indicating that PGG has the potential to be further studied for promoting RCT and conferring atheroprotective effects.

2. *Curcumin*. Curcumin is a potent antioxidant present in *Curcuma longa* (turmeric or Jiang Huang) that has been demonstrated to confer protection against atherosclerosis in ApoE $^{-/-}$ (Zhao et al., 2012) and LDLR $^{-/-}$ mice (Hasan et al., 2014). It has been shown that curcumin and other bioactive phenolic compounds from turmeric have powerful bioactivities, including antioxidation associated with preventing lipid peroxidation (Ramirez Bosca et al., 1997). Curcumin was also used as a tool compound for inhibiting histone methyltransferase p300, c-Jun N-terminal kinases (JNK), and transcriptional factor AP-1 (Li et al., 2004b; Lee et al.,

2009b; Huwait et al., 2011). By modifying AP-1, curcumin inhibited the resistin-induced dysregulation of SR-A, CD36, and ABCA1 (Lee et al., 2009b). In 2012, Zhao et al. (2012) systematically analyzed the effects of curcumin on macrophage-derived foam cell formation. The authors observed that curcumin (20 and 40 μ M) significantly ameliorated lipid accumulation in J774.A1 macrophages induced by oxLDL by both decreasing the SR-A-dependent oxLDL uptake and increasing the ABCA1-dependent cholesterol efflux, without significant effect on other cholesterol transporters. Mechanistic experiments indicate that curcumin reduces SR-A expression via a ubiquitin/proteasome pathway. Furthermore, curcumin upregulated ABCA1 expression via LXR α -dependent transcriptional regulation (Zhao et al., 2012). Additional mechanisms, such as an activation of the AMPK/Sirt1/LXR α (Lin et al., 2015c) and the Nrf2/HO-1 pathway (Kou et al., 2013) and inhibition of the p38MAPK pathway (Min et al., 2013) were also involved in its effects. These concerted mechanisms together contribute to the inhibitory effect on foam cell formation mediated by curcumin. Recently, several curcumin derivatives, such as demethoxycurcumin (50 μ M) (Kou et al., 2013) and nicotinate-curcumin (10 μ M) (Gu et al., 2016), have also been shown to inhibit THP-1 macrophage-derived foam cell formation. In addition, curcumin functions as an inhibitor of PCSK9 and upregulates hepatic LDLR expression (Tai et al., 2014).

More importantly, curcumin (500–1000 mg/kg diet) attenuated the atherosclerosis development in ApoE $^{-/-}$ mice by reducing the SR-A expression and increasing the ABCA1 expression in vivo (Hasan et al., 2014). The inhibitory activity against foam cell formation and the antiatherosclerotic effects of curcumin were also confirmed by several other studies (Kou et al., 2013; Min et al., 2013; Lin et al., 2015c; Soltani et al., 2017). Interestingly, curcumin lowered the level of LDL-C and TG in patients at risk for CVD (Qin et al., 2017). Therapeutic efficacy and molecular targets of curcumin in cardiovascular diseases have been reviewed elsewhere (Li et al., 2019).

3. Danshensu. Danshensu is an active component isolated from an eminent Chinese medicinal herb *Salvia miltiorrhiza* (Danshen), which is known for improving blood microcirculation. Danshen is widely used in China and other countries for treating various cardiovascular disorders, including atherosclerosis, angina pectoris, and myocardial infarction, due to potent anti-inflammatory, antioxidative, and lipid-lowering effects (Xu and Liu, 2013). It was shown that danshensu suppressed the LPS- and oxLDL-induced lipid accumulation in RAW 264.7 macrophages at the concentrations of 5–20 μ M by activating LXR and inhibiting NF- κ B, as well as the LPS-induced expression of fatty acid binding protein 4 and perilipin-2 (Xie et al., 2011; Wang et al., 2017c). Further studies also showed that danshensu (1–10 μ M) prevented cholesterol accumulation and foam

cell formation in RAW264.7 mouse macrophages by inhibiting CD36-mediated lipid uptake, while enhancing ABCA1 (G1)-mediated cholesterol efflux (Wang et al., 2010b; Gao et al., 2016). In addition, danshensu could improve dyslipidemia by decreasing the levels of LDL-C and fatty acid by inhibiting HMG-CoA reductase and fatty acid synthase expression (Yang et al., 2011).

An earlier in vivo study has revealed that danshensu (67.5 mg/kg body weight per day) attenuated high methionine-rich diet-induced accumulation of foam cells in rat aortic endothelium by suppressing the expression of TNF- α and intercellular adhesion molecule 1 (ICAM1) (Yang et al., 2010). Furthermore, Danshensu Bingpian Zhi (20 and 40 mg/kg body weight), which has the main bioactive constituent Danshensu, attenuated atherosclerosis in ApoE $^{-/-}$ mice.

4. 6-Dihydroparadol. Ginger (*Zingiber officinale*) is a common food-derived health supplement, used worldwide due to its potential preventive effects in multiple diseases, including atherosclerosis and other inflammatory disorders (Aktan et al., 2006). Gingerols are the main bioactive compounds from ginger with potent anti-inflammatory properties in cultured cells. 6-Dihydroparadol, a bioactive metabolite of gingerols, displayed potent anti-inflammatory effects by blocking the NF- κ B/inducible NO synthase/NO pathway in LPS-stimulated macrophages (Aktan et al., 2006). 6-Dihydroparadol (30 μ M) was recently shown to promote cholesterol efflux from human THP-1 macrophages by increasing the expression of ABCA1 and ABCG1 via preventing the proteasome-dependent protein degradation, underscoring its therapeutic potential in preventing foam cell formation and possibly atherosclerosis (Wang et al., 2018a).

5. Paeonol. Paeonol is a bioactive phenolic compound isolated from traditional Chinese medicine *Paeonia suffruticosa* (Cortex Moutan), which is commonly used to treat inflammatory disorders including atherosclerosis (Zhao et al., 2013b). The antiatherosclerotic effects of paeonol have been well documented in several experimental animal models of atherosclerosis, including rabbits (Shi et al., 1988; Li et al., 2009a), quails (Dai et al., 1999), and ApoE $^{-/-}$ mice (Zhao et al., 2013b; Li et al., 2015c). Four major antiatherosclerotic mechanisms of paeonol include 1) endothelial protection (reducing monocyte adhesion to inflamed endothelium, endothelial apoptosis, and senescence) (Nizamutdinova et al., 2007; Pan and Dai, 2009; Wang et al., 2012d; Bao et al., 2013; Chen et al., 2013; Jamal et al., 2014; Liu et al., 2014b; Yuan et al., 2016); 2) inhibiting the proliferation and migration of VSMC (Chen et al., 2014; Hu et al., 2016a); 3) antiplatelet activation (Shi et al., 1988); and 4) anti-foam cell formation (Zhao et al., 2013b; Li et al., 2015c).

Studies performed in isolated macrophages from ApoE $^{-/-}$ mice treated with paeonol (50 and 100 μ g/ml) showed that it significantly reduced the oxLDL-induced

lipid accumulation, probably by promoting cholesterol efflux via activating the LXR α /ABCA1 pathway, which was suggested by study in J774.A1 macrophages (Zhao et al., 2013b). Silencing ABCA1 or LXR α abolished the paeonol-induced effects on cholesterol efflux and lipid accumulation, supporting the indispensable effect of LXR α and ABCA1 in mediating the protective effects. The inhibition of foam cell formation and antiatherosclerotic effects of paeonol were reproduced by another independent group, who confirmed the ABCA1-activating effects of this compound (5, 10 and 50 μ M) in RAW264.7 macrophages and suggested that the anti-foam cell formation effects of paeonol also depended on CD36 inhibition and activation of HO-1 (Li et al., 2015c).

More importantly, paeonol treatment led to reduced atherosclerotic lesions formation and attenuated systemic inflammation, as well as increased ABCA1 expression in ApoE $^{-/-}$ mice (Zhao et al., 2013b). In addition to effects mentioned above, paeonol also reduced the levels of malondialdehyde and oxidized LDL in hyperlipidemia rats (Dai et al., 2000).

6. Polydatin. Polydatin represents one of the major bioactive ingredients from *Rhizoma Polygoni Cuspidati* (Da Huang), an eminent Chinese medicinal herb, which dispels dampness, alleviates jaundice, reduces fever, subsides toxins, and removes stasis (Du et al., 2009; Deng et al., 2011; Liu et al., 2012b; Ma et al., 2016; Gugliandolo et al., 2017). Pharmacological studies in the past decade have shown that polydatin exhibits a broad range of bioactivities with cardiovascular relevance, including antioxidation, anti-inflammation, cardioprotection, blood vessel dilation, lipid-lowering effect, as well as inhibitory effects on platelet aggregation, monocyte adhesion to activated endothelium, thrombus formation, and atherosclerosis development (Du et al., 2009; Deng et al., 2011; Liu et al., 2012b; Ma et al., 2016; Gugliandolo et al., 2017). The preventive effects of polydatin on foam cell formation were reported recently (Wu et al., 2015b). Polydatin treatment of 48 hours reduced the level of TC, FC, and CE, together with reducing the secretion of TNF- α and IL-1 β in oxLDL-stimulated ApoE $^{-/-}$ mouse macrophages. The mechanism of these effects is linked to the activation of PPAR γ -dependent ABCA1 upregulation and the decrease of CD36 expression (Wu et al., 2015b). Polydatin also improved dyslipidemia via suppressing PCSK9 and upregulating hepatic LDLR expression (Li et al., 2018a).

7. Protocatechuic Acid. Protocatechuic acid (PCA) is a bioactive compound present in some medicinal herbs such as Danshen (Li et al., 2018d)). It is a major metabolite of fruit/vegetable-derived anthocyanins (such as C3G) generated by gut microflora (Hidalgo et al., 2012; Wang et al., 2012a; Lin et al., 2015b). Consumption of the PCA-rich vegetable chicory (5 g/kg diet) reduced the TC and CE accumulation in isolated macrophages via upregulation of the ABCA1/ABCG1-mediated cholesterol efflux

(Lin et al., 2015b). Because of the fact that PCA is the major component of chicory, a later study found that PCA, rather than its parent drug C3G, promoted the ABCA1 (G1)-dependent cholesterol efflux from macrophages. miRNA microarray assay elucidated that PCA reduced the miRNA-10b expression, thereby upregulating the expression of ABCA1 (G1) in MPMs (Wang et al., 2012a). Protocatechuic acid could also regulate lipid metabolism via suppressing the expression of HMG-CoA reductase (Liu et al., 2010b). In in vivo study, C3G (50 mg/kg body weight) induced RCT in the ApoE $^{-/-}$ mice model and the atheroregression could be inhibited by antibiotic treatment, suggesting that the atheroprotective effect of C3G is gut microbiota dependent (Wang et al., 2012a).

In addition to influence of cholesterol metabolism, PCA (10, 20, and 40 μ g/ml) was also shown to inhibit ICAM1 and vascular cell adhesion molecule 1 (VCAM-1)-dependent monocyte adhesion to activated HUVECs, as well as CCL2-mediated monocyte transmigration, thereby reducing the development of atherosclerosis in ApoE $^{-/-}$ mice at the dose of 0.03 g/kg (Wang et al., 2010a, 2011; Stumpf et al., 2013). PCA (150 μ g/ml) also exhibited inhibitory effects on VSMC proliferation in A7r5 smooth muscle cell line (induced by oleic acid) by activating AMPK and arresting cell cycle at G $_0$ /G $_1$ phase (Lin et al., 2015a). Also, PCA increased the endothelium-dependent vasorelaxation as well as tetrahydrobiopterin levels and combated eNOS uncoupling (Liu et al., 2016b).

8. Salicylic Acid. Aspirin (acetyl salicylic acid) is an anti-inflammatory drug used as a cardiovascular therapeutic. It (600 and 1200 μ M) upregulated the expression of ABCA1 and SR-BI, thereby stimulating the HDL-mediated cholesterol efflux in THP-1 macrophages (Viñals et al., 2005; Lu et al., 2010). In light of the key role of AMPK in regulating lipid and energy metabolism, Fullerton et al. (2015) explored whether AMPK was involved in the induction of ABCA1 and ABCG1 expression by aspirin. The authors observed that AMPK β 1 deletion significantly impaired cholesterol efflux, without affecting lipid uptake in macrophages. Moreover, the AMPK activation by salicylate (salts and esters of salicylic acid) prevented foam cell formation via promoting HDL and ApoA-1-mediated cholesterol efflux by increasing the ABCA1 and ABCG1 expression in BMDMs. However, the preventive effect of salicylate was reduced in AMPK β 1-deficient BMDMs, indicating that the effect of salicylate on cholesterol efflux and foam cell formation is dependent on AMPK (Fullerton et al., 2015). Another study confirmed this result and observed that a low-dose of aspirin (<0.5 mM) also upregulates the ABCA1-dependent cholesterol efflux via activating the PPAR α pathway, which provides additional insights to explain the cardiovascular actions of aspirin (Wang et al., 2010e). In addition, aspirin attenuated atherosclerosis in ApoE $^{-/-}$ mice partly by suppressing systemic

inflammation and promoting inflammation resolution (Petri et al., 2017).

9. Salvianolic Acid B. Salvianolic acid B is a major hydrophilic constituent from Danshen, which has been demonstrated to exhibit antiatherosclerotic effects in a model of neointimal hyperplasia in rabbits (Yang et al., 2011) and in ApoE^{-/-} mice (Chen et al., 2006; Lin et al., 2007). Salvianolic acid B has shown to inhibit lipid peroxidation (LDL oxidation) (Yang et al., 2011) and activate AMPK (Cho et al., 2008). A high-throughput screening assay identified salvianolic acid B (15 and 30 μ M) as an effective CD36 antagonist that blocks the oxLDL uptake in RAW264.7 macrophages (Wang et al., 2010b). Further follow up studies showed that salvianolic acid B directly bound to CD36 ($K_d = 3.74 \mu$ M) and inhibited the CD36 expression. By doing so, salvianolic acid B (1, 10, and 100 μ M) reduced the CD36-dependent lipid uptake and foam cell formation in mouse macrophages, as well as in PMA-stimulated THP-1 human macrophages (Bao et al., 2012). Salvianolic acid B has been reported to promote the HDL- and ApoA1-mediated cholesterol efflux in differentiated THP-1 macrophages via inducing the expression of ABCA1 (Yue et al., 2015). Further mechanistic studies showed that the upregulation of ABCA1, promoted by salvianolic acid B (1 and 10 μ M), was reversed by PPAR γ and LXR α inhibitors. This evidence indicates that salvianolic acid B reduces lipid accumulation by promoting cholesterol efflux via a PPAR γ /LXR α /ABCA1-dependent pathway in THP-1 macrophages (Yue et al., 2015).

10. Sesamol. Sesamol is an essential bioactive compound of sesame oil (*Sesamum indicum*), which is a cardiovascular protective dietary supplement. Previous studies have shown that a sesame oil aqueous extract (0.75 mg/mouse per day) prevented or regressed atherosclerosis in LDLR^{-/-} mice (Narasimhulu et al., 2018) and sesamol derivative (INV-403) (20 mg/kg per day) played a positive role in hyperlipidemic rabbits fed with an atherogenic diet (Ying et al., 2011). Mechanistic studies showed that both sesame oil and sesame oil aqueous extract slightly increased the ABCA1 expression, while decreasing the mRNA expression of CD36, CD68, SR-A, and LOX-1 in the aortic arch segments of LDLR^{-/-} mice model (Narasimhulu et al., 2018).

Furthermore, it is possible that sesamol is mainly responsible for the observed atheroprotective effects of sesame oil. A recent study identified that both sesamol (25–100 μ M) and sesame oil (1–10 μ g/ml) increase the expression/activity of PPAR γ and LXR α in Chinese hamster ovary cells via an MAPK-dependent mechanism. Most importantly, sesamol and sesame oil boosted cholesterol efflux from MPM (Majdalawieh and Ro, 2015). This evidence, together with a previous report showing that sesamol (10, 30, and 100 μ M) suppressed inflammatory response in LPS-stimulated RAW264.7 mouse macrophages (via AMPK-dependent NF- κ B suppression) (Wu et al., 2015d), collectively

indicates that sesamol has the potential to reduce foam cell formation and atherogenesis (Majdalawieh and Ro, 2015).

11. Resveratrol. Resveratrol is a major stilbenoid compound isolated from red wine. Resveratrol displays reproducible antiatherosclerotic effects in several animal models, including ApoE^{-/-} mice (Do et al., 2008; Chang et al., 2015), ApoE*3-Leiden CETP mice (Bebbée et al., 2013), and ApoE^{-/-}/LDLR^{-/-} mice (Fukao et al., 2004). The atheroprotective mechanisms of resveratrol include inhibition of LDL oxidation (Berrougui et al., 2009), enhancement of endothelial protection, decrease of TMAO via gut microbiota (Chen et al., 2016), inhibition of the proliferation and migration of VSMCs, monocyte/macrophage differentiation, and platelet activation (Vasamsetti et al., 2016). It was reported that resveratrol (2.5 μ M) reduced the LPS-induced RAW264.7 foam cell formation via attenuating the NADPH oxidase 1 (Nox1)-dependent ROS production and MCP1 expression via Akt/Foxo3a and AMPK/Sirt1 pathways (Park et al., 2009a; Dong et al., 2014). Follow up studies in human macrophages identified that resveratrol at the concentrations of 10 or 100 μ M reduced oxLDL uptake in THP-1 macrophages (Voloshyna et al., 2013). Resveratrol promoted ApoA1- and HDL-mediated cholesterol efflux in both mouse (RAW264.7, J774.A1, MPMs) and human macrophages (THP-1) by increasing the expression of ABCA1 (Berrougui et al., 2009; Allen and Graham, 2012) and ABCG1 via PPAR γ /LXR α and adenosine 2A receptor pathway (Voloshyna et al., 2013). In addition to the therapeutic effects in foam cell formation induced by oxLDL, resveratrol (10 μ M) also ameliorated foam cell formation in J774.A1 macrophages caused by *Chlamydia pneumonia* infection by inhibiting the synthesis of IL-17A (Di Pietro et al., 2013). Clinical studies have shown that resveratrol lowers the level of TC and TG in patients with dyslipidemia (Simental-Mendia and Guerrero-Romero, 2019). Resveratrol also regulated lipid metabolism via inhibiting cholesterol-ester-transport protein and HMG-CoA expression/level (Cho et al., 2008).

12. Epigallocatechin Gallate. EGCG is the most studied polyphenol (catechin), derived from tea and possessing antiatherosclerotic and plaque-stabilizing effects in rats, rabbits, and ApoE^{-/-} mice (Chyu et al., 2004; Xu et al., 2014a; Wang et al., 2018e,f). Previous studies have shown that EGCG (25 μ M) attenuated the oxLDL-induced apoptosis of HUVECs by blocking JNK activation (Choi et al., 2008). Furthermore, EGCG (40 and 80 μ g/ml) reversed the TNF- α -induced ABCA1 downregulation and reduced the cholesterol efflux from THP-1 macrophages by activating the Nrf2-dependent NF- κ B inhibitory effects (Jiang et al., 2012). In the same cell line, EGCG (10 μ M) also blocked the oxLDL-induced upregulation of SR-A, thus blocking the oxLDL uptake and foam cell formation (Chen et al., 2017). Mechanistic studies also showed that EGCG is having a preventing

action on hyperlipidemia by increasing the expression and activity of LDLR (Lee et al., 2008).

D. Phenylpropanoids

Phenylpropanoids are diverse natural aromatic products comprising a hydroxy- and/or alkoxy-substituted aromatic phenyl moiety and a three-carbon propene tail of coumaric acid, and the key intermediate in the biosynthesis of phenylpropanoid-derived plant compounds (Barros et al., 2016). These compounds have a wide variety of biologic activities, including antimicrobial, antitumor, anti-inflammatory activities, and a cholesterol-lowering effect (Okonkwo et al., 2016).

1. *Lignans*. Lignans represent a class of natural polyphenols, which are dimers derived from two molecules of a phenylpropanoid derivative (a C6-C3 monomer). They are present in flaxseed, sesame, soybeans, and some fruits. By acting as phytoestrogens, dietary lignans exhibit potent antiviral, antioxidative, antitumor, and antiatherosclerotic activities (Peterson et al., 2010).

a. *Arctigenin*. Arctigenin, a phenylpropanoid dibenzylbutyrolactone lignin, has many beneficial biologic effects, such as immune modulation and regulation of metabolic disorders (Huang et al., 2012a; He et al., 2018). In oxLDL-loaded THP-1 macrophages, the expression of ApoE, ABCA1, and ABCG1 were increased by arctigenin (50 and 100 μ M), resulting in promoting cholesterol efflux (Xu et al., 2013d). Arctigenin has no obvious effects on the expression of SRs, such as SR-BI, SR-A1, and CD36 (Xu et al., 2013d). Further studies indicated that arctigenin (200 mg/kg body weight per day) decreased the cholesterol levels without altering serum TG and adiponectin levels in mice (Huang et al., 2012a), and suppressed the lipid accumulation and body weight gain in HFD-induced obese mice (Han et al., 2016).

b. *Leoligin*. Leoligin, the major lignan of the alpine flower Edelweiss (*Leontopodium alpinum* Cass.), has shown obvious antihyperplastic effects and regulatory activity of lipoprotein metabolism through interference with CETP (Reisinger et al., 2009; Duwensee et al., 2011). Recently, it was reported that leoligin reduced LDL-C levels and postprandial serum glucose peaks due to the direct inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase and moderated PPAR γ agonistic activity in ApoE $^{-/-}$ mice (Scharinger et al., 2016). Additionally, it (3–20 μ M) increased cholesterol efflux from THP-1 macrophages by upregulating both protein and mRNA levels of the ABCA1 and ABCG1 (Wang et al., 2016a). These novel activities suggest that leoligin may be of promise to be further studied as a therapeutic agent for preventing the formation of foam cells.

c. *Sesamin*. Sesamin is a phytochemical that possesses diverse bioactivities, such as prevention of fat storage, decrease of cholesterol in serum, anti-inflammatory, and antioxidative activities (Lee et al.,

2009c; Røgi et al., 2011). It was shown that sesamin (0.1, 1, and 10 μ M) inhibited the oxLDL-induced cholesterol accumulation and enhanced cholesterol efflux from RAW264.7 macrophages, possibly via an upregulation of PPAR γ , LXR α , and ABCG1 (Liu et al., 2014a). This study also indicated that PPAR γ played an essential role in sesamin-mediated cholesterol efflux, since a PPAR γ antagonist (GW9662) could abolish the cholesterol efflux-promoting effect of sesamin. Furthermore, sesamin increased the PPAR γ and LXR α transcriptional activity in a concentration- and time-dependent manner via MAPK signaling (Majdalawieh and Ro, 2014). In vivo studies showed that sesamin attenuated atherosclerosis in ApoE $^{-/-}$ mice by suppressing vascular inflammation (Wu et al., 2010). The lipid-lowering effect of sesamin was exerted through promoting the fecal excretion of sterols and inhibiting HMG-CoA reductase (Liang et al., 2015).

d. *Honokiol*. Honokiol is a biphenolic natural product, which is present in the traditional Chinese herbal medicine Magnolia bark. During the last decades, Magnolia bark has been used as an analgesic to treat anxiety and mood disorders (Lee et al., 2011; Sarris et al., 2013). With more and more biologic activities being discovered, this neolignan is also being extensively studied for its therapeutic potential in atherosclerosis. It was found that honokiol (30 μ M) was capable of activating the RXR/LXR heterodimer in RAW264.7 cells, resulting in the induction of ABCA1 expression and enhancement of cholesterol efflux from MPMs (Kotani et al., 2010). Consistent with these data, another study showed that honokiol increased ABCA1 expression by binding to RXR β . It also increased the ABCG1 and ApoE expression in THP-1 macrophages (Jung et al., 2010). Honokiol and the structurally related neolignan magnolol have also been characterized as dual ligands for the transcriptional activity of the RXR/PPAR γ dimer (Fakhrudin et al., 2010; Atanasov et al., 2013; Wang et al., 2014b). It has been also shown that hepatic PPAR γ and its target genes could be upregulated by this neolignan at 10 μ M (Zhong and Liu, 2018).

2. *α -Asarone*. As a major active constituent of *Acorus tatarinowii* Schott, α -asarone exhibits a wide range of bioactivities. It was observed that purple perilla extract with α -asarone increased the expression of ABCA1 and ABCG1 and accelerated the cholesterol efflux from lipid-loaded J774A.1 macrophages. It also enhanced the expression of LXR α and PPAR γ in vitro (Park et al., 2015). These data indicated that α -asarone promoted the macrophage cholesterol efflux through the PPAR γ -LXR α -ABC transporters pathway.

In terms of lipid metabolism, a previous study has shown that there is an association between the intake of α -asarone (80 mg/kg body weight per day) and the decreased level of serum cholesterol in hypercholesterolemic rats by inhibition of HMG-CoA reductase (Rodríguez-Páez

et al., 2003). Another animal study revealed that 2,4,5-trimethoxycinnamic acid, the major and nontoxic metabolite of α -asarone, had most of the pharmacological properties of α -asarone. Both compounds lowered TC, LDL-C, and HDL-C in hypercholesterolemic rats (Antunez-Solis et al., 2009).

3. Chlorogenic Acid. Chlorogenic acid, a naturally occurring phenolic acid present in coffee, as well as in the leaves and fruits of diverse dicotyledonous plants, acts as an important intermediate of lignin biosynthesis. Chlorogenic acid exhibited various effects, like antioxidative activity and modulation of blood glucose and cholesterol metabolism (Rodriguez de Sotillo and Hadley, 2002; Tošović et al., 2017). In vivo, it reduced (at 200 and 400 mg/kg body weight per day) the percentage and the total atherosclerotic lesion area and aortic dilatation in cholesterol-rich diet-fed ApoE^{-/-} mice, as well as decreased levels of TC, LDL-C, and TG in serum (Wu et al., 2014).

Recent reports suggested that chlorogenic acid also displays a modulatory effect on foam cell formation. Chlorogenic acid (1 and 10 μ M) inhibited foam cell formation and decreased the oxLDL-elicited neutral lipid and cholesterol accumulation in RAW264.7 macrophages via increasing the transcription of PPAR γ , LXR α , ABCA1, and ABCG1 (Wu et al., 2014). Interestingly, the serum containing chlorogenic acid metabolites inhibited the oxLDL-induced lipid accumulation and increased the cholesterol efflux in RAW264.7 cells. Furthermore, five serum metabolites of chlorogenic acid were tested and the results showed that caffeic, ferulic, and gallic acids significantly increased the HDL-mediated cholesterol efflux from RAW264.7 cells (Wu et al., 2014). These data suggest that these metabolites might be potential bioactive compound, accounting for the in vivo effect of chlorogenic acid. In addition, it is likely that other mechanisms are involved in the lipid regulation by this natural product. In this line, it was reported that chlorogenic acid (30 μ M) promoted the efflux of TC and triacylglycerol and increased mRNA expression of ABCA1, CYP7A1, and AMPK α 2 in HepG2 cells (Hao et al., 2016).

4. Caffeic and Ferulic Acid. Caffeic acid is a well-known phenolic phytochemical present in coffee and diverse other plants, since it represents a key intermediate in the biosynthesis of lignin. The closely related ferulic acid is a hydroxycinnamic acid formed by the conversion of caffeic acid and it is also present in the cell walls of diverse plants. Both caffeic acid and ferulic acid exhibit anticancer, antioxidative, and diverse other biologic activities (Sato et al., 2011; Rosendahl et al., 2015). Both compounds are being extensively studied for their potential benefits in various disorders, such as inflammation, neurodegenerative diseases, cancer, CVDs, and atherosclerosis (Zhao and Moghadasian, 2008).

It was reported that caffeic and ferulic acid, the major phenolic acids of coffee, enhanced HDL-mediated cholesterol efflux, but not the ApoA-1-mediated efflux in THP-1 macrophages. Both compounds (1 μ M) increased the expression of ABCG1 and SR-BI, but not ABCA1 (Uto-Kondo et al., 2010). Further experiments showed that caffeic acid was identified as a PPAR α agonist in vitro (Kim et al., 2014). As a metabolite of chlorogenic acid, ferulic acid (0.25, 0.5, and 1 μ M) has also been shown to have an enhancement effect on HDL-mediated cholesterol efflux from macrophages through increasing the expression of ABCG1 and SR-BI (Uto-Kondo et al., 2010). Furthermore, it was demonstrated that ferulic acid (1 μ M) displays antiatherosclerotic potential by increasing the ABCA1 and ABCG1 expression in macrophage foam cells and further promoting cholesterol efflux (Chen and Wang, 2015). In this light, counteraction of foam cell formation can be also considered in relation to the potential antiatherogenic properties of phenylpropanoids, in addition to their antioxidative/anti-inflammatory functions.

E. Alkaloids

1. Arecoline. Arecoline is a nicotinic acid-based bioactive alkaloid isolated from areca nut, which has a medicinal potential in the treatment of neurodegenerative diseases (Ghelardini et al., 2001). Cardiovascular benefits of arecoline are largely unknown. In oxLDL-stimulated macrophages, arecoline reduced the cholesterol accumulation in a dose-dependent manner by reducing TC, FC, and CE. In addition, arecoline also promoted the cholesterol efflux by inducing ABCA1 expression. Further studies were warranted to evaluate the effects of arecoline on lipid uptake in RAW264.7 macrophage and its therapeutic effect on atherosclerosis in vivo (Ouyang et al., 2012). In vivo study showed that arecoline suppressed atherosclerosis in ApoE^{-/-} mice by inhibiting NF- κ B activation (Zhou et al., 2014).

2. Berberine. Berberine is a bioactive alkaloid isolated from several medicinal plants, including Berberis (Huang Lian). Berberine-containing plants have been used in China for a long time to treat various disorders, including CVD (Feng et al., 2019). Berberine protects against atherosclerosis in various animal models due to its lipid-modulating effects. Two well-elucidated molecular targets of berberine in modulating lipid levels are LDLR (Kong et al., 2004) and proprotein convertase subtilisin/kexin type 9 (PCSK9) (Dong et al., 2015). In 2010, Lee et al. (2010) observed that berberine (5, 10, and 20 μ M) inhibited THP-1 macrophage foam cell formation by promoting LXR α /ABCA1-dependent cholesterol efflux. However, berberine did not affect ABCG1, SR-BI, CD36, and SR-A. Further studies indicate that berberine (5 and 10 mg/l) also prevented the oxLDL-induced upregulation of LOX-1 and downregulation of SR-BI in THP-1 macrophages, without affecting the SR-A and ABCA1 expression (Guan et al., 2010;

Chi et al., 2014a). In addition, several derivatives of berberine, such as 13-hexylberberine (Li et al., 2010), were shown to act as potential CD36 inhibitors. Possible inhibition of foam cell formation and antiatherosclerotic potential of these derivatives needs to be further evaluated in vitro and in vivo. Other mechanisms linked to the effect of berberine on foam cell formation include activation of AMPK/Sirt1 (Chi et al., 2014b), autophagy induction (Kou et al., 2017), as well as inhibition of adipocyte enhancer-binding protein 1 (Huang et al., 2012b).

However, a contradictory study reported that berberine (5 mg/kg per day) unexpectedly promoted atherosclerosis in mice by enhancing the SR-A-mediated oxLDL uptake and foam cell formation in human and mouse macrophages (Li et al., 2009b). Mechanistic studies revealed that berberine-mediated SR-A upregulation was exerted through suppressing the phosphatase and tensin homolog expression, thus promoting the activation of Akt in RAW264.7 macrophages (Li et al., 2009b). The discrepancy of the atherosclerosis-modulating effects of berberine may be due to different animal models and doses, which were used in these studies. Despite most of the literature indicating that berberine has beneficial effects in cardiovascular and metabolic diseases, the precise effects and mechanisms of berberine action in the modulation of foam cell formation need to be further evaluated. In patients with dyslipidemia, berberine reduces TC, LDL-C, TG and increases HDL-C, partially through inhibiting PCSK9 and increasing LDLR expression/activity (Kong et al., 2004; Cameron et al., 2008; Ju et al., 2018).

3. Piperine. Piperine is a biologically active ingredient isolated from the fruits of black pepper (*Piper nigrum*). It has been shown that piperine (100 $\mu\text{g/ml}$) decreases cholesterol uptake dose dependently in Caco-2 cells by reducing the levels of the membrane localized cholesterol transporter protein-Niemann-Pick disease, type C1 (NPC1) like intracellular cholesterol transporter 1 (NPC1L1) and SR-BI (Duangjai et al., 2013). More recently, piperine (25, 50, and 100 μM) was also found to promote the ABCA1 protein expression in THP-1-differentiated human macrophages, without affecting the ABCG1 and SR-BI expression (Wang et al., 2017d). Further studies revealed that piperine did not affect the gene expression of ABCA1, but increased the ABCA1 protein stability by preventing calpain-mediated ABCA1 protein degradation (Wang et al., 2017d). In addition, piperine regulated lipid metabolism via increasing hepatic LDLR expression via proteolytic activation of SREBPs in HepG2 cells (Ochiai et al., 2015). These pharmacological effects placed piperine as a promising food-derived bioactive compound with potential therapeutic implications in atherosclerosis.

4. Rutaecarpine. Rutaecarpine (or rutecarpine) is a nonbasic alkaloid isolated from the unripe fruits of the medicinal herb *Evodia rutaecarpa* (Wu Zhu Yu), which

has been used in treating cardiovascular and cerebrovascular diseases (Tian et al., 2019b). A high-throughput screening assay for ABCA1 upregulators identified rutaecarpine as a potential active compound that increased the ABCA1 promoter activity in HepG2 cells ($\text{EC}_{50} = 0.27 \mu\text{M}$) (Xu et al., 2014b). Further studies showed that rutaecarpine upregulated the expression of ABCA1 and SR-BI (without affecting ABCG1 and CD36) via LXR α and LXR β , thereby reducing the lipid accumulation and foam cell formation via promoting cholesterol efflux in vitro (RAW264.7 macrophages and HepG2 cells) and in vivo (ApoE $^{-/-}$ mouse). By this mechanism, rutaecarpine (20 mg/kg body weight per day) reduced atherosclerotic plaque development in ApoE $^{-/-}$ mice. The atheroprotective effects of rutaecarpine are accompanied by reduced macrophage and lipid content in atherosclerotic plaques (Xu et al., 2014b). Rutaecarpine lowered the level of TC, TG, LDL-C, and hs-CRP in hyperlipidemic and hyperglycemic rats via AMPK activation and NF- κB inhibition (Nie et al., 2016; Tian et al., 2019b). Several derivatives of rutaecarpine also exhibited antiatherosclerotic potential by enhancing cholesterol efflux from RAW264.7 macrophages to HDL and thus inhibiting foam cell formation (Li et al., 2014).

5. Evodiamine. Evodiamine, an indoloquinazoline alkaloid, is present in the traditional Chinese medicine *Fructus Evodiae* (Chinese name: Wuzhuyu) (Shoji et al., 1986; Wagner et al., 2011). Evodiamine (3–20 μM) increased cholesterol efflux from THP-1-derived human macrophages significantly by directly binding to ABCA1 and thereby increasing ABCA1 stability and protein level (Wang et al., 2018c). Moreover, treatment of evodiamine (10 mg/kg body weight) for 4 weeks decreased the size of atherosclerotic lesions and alleviated the hyperlipidemia, as well as hepatic macrovesicular steatosis in ApoE $^{-/-}$ mice, probably through transient receptor potential vanilloid type 1 (TRPV1) pathway (Su et al., 2014).

6. Leonurine. Leonurine is an anti-inflammatory, antioxidative, and antiatherosclerotic pseudoalkaloid isolated from *Herba leonuri* (Jiang et al., 2017a). Recently, Jiang et al. (2017a) have demonstrated that leonurine (5–80 μM) dose dependently inhibited the lipid accumulation (TC, FC, and CE) and foam cell formation in oxLDL-stimulated THP-1 macrophages. Mechanistic investigations indicated that leonurine inhibited foam cell formation by promoting ApoA-1- and HDL-mediated cholesterol efflux via the PPAR γ /LXR α /ABCA1 (G1) pathway (Jiang et al., 2017a). In this line, leonurine also increased the expression of key proteins in cholesterol efflux, including PPAR γ , LXR α , ABCA1 (G1), and reduced atherosclerotic development in ApoE $^{-/-}$ mice fed with an atherogenic diet (10 mg/kg body weight per day). More studies are warranted to study potential effects of leonurine on suppressing lipid uptake and the related mechanisms.

F. Steroids

1. Diosgenin. Diosgenin and its glycoside form dioscin are pharmacologically active steroidal saponin present in *Dioscorea* plant species. Both diosgenin and dioscin have been shown to exhibit antioxidative, hypolipidemic, antithrombotic, and endothelial-protective effects (Son et al., 2007; Gong et al., 2011; Liu et al., 2012a; Lv et al., 2015; Wu et al., 2015c; Wang et al., 2017g). Due to their structural similarity to cholesterol, diosgenin and dioscin were used in industrial production of steroidal drugs and are known to be increasing cholesterol secretion as well as inhibiting cholesterol absorption (Son et al., 2007). Diosgenin displayed antiapoptotic effects against H₂O₂-induced apoptosis (Gong et al., 2010), as well as anti-inflammatory effects in VSMCs by inhibiting the MAPK/Akt/NF- κ B pathway (Choi et al., 2010). Diosgenin (14 μ M) also blocked atherosclerosis by inhibiting the nuclear translocation of notch intracellular domain in THP-1 cells (Binesh et al., 2018). It also inhibited the TNF- α -induced leukocyte adhesion to activated endothelial cells by inhibiting the upregulation of ICAM1, VCAM1, and endothelial lipase (Wu et al., 2015c). In addition, dioscin (1–4 μ M) inhibited oxLDL uptake by blocking systemic inflammation and the LOX-1/NF- κ B pathway in MPMs from atherosclerotic rats (Wang et al., 2017g). Also, diosgenin promoted cholesterol efflux by increasing the ABCA1 expression, independent of LXR α (Lv et al., 2015). The potential mechanism of diosgenin (10–80 μ M) in reducing foam cell formation in THP-1 macrophages as well as in atherogenesis is proposed to be through inhibiting of miRNA-19b (Lv et al., 2015).

2. Fucosterol. Fucosterol is a sterol that is present in marine algae. It has beneficial effects in hypercholesterolemia, due to its activity to reduce LDL-C and increase HDL-C (Hoang et al., 2012). A recent study (Hoang et al., 2012) has shown that fucosterol is a dual LXR α/β agonist that promotes cholesterol efflux from THP-1 macrophages at 100 and 200 μ M, by increasing the expression of efflux transporters-ABCA1, ABCG1, as well as ApoE; meanwhile, it also reduces the intestinal NPC1L1-mediated cholesterol absorption. This is a beneficial effect, as it can avoid the side effects associated with the LXR activation, probably due to upregulating Insig-2a, which is a negative regulator of the lipogenic transcription factor SREBP-1c (Hoang et al., 2012).

3. Panax Notoginseng Saponins. PNS are the major bioactive ingredients of the medicinal herb *P. notoginseng* (Duan et al., 2017). PNS have extensive cardiovascular protective effects, including preventing endothelial dysfunction and increasing blood flow, antioxidation, anti-inflammation, antithrombosis, inhibition of foam cell formation, and regulation of cardiac function (Jia et al., 2010; Yuan et al., 2011). PNS (40 and 80 mg/l) decreased the accumulation of cholesterol esters via increasing the ABCA1 expression in macrophages (Jia

et al., 2010). In vivo study shows that PNS inhibited foam cell formation in zymosan A-induced atherosclerosis rats at the dose of 100 mg/kg per day (Yuan et al., 2011). Recently, ginsenoside Rd, a purified constituent from PNS, also demonstrated antiatherosclerotic effects in ApoE^{−/−} fed with atherogenic diet by attenuating foam cell formation (Li et al., 2011). Mechanistic studies indicated that ginsenoside Rd (20 μ M) blocked SR-A-mediated oxLDL uptake via blocking voltage-independent Ca²⁺ channels in RAW264.7 cells (Li et al., 2011). It remains to be elucidated whether other saponins from PNS have protective effects against foam cell formation and may contribute to the atheroprotective effects of PNS.

4. Vitamin D. Vitamin D deficiency is associated with an increased risk of CVDs, such as hypertension and atherosclerosis (Weng et al., 2013). A landmark study in 2009 showed that deficiency of vitamin D promoted the modified LDL-induced foam cell formation of macrophages from patients with diabetes (Oh et al., 2009). Similarly, deficiency of macrophage vitamin D aggravated CD36 and SR-A-mediated lipid uptake (via JNK activation), as well as promoted insulin resistance to increase atherosclerosis in mice (Oh et al., 2015). Vitamin D deficiency-induced hypertension and atherosclerosis in LDLR^{−/−} mice were reversed by JNK2 deficiency (Oh et al., 2018). A recent study has shown that vitamin D deficiency decreased the HDL level and LXR/ABCA1(G1) expression, thus augmenting cholesterol accumulation and atherosclerosis in hypercholesterolemic microswine (Yin et al., 2015). On the other side, vitamin D supplementation inhibited the CD36 and SR-A-mediated lipid (oxLDL and ac-LDL) uptake and promoted the nascent HDL generation in HepG2 cells via ABCA1-dependent cholesterol efflux. The final outcome of these effects is to reduce foam cell formation in vitamin D-treated cells (Oh et al., 2009; Yin et al., 2015). Vitamin D supplementation improves glycemic control, increases HDL-C, and decreases hs-CRP levels in patients with CVD (Ostadmohammadi et al., 2019).

G. Fatty Acids

1. Docosahexaenoic Acid and Eicosapentaenoic Acid. Increasing evidence has shown that the consumption of fish oil and its main bioactive components EPA and DHA leads to a reduced risk of CVD. One major mechanism of the cardiovascular effects of fish oil is modulation of lipid homeostasis and foam cell formation (McLaren et al., 2011b). Studies observed that free polyunsaturated fatty acids buffer including DHA and EPA at 5 μ M significantly reduced the CD36 expression in human U937 monocytes (Pietsch et al., 1995). Furthermore, DHA and EPA (25, 50, and 100 μ M) inhibited acLDL uptake in human THP-1 macrophages partially through reduction of mRNA and protein expression of CD36 and SR-A. Other SR-independent mechanisms include reduction of macropinocytosis and

expression of syndecan-4, which is involved in the uptake of other forms of modified LDL (McLaren et al., 2011b). Moreover, an earlier study in 1992 showed that EPA (100, 300 mg/kg body weight per day) inhibits the CE accumulation in macrophages by decreasing the expression of receptors of acLDL in Wistar rats (Saito et al., 1992). These studies underscore the preventive and therapeutic potential of EPA and DHA in atherosclerosis.

2. 13-Hydroxyoctadecadienoic Acid.

13-Hydroxyoctadecadienoic acid (also known as 13-HODE, 13-hydroxy linoleic acid) is a major oxidized lipid component of oxLDL and a natural and endogenous PPAR agonist (Nagy et al., 1998; Kämmerer et al., 2011). Treatment with 13-hydroxyoctadecadienoic acid (1 and 2.5 μ M), but not with linoleic acid, increased the transactivation activity of PPAR, and downstream targets of PPAR/LXR α pathway, including ABCA1 (G1) and SR-BI. By doing so, 13-HODE (2.5 μ M) promoted ApoA-1-mediated cholesterol efflux in RAW264.7 macrophages, thus decreasing cellular cholesterol level and foam cell formation (Kämmerer et al., 2011).

3. *Linoleic Acid*. Dietary supplementation of isomers of conjugated linoleic acids has been known for a long time to promote the regression of pre-established atherosclerotic plaques (Mooney et al., 2012; Song et al., 2013). These compounds conferred atheroprotection mainly by functioning as endogenous activators of PPAR α , PPAR γ , and PPAR γ coactivator 1 alpha (PGC1 α) (Ringseis et al., 2008). Conjugated linoleic acids isomers, such as c9t11-CLA (50 μ M) and t10c12-CLA (50 μ M), were shown to stimulate the ApoA-1-mediated cholesterol efflux, thus reducing lipid accumulation by increasing the expression of NPC-1, NPC-2, ABCA1, and LXR α (Ringseis et al., 2008; Reza et al., 2009). In addition, 1% conjugated linoleic acid blend (80:20 *cis*-9,*trans*-11-CLA:*trans*-10,*cis*-12-CLA) also induced the regression of pre-established atherosclerotic plaques in ApoE^{-/-} mice by promoting macrophage polarization toward a M2 anti-inflammatory phenotype (McCarthy et al., 2013). Published literature suggests that linoleic acid could possibly reduce TC via increasing the hepatic LDLR expression and activity (Ringseis et al., 2006).

H. Amino Acids

1. *L-(+)-Citrulline*. In the NO cycle, L-(+)-citrulline is a side product of the eNOS-mediated NO production which uses L-arginine as a substrate. L-(+)-Citrulline reduces endothelial senescence, VSMC proliferation, and atherosclerosis in several animal models, partially through increasing the NO bioavailability (Ruiz et al., 1999; Hayashi et al., 2005, 2006; Morita et al., 2014; Tsuboi et al., 2018). Citrulline (1 mM) also increased the ABCA1 and ABCG1 expression in differentiated THP-1 macrophages, thereby promoting HDL- and ApoA-1-mediated cholesterol efflux (Uto-Kondo et al., 2014). Of clinical relevance, citrulline consumption (3.2 g/day for

1 week) increased the level of citrulline and arginine post citrulline sera and promoted the HDL- and ApoA-1-mediated cholesterol efflux by increasing the expression of both ABCA1 and ABCG1 in BMDM (Uto-Kondo et al., 2014). This finding provides additional support for citrulline consumption conferring antiatherogenic effects by regulating cholesterol homeostasis (Uto-Kondo et al., 2014).

2. *S-Allyl Cysteine*. S-allyl cysteine is the most abundant bioactive compound from aged garlic extract. S-allyl cysteine exhibits potent antioxidative and anti-inflammatory effects by inhibiting LDL oxidation and NF- κ B activation and by counteracting atherogenic events, including foam cell formation (Ho et al., 2001). Furthermore, S-allyl cysteine (10, 20, and 40 mM) can increase the ABCA1 expression in differentiated THP-1 macrophages, indicating a potential to reduce lipid accumulation by promoting cholesterol efflux (Malekpour-Dehkordi et al., 2013).

I. Carbohydrates

1. *Phellinus Linteus Polysaccharides*. *Phellinus linteus* polysaccharide extracts (PLPEs) have immunomodulatory effects. In lipid-laden THP-1 macrophages, low concentration of PLPEs (from 5 to 20 μ g/ml) promoted ApoA-1-mediated cholesterol efflux by upregulating PPAR γ /ABCA1(G1) in dose-dependent manner. However, high concentration of PLPEs (up to 100 μ g/ml) inhibited ApoA-1-mediated cholesterol efflux, increased the NADPH oxidase-dependent ROS production, and decreased the mitochondrial membrane potential and ATP release (Li et al., 2015d). Thus, the dose is an important consideration for future studies with experimental animals or human patients.

2. *Astragalus Polysaccharides*. *Astragalus* polysaccharides (APS) represent the polysaccharide fraction of the medicinal herb *Astragalus membranaceus*. APS (from 25 to 100 μ g/ml) has been shown to promote the ABCA1 expression in foam cells exposed to TNF- α . As a consequence, APS promoted the cholesterol efflux and affected lipid accumulation (Wang et al., 2010d). Further studies indicate that APS (100 μ g/ml) reversed TNF- α -induced NF- κ B activation in THP-1-derived foam cells. The antiatherosclerotic properties of APS and their molecular mechanisms of action remain to be further elucidated (Wang et al., 2010d).

J. Others

1. *Organosulfur Compounds: Allicin*. Allicin is a sulfur-containing compound present in garlic, which has been shown to inhibit cholesterol synthesis in modified liver homogenates (Sendl et al., 1992). It also has inhibitory effects on inducible NO synthase expression in LPS-stimulated mouse macrophages (Dirsch et al., 1998). Moreover, allicin inhibited the LDL oxidation. The lipid-lowering, anti-inflammatory, and antioxidative properties are underlying its atheroprotective

effects observed in hyperlipidemic mice and rabbits (Abramovitz et al., 1999; Gonen et al., 2005; Yokoyama et al., 2012). Importantly, allicin (40 mg 3 times daily for 12 weeks) also decreased the carotid intima/media thickness in CAD patients with hyperhomocysteinemia (Liu et al., 2017a). A recent study (Lin et al., 2017) also showed that allicin reduced the TC, FC, and CE levels in THP-1 macrophage-derived foam cells by upregulating the ABCA1-dependent cholesterol efflux via PPAR γ /LXR α signaling pathway.

2. *Pyranone Derivatives: Asperlin.* Asperlin is a natural compound from the marine fungus *Aspergillus versicolor* LZD4403, which has potent anti-inflammatory activity (Zhou et al., 2017). A recent study showed that asperlin (1–10 μ M) has specific protective effects against LPS-induced foam cell formation by promoting cholesterol efflux from RAW264.7 mouse macrophages (Zhou et al., 2017).

3. *Anthraquinone Derivatives: Emodin.* Emodin is a pharmacologically active compound isolated from the roots of *Rheum palmatum* (Da Huang). A recent study showed that emodin (5 and 10 μ M) promoted ApoA-1-mediated cholesterol efflux from THP-1 macrophages via PPAR γ /LXR α /ABCA1 (G1) signaling pathway (Zhou et al., 2008; Fu et al., 2014) and thereby ameliorated diet-induced atherosclerosis in rabbits at the dose of 10 mg/kg body weight (Hei et al., 2006). Emodin was also reported to reduce atherosclerosis in ApoE^{−/−} mice (Zhou et al., 2008) and rabbits (Hei et al., 2006). In addition, emodin lowered blood glucose, TC, and TG in diabetic and hyperlipidemic rats (Zhao et al., 2009) by inhibiting SREBP-1 and SREBP-2 (Li et al., 2016).

4. *Polyacetylene Derivatives: Falcarindiol.* Falcarindiol is a common bioactive compound found in some vegetables and medicinal herbs. Falcarindiol (10 μ M) has been reported to promote ApoA-1-mediated cholesterol efflux in differentiated macrophages by increasing the mRNA and protein expression of ABCA1 via PPAR γ (Wang et al., 2017e). One unique mechanism of falcarindiol is that it not only increased ABCA1 gene expression but also prevented cathepsin-dependent ABCA1 protein degradation (Wang et al., 2017e).

5. *Marine Natural Products.* In addition to the compounds mentioned above, several marine natural products have also demonstrated an antiatherosclerotic potential by inhibiting foam cell formation. For example, spiromastixones 6 and 14 (10 μ M) (Wu et al., 2015a) significantly inhibited oxLDL-induced RAW264.7 foam cell formation in mouse macrophages by inhibiting lipid uptake, as well as promoting cholesterol efflux mediated by HDL and ApoA-1. Mechanistic studies reveal that both compounds significantly reduced the expression of CD36, while upregulating PPAR γ /ABCA1 (G1) (Wu et al., 2015a), indicating that both compounds could serve as promising leads with an antiatherogenic potential.

V. Clinically Used Drugs that Influence Foam Cell Formation

Macrophage foam cells play a critical role in the development of atherosclerosis (Sharma et al., 2010). The inhibition of foam cell formation is emerging as an attractive strategy for therapeutic intervention of atherosclerosis in clinics.

A. Approved Drugs

1. *Statins.* Statins, used as cholesterol-lowering drugs, effectively reduce CVD and mortality in patients with high risk of CVD (Robson, 2008). The mechanism of their action is related to decrease in cholesterol biosynthesis mediated through competitive inhibition of HMG-CoA reductase and their cholesterol-independent pleiotropic effects. Statins are highly efficacious (in lowering atherogenic LDL), safe, and generally well tolerated in patients with CVD. Statins are reported to reduce the risk for developing nonfatal myocardial infarction, ischemic stroke, cardiovascular, and all-cause mortality. Statins have also been reported to promote the stabilization and regression of pre-established atherosclerotic plaques (Toth and Banach, 2019). Clinically used statins can be grouped in two categories, the lipophilic statins (such as simvastatin and atorvastatin) and hydrophilic statins (such as fluvastatin, pravastatin, and rosuvastatin). Although statins share a common mechanism of action by inhibiting HMG-CoA reductase, they differ in terms of chemical structures/water solubility, pharmacokinetic properties (absorption, distribution, metabolism, and excretion), and efficacy of modulating lipids (Schachter, 2005). The lipophilicity/hydrophilicity of statins may have differential effects and mechanisms in suppressing endothelial dysfunction, foam cell formation, and CVD development. For example, a systematic meta-analysis showed that hydrophilic statins, but not hydrophobic statins, significantly reduced the level of asymmetric dimethylarginine (which inhibits NO formation and promotes endothelial dysfunction) (Serban et al., 2015). Another meta-analysis showed that both the hydrophilic and the lipophilic statins showed similar risk reduction for major adverse cardiac events, cardiovascular death, all-cause mortality, and statin-associated muscle symptoms. However, the authors observed that hospitalization caused by CVDs was lower and elevation of alanine aminotransferase was higher in lipophilic statin- than in hydrophilic statin-treated patients (Bytyçi et al., 2017). In a separate study, Kim et al. (2011) observed that treatment of patients with myocardial infarction with lipophilic statins lead to a better short-term cardiovascular outcome; however, both lipophilic and hydrophilic statins lead to a similar reduction of lipids and 1-year cardiovascular outcomes. Therefore, we might expect different clinical outcomes in different patient populations after

treatment with lipophilic or hydrophilic statins for different periods.

In cultured macrophages, both lipophilic and hydrophilic statins can ameliorate foam cell formation. For example, rosuvastatin reduces oxLDL-induced foam cell formation in macrophages by reducing CD36 expression, without affecting SR-A expression (Yu et al., 2018). Another study demonstrated that preincubation of THP-1 macrophages with atorvastatin enhanced cholesterol efflux to ApoA-1 and HDL3 dose dependently (Argmann et al., 2005). Atorvastatin also increased PPAR γ activity, enhanced LXR activation, and increased ABCA1 expression (Argmann et al., 2005). A recent study showed that reduced protein expression of calpain-1 is accountable for simvastatin-mediated protective effects against foam cell formation (Yang et al., 2016). However, there are several other studies that indicated that simvastatin decreased the ABCA1 protein levels in THP-1 via miRNA-33 (Horie et al., 2010; Niesor et al., 2015). Therefore, overall the effects of statins on macrophage foam cell formation are still controversial. A genome-wide comparison of the differentially expressed genes in macrophage foam cells treated with hydrophilic or lipophilic statins will provide a clear picture of the cardiovascular protective transcriptome of different statins.

2. Nicotinic Acid. Nicotinic acid (NA) has been used for decades as a drug to reduce the progression of atherosclerosis by decreasing LDL-C and increasing HDL-C levels in plasma (Meyers et al., 2004; Carlson, 2005). However, one recent trial suggests that there were no additional clinical effects upon adding niacin to statin therapy during a 36-month follow up period, though HDL-C and TG levels were significantly increased in the patients with atherosclerotic CVDs (Boden et al., 2011). In macrophages from wild-type mice, NA enhanced ABCG1 expression and promoted cholesterol efflux (Lukasova et al., 2011). It is reported that NA increased the production rate of ApoA-1 in both liver and intestinal cells (Rubic et al., 2004; Lamon-Fava et al., 2008), probably through an activation of MAPK and PPAR pathways (Lamon-Fava and Micherone, 2004; Pandey et al., 2008). On the contrary, other studies reported that there are no effects of NA on ApoA-1 production rate (Jin et al., 1997). Furthermore, NA did not exhibit effects on either cholesterol efflux or key RCT gene transcription in THP-1-derived foam cells (Chai et al., 2013).

3. Ezetimibe. Ezetimibe, a selective inhibitor of intestinal cholesterol absorption, has been shown to reduce plasma cholesterol levels and exhibit an anti-atherosclerotic effect (Al-Shaer et al., 2004). One study showed that ezetimibe inhibited foam cell formation via the caveolin-1/MAPK signaling pathway, which might be another mechanism of its anti-atherosclerotic effect (Qin et al., 2016).

4. Proprotein Convertase Subtilisin/Kexin Type 9Antibodies. PCSK9 is an enzyme encoded by the *PCSK9* gene on chromosome 1 in human beings (Seidah et al., 2003). PCSK9 reduced the amount of LDLRs in hepatocytes by promoting their degradation (Denis et al., 2012). Blocking PCSK9 expression/activity can increase the LDLR amount on the cellular surface and decrease blood LDL-particle concentrations (Weinreich and Frishman, 2014; Joseph and Robinson, 2015). Monoclonal PCSK9 antibodies have been developed as a very effective approach to inhibit PCSK9 and reduce LDL levels (Chaudhary et al., 2017). Several monoclonal antibodies have been or are being tested in clinical studies. Among them, Alirocumab and Evolocumab were recently approved by the Food and Drug Administration for adult patients with heterozygous familial hypercholesterolemia or with clinically significant atherosclerotic CVD requiring additional LDL lowering (Chaudhary et al., 2017). One study displayed that PCSK9 directly decreased cholesterol efflux by the downregulation of ABCA1 expression (Adorni et al., 2017), which might be another mechanism of the anti-CVD effect conferred by inhibition of PCSK9.

B. Drugs in Clinical Trials

1. Glucagon-like Peptide-1 Receptor Agonists. GLP-1 is a gut hormone that activates a G protein-coupled receptor (GLP-1R) in a glucose-dependent manner to stimulate pancreatic β cells and secretion of insulin postprandially (Campbell and Drucker, 2013). GLP-1R agonists (e.g., liraglutide, lixisenatide, albiglutide) or incretin mimetics are used as medicines for the treatment of type 2 diabetes. Recent evidence has suggested that the augmentation of GLP-1R signaling by administration of GLP-1R agonists has beneficial effects on the cardiovascular system in patients with diabetes (Ussher and Drucker, 2012). Further study indicated that GLP-1R signaling induced autophagy, thereby suppressing foam cell formation in nonobese subjects. In obese patients, stimulation of GLP-1R promoted formation of foam cell and production of TNF- α , IL-1 β , and IL-6 (Tanaka et al., 2016).

2. High-density Lipoprotein/Apolipoprotein A-1-raising Agents. Current treatment of atherosclerotic CVD is dominated by lowering LDL-C, while increased plasma levels of cholesterol efflux acceptors HDL-C and ApoA-1 expression have been viewed as an alternative therapeutic strategy against CVD for more than three decades (Bailey et al., 2010). The idea to treat CVD by raising HDL comes from a concept relying on the inverse correlation of CVD and human plasma HDL-C (Brewer, 2004), which retrieves excess cholesterol from peripheral cells, including vessel wall macrophages, to the liver for excretion into the bile (Duffy and Rader, 2006). Although there are some animal studies and human trials demonstrating that infusion of HDL or ApoA-1 limit the progression of atherosclerosis (Tall,

1990; Nissen et al., 2003), a randomized, double-blind study involving 15,067 patients at high cardiovascular risk indicated that the CETP inhibitor torcetrapib raised the levels of HDL particles but failed to counteract atherosclerosis (Barter et al., 2007). Two trials have also compared niacin with placebo, added to simvastatin, and although niacin raised HDL-C by ~15%, there was no clinical benefit to atherosclerosis (Boden et al., 2011; HPS2-THRIVE Collaborative, 2013). These studies indicate the complexity of HDL biology and suggest that not only HDL-C levels but also size, composition, and functionality of the HDL particles may be important. The focus of drug development should shift from raising HDL-C levels to enhancing HDL function. Current knowledge on the role of HDL in preventing various diseases is threefold: 1) HDL itself is not a reliable biomarker/predictor of CVD and/or cancer; 2) the quality/functionality (such as cholesterol efflux assay in patients derived macrophages), rather than the quantity of HDL, is more important for atheroprotection and CVD prevention; and 3) the functionality of HDL plays an important role not only in CVD (such as atherosclerosis), but also in cancer diagnosis/monitoring (Otocka-Kmiecik et al., 2012; Toth et al., 2014; Ganjali et al., 2019; Penson et al., 2019).

RVX-208 (apabetalone) is a selective antagonist of bromodomain and extra terminal (BET) bromodomains (McLure et al., 2013; Picaud et al., 2013). It interferes with the BET protein bromodomain 4 (BRD4), resulting in an increased expression of ApoA-1 in cells, mice, monkeys, and humans (Bailey et al., 2010; Jahagirdar et al., 2014). RVX-208 is being developed as an orally active small molecule for the treatment of CVD (Nicholls et al., 2011). A clinical study showed that RVX-208 increased ApoA-1, pre- β -HDL, and HDL functionality and increased cholesterol efflux in vitro (Bailey et al., 2010). In two Phase II clinical trials, RVX-208 increased the HDL-C and ApoA-1 levels, exhibiting the ability to treat atherosclerosis in patients with established CVD (Johansson et al., 2014). An international, multicenter Phase III trial for treatment of atherosclerosis commenced in October 2015. In 2018, Resverlogix Corp. announced that it has successfully surpassed the planned enrollment target of over 2400 patients in the ongoing Phase III trial (BETonMACE). The scientific community is looking forward to the results of the Phase III trial. The findings discussed here indicate that the regulation of ApoA-1 expression would be a very promising approach for treating atherosclerosis.

One potential therapeutic strategy related to ApoA-1 is the application of small peptides that mimic the ApoA-1 function. ApoA-1 comprises a total of 243 amino acids and involves 10 amphipathic α -helices, which are very important for its interaction with lipids. Peptides that mimic the amphipathic helices in ApoA-1 (ApoA-1 mimetic peptides) are lately used as therapeutic agents

(such as 4F, 6F, FX-5A, ATI-5261, ETC-642) (Stoekenbroek et al., 2015). At present, these peptides are being tested in preclinical models, which show that they increase macrophage cholesterol efflux and exhibit antiatherosclerosis action (Stoekenbroek et al., 2015). A small pilot study (ApoA-1 Milano clinical trial) indicated that a complex of recombinant ApoA-1 Milano with phospholipid carriers (ETC-216) significantly reduced percentage and total atheroma volume and plaque thickness in patients (Nissen et al., 2003). Pfizer purchased the producer of ETC-216, Esperion Therapeutics in 2003, in the hope of developing a more effective treatment than ETC-216. However, Pfizer did announce a progress with the development of such product. Currently, no drugs based on ApoA-1 Milano are commercially available.

CSL-111, an rHDL, is composed of human ApoA-1 and soybean phosphatidylcholine, which mimics native HDL (Stoekenbroek et al., 2015). In the “Effect of rHDL on Atherosclerosis-Safety and Efficacy” (ERASE) trial, although CSL-111 remarkably decreased atheroma volume compared with baseline, it induced a high incidence of liver function abnormalities (Tardif et al., 2007). Therefore, further clinical study on CSL-111 was not continued. CSL-112, a second-generation of CSL-111 with no liver toxicity, increased the ApoA-1, pre- β HDL levels, and ABCA1-mediated cholesterol efflux in two Phase I studies (Krause and Remaley, 2013; Easton et al., 2014). In the Phase II trial, infusion of CSL112 for 4 weeks was well tolerated and did not induce any significant side effects in liver or kidney function. CSL112 significantly enhanced cholesterol efflux (Michael Gibson et al., 2016). In 2018, CSL Behring has started the “ApoA-1 Event reducinG in Ischemic Syndromes II” (AEGIS-II) Phase III clinical trial of CSL112, which is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. The scientific community is looking forward to the results of the Phase III trial of CSL112.

CER-001, a pre- β HDL mimetic, comprises recombinant ApoA-1, diphosphatidylglycerol, and sphingomyelin (Stoekenbroek et al., 2015). In a Phase I trial, infusion of CER-001 was well tolerated and did not show any side effects at any doses (Keyserling et al., 2011). The Phase II trials indicated that CER-001 increased RCT and might significantly decrease aortic atheroma volume. CER-001 has already reached Phase III for the treatment of patients with genetic HDL deficiencies. However, CER-001 has failed in Phase II trial for the treatment of patients with coronary atherosclerosis following acute coronary syndromes (Nicholls et al., 2018). The results show that CER-001 did not produce plaque regression in statin-treated patients following acute coronary syndrome (Nicholls et al., 2018).

3. *Bempedoic Acid (ETC-1002)*. Bempedoic acid (ETC-1002), a small-molecule inhibitor of ATP citrate lyase, has been shown to reduce the level of low-density lipoprotein (LDL) cholesterol and the development of

atherosclerosis in hypercholesterolemic ApoE^{-/-} mice (Pinkosky et al., 2016), LDLR^{-/-} mice (Samsoondar et al., 2017), LDLR-deficient miniature pigs (Samsoondar et al., 2017), and statin-intolerant hypercholesterolemic patients (Ballantyne et al., 2018; Laufs et al., 2019). Bempedoic acid, as a prodrug, is converted to the active agent in liver, but not in skeletal muscle; therefore, bempedoic acid may avoid myotoxicity associated with statin therapy (Penson et al., 2017; Ruscica et al., 2019). A recent Phase III clinical trial has shown that treatment with bempedoic acid for 52-weeks added to the maximally tolerated statin therapy significantly lower LDL-C levels without causing higher incidence of overall adverse events (Ray et al., 2019). To date, no information is available whether bempedoic acid can affect foam cell formation. Based on the promising LDL-lowering effects of bempedoic acid, it is plausible that bempedoic acid could also affect lipid uptake and cholesterol efflux.

VI. The Role of Inhibition of Foam Cell Formation in Antiatherosclerosis Therapy

Atherosclerotic lesions in the early stages of atherosclerosis are characterized by the subendothelial accumulation of lipid-laden macrophages (foam cells) in the large arteries (Lusis, 2000). With time, the foam cells eventual demise within the atherosclerotic lesion contributes to their lipid-filled contents in the necrotic core of the advanced lesion, as shown in animal models (Cookson, 1971; Tamminen et al., 1999). In humans, such fatty streak lesions were also found in the aorta, the coronary arteries, and the cerebral arteries (Lusis, 2000), suggesting that foam cell formation also play a critical role in atherosclerotic development in humans. Thus, foam cell formation could be a promising therapeutic target for atherosclerosis.

As we discussed in section II above, disruption of macrophage cholesterol uptake, prevention of CE formation, and enhancement of macrophage cholesterol efflux in animals generally reduced foam cell formation and atherosclerotic plaque area. Although animal models are widely used to study the molecular mechanisms that connect altered cholesterol metabolism to the atherosclerotic plaque progression, the possible differences in atherosclerosis development between animal models and humans must be taken into consideration (Maguire et al., 2019). Therefore, it is very important to ascertain whether inhibition of foam cell formation also contributes to atherosclerosis regression in humans.

As we discussed in section V.A, current clinically used drugs (e.g., statins, NA, ezetimibe, Alirocumab, and Evolocumab) to treat CVDs also exhibit inhibitory effects on macrophage foam cells in vitro and in animal models (FERENCE et al., 2017). However, it remains to be verified how much their therapeutic effects are attributed to their inhibition on foam cell formation in

humans. One clinical study showed that pravastatin has the capacity to reduce lipid content and foam cell accumulation in carotid atherosclerotic lesions (Crisby et al., 2001), which indicates that inhibition of foam cell formation might contribute to its therapeutic effects. NA was demonstrated to significantly increase HDL-C in patients (Lee et al., 2009a), which is an acceptor to mediate cholesterol efflux from macrophages, suggesting that NA might possibly also exhibit its effects by influencing foam cell formation. Intriguingly, treatment with PCSK9 monoclonal antibodies in patients with familial hypercholesterolemia reduced intracellular lipid accumulation in circulating monocytes (Bernelot Moens et al., 2017). Furthermore, this study indicated that LDL-C lowering by inhibition of PCSK9 was paralleled by decreased intracellular lipid accumulation, indicating that LDL-C lowering itself is associated with inhibited foam cell formation (Bernelot Moens et al., 2017). It also suggests that inhibition of PCSK9 reduces monocyte levels of intracellular lipids, and might thereby prevent progression and enhance regression of atherosclerosis (Wu and Ballantyne, 2017). Although these drugs exhibit inhibitory effects on foam cell formation in humans, it is unclear how much the inhibition of foam cell formation contributes to their efficacy on CVDs, since their effect on CVDs is mainly due to pleiotropic activities, such as decrease of cholesterol and LDL-C, antioxidant activity and others.

Also, as we discussed in section V.B, enhancement of HDL-C and ApoA-1 levels has been viewed as alternative therapeutic strategies against CVD. Although HDL mediates a number of atheroprotective processes, such as antioxidative, anti-inflammatory, vasodilatory activities, protection against endothelial cell activation and apoptosis and others; very importantly it is also the critical acceptor to mediate cholesterol efflux from foam cells to inhibit foam cell formation (Linton et al., 2000). Recent clinical reports indicated that HDL cholesterol efflux capacity from macrophages has a strong inverse association with both the likelihood of angiographic CAD and carotid intima-media thickness, independent on the HDL-C levels (Khera et al., 2011). HDL cholesterol efflux capacity was also inversely related with the incidence of cardiovascular events in a large and multiethnic population cohort (Rohatgi et al., 2014) and with incident coronary heart disease events (Saleheen et al., 2015). These clinical studies indicated that enhancement of cholesterol efflux might decrease CVDs, providing compelling evidence that the inhibition of foam cell formation is antiatherogenic in humans. Moreover, RVX-208 increased the expression of cholesterol efflux acceptor ApoA-1 in humans, reducing major adverse cardiovascular events in treated patients in several Phase II trials as discussed above (section V.B), suggesting targeting foam cell formation might be a promising target to treat CVDs. Unfortunately, these clinical studies were not able to test the

foam cell formation and accumulation. Therefore, there is no direct and clear evidence to verify how much the inhibition of foam cell formation contributes to the respective therapeutic effects on CVDs. At present, the examined endpoints in these clinical studies include death from CAD, ischemic stroke, nonfatal myocardial infarction, carotid intima-media wall thickness (Cheng et al., 2016), hospitalization for an acute coronary syndrome, symptom-driven coronary or cerebral revascularization (Boden et al., 2011), lipid parameters (e.g., ApoA-1, LDL, HDL) (Rohatgi et al., 2014), none of which can directly and unambiguously represent the foam cell formation. In this context, we suggest that future clinical trials may use foam cell formation as a further clinical endpoint to confirm whether inhibition of foam cell formation can directly contribute to anti-CVDs therapy.

VII. Concluding Remarks and Future Perspectives

Atherosclerosis is traditionally considered as a lipid disorder, in which multiple pathologic factors, such as immunity disorders (Hansson and Hermansson, 2011), unresolved inflammation (Kasikara et al., 2018), and epigenetics (Xu et al., 2018), add to the complexity of the disease. Targeting diverse mechanisms of atherosclerosis could facilitate the therapeutic interventions to combat atherosclerosis (Maguire et al., 2019).

Based on the lipid and inflammation hypothesis of atherosclerosis, lipid-modulating strategies (i.e., by statins, fibrates, and PCSK9 inhibitors) and anti-inflammatory therapies (i.e., by IL-1 β monoclonal antibody injection) remain the mainstream therapy for atherosclerosis. Macrophages are one main cell type that handles inflammatory response, immunity, and lipid metabolism in the atherosclerotic lesions. Our understanding of how macrophages govern the inflammatory response, lipid transport, and storage within lesions has significantly progressed over the last 10 years. In humans, atherosclerotic lesions (fatty streaks), characterized by the subendothelial accumulation of lipid-laden macrophages (foam cells), were found in the aorta, the coronary arteries, and the cerebral arteries (Lusis, 2000), which were also confirmed in animal models (Cookson, 1971; Tamminen et al., 1999). It was assumed that foam cell formation plays a critical role in atherosclerotic development in humans, and inhibition of foam cell formation would be a promising target to treat atherosclerosis. The formation of foam cell is a multistep cellular process, which involves lipid uptake, cholesterol ester accumulation, and cholesterol efflux. These three processes seem to be independent of each other, but indeed constitute an interrelated gene regulation network. The SR-mediated uptake is the major pathway of cholesterol uptake. CD36, SR-A, and LOX-1 are the major SRs responsible

for the binding and following uptake of modified LDL by macrophages (Kunjathoor et al., 2002), whose regulation and functions are addressed in the review. Cholesterol esterification and CE hydrolysis involved in foam cell formation could also be alternative targets for the treatment of atherosclerosis. ACAT1 and ACAT2 involving in cholesterol esterification, as well as NCEH1, LIPA, and lipase E involving in CE hydrolysis are also concluded here. In addition, current understanding of the function and regulation of the cholesterol transporters (ABCA1 and ABCG1), SR-BI, and the acceptors (ApoA-1, HDL and ApoE), which are related to cholesterol efflux from macrophages, are reviewed. Inhibition of LDL uptake, prevention of cholesterol esterification, and promotion of CE hydrolysis, as well as increase of cholesterol efflux in macrophages could represent novel therapeutic modalities of atherosclerosis. A multifaceted approach, which blocks lipid uptake and CE accumulation while promoting cholesterol efflux, could be the most effective way to reduce foam cell formation with reduced side effects (such as FC accumulation) (Maguire et al., 2019).

There are a variety of models to study the process of foam cell formation and to screen the promising compounds targeting foam cell formation. We reviewed the cellular models for studying cholesterol uptake, cholesterol efflux, and animal models for study on macrophage RCT and foam cell formation. All these models provide a good platform to evaluate the effect of natural products on foam cell formation in vitro and in vivo and to further identify promising drug candidates for treatment of atherosclerosis (Getz and Reardon, 2012; Hilgendorf and Swirski, 2012). However, it should be pointed out that studies in animal models have limited suitability because of significant species differences compared with humans (Lusis, 2000). For example, contradictory results related to the pathologic roles of CD36, SR-A, and ACAT1 in atherosclerosis have indicated the translation of the findings from mice to human as a big challenge for cardiovascular biology and drug discovery. Thus, it is critical to select a unique animal model(s) that mimic human atherosclerosis pathophysiology and to minimize the variables arising from different sexes, study duration, and type of atherogenic diet. Differences in lipid profile, topography of arterial lesions, and the susceptibility to plaque rupture are key factors that must be taken into consideration when choosing the suitable animal model (Emini Veseli et al., 2017).

Natural products remain a promising source for new lead structures. Their great structural diversity and biodiversity makes them an attractive pool in the quest for new therapeutics. In this review, natural products regulating foam cell formation in different models are outlined, including flavonoids, terpenoids, phenolic compounds, phenylpropanoids, alkaloids, steroids, fatty acids, amino acids, carbohydrates, and others. Among them, cyanidin-3-glucoside, ICA, iristectorigenin B, pratensein,

isosilybin A, β -carotene, lycopene, erythrodiol, ginsenoside Rb1, tanshindiol C, PGG, berberine, 13-HODE, and spiromastixones appeared to be very active in cellular models. Thus, in vivo corroboration of their activity appears worthwhile. For some of the natural compounds, like anthocyanins, baicalin, chrysin, cyanidin-3-*O*- β -glucoside, daidzein, ellagic acid, hesperetin, quercetin, isosilybin A, ATRA, 9-*cis*- β c, 9-*cis*-RA, UA, ginsenoside Rd, zerumbone, curcumin, danshensu, paeonol, protocatechuic acid, salvianolic acid, sesamol derivative (INV-403), resveratrol, EGCG, sesamin, chlorogenic acid, caffeic acid, ferulic acid, rutaecarpine, leonurine, diosgenin, DHA, linoleic acid, allicin, asperlin, and emodin, in vivo studies in models for atherosclerosis already exist, which makes these compounds even more promising. The therapeutic effects of these compounds on foam cell formation and atherosclerosis remain to be investigated in clinical studies. Some natural compounds, like pratensein, astaxanthin, betulinic acid, tanshinone IIA, vitamin D, have even been investigated in clinical trials. Large and multiethnic population cohorts are required to further confirm their therapeutic effect on atherosclerosis.

We also reviewed the effect of clinically used drugs on foam cell formation, including statins, NA, ezetimibe, and PCSK9 antibodies, as well as drugs in clinical trials, such as GLP-1 receptor agonists and HDL/ApoA-1-raising agents. Although these drugs exhibit positive effects on foam cell formation in humans, there is no direct evidence to verify how much the inhibition of foam cell formation contributes to the therapeutic effects of these drugs on CVDs.

Future directions in studying the mechanisms of foam cell formation and the discovery of foam cell-targeted therapies include:

- Further understanding the regulatory mechanisms of foam cell formation by new biotechnologies (such as RNA-sequencing, lncRNA arrays, RNA interference (RNAi), or CRISPR/Cas9 library screening). Although significant progress has been made recently in characterizing regulatory mechanisms controlling the formation of foam cells, targeting some of these known regulatory mechanisms has yielded negative or controversial results, such as pathologic roles of CD36, SR-A, ACAT1, ABCA1, and rHDL in atherosclerosis. Therefore, it is important to further understand the regulatory mechanisms of foam cell formation by new biotechnologies. The widespread use of RNA-sequencing and lncRNA arrays (Xu, 2017) has empowered the discovery of new epigenetic regulators (such as lncRNAs) that are associated with or regulate foam cell formation, atherosclerosis, and related vascular diseases. Further elucidation of the role of these new regulators will provide us a clear

picture of how foam cell formation is regulated and can be therapeutically targeted. Methods of systems biology, such as RNAi or CRISPR/Cas9 library screening are very useful high-throughput methods to elucidate novel regulators of foam cell formation at the genome-wide scale (Domschke et al., 2018). The establishment of new screening systems based on RNAi or CRISPR/Cas9 library screening will significantly accelerate understanding the regulatory mechanisms of foam cell formation.

- High-throughput screening of natural products targeting foam cell formation. Natural products are a well-established source for the development of new drugs in general (Atanasov et al., 2015; Waltenberger et al., 2016). They display a great structural diversity and also cover a large range of biologic activity compared with combinatorial and synthetic compounds (Hiebl et al., 2018). A huge number of natural products were found to regulate ABCA1 expression. Nevertheless, many natural products have never been investigated concerning a potential regulation of foam cell formation. To identify potential drug leads with capability of suppressing foam cell formation from such large pool, high-throughput drug screening platforms are important. For example, a recent study has used a high-throughput screening platform to identify novel candidate genes involved in lipid uptake by human macrophages (Domschke et al., 2018). This platform can similarly be used to identify natural products that have inhibitory effects on lipid uptake.
- Validation of anti-foam cell formation and anti-atherosclerotic effect of bioactive natural products in vitro, in vivo, and in clinical studies. Most of studies evaluating the anti-foam cell formation capabilities of natural products were performed using RAW264.7 macrophages and differentiated THP-1 macrophages, two common cell lines used in macrophage biology research. To further evaluate the potential of promising natural products, pharmacological activities need to be validated in primarily cultured HMDMs and, most importantly, in animal models of atherosclerosis. However, we have to bear in mind that the mechanisms of actions of these natural products with potential anti-foam cell formation effects are very wide, ranging from reduction of proinflammatory factors/biomarkers (such as CRP), inhibition of oxidative stress, and direct inhibition of lipid synthesis (by inhibiting the activity of HMG-CoA reductase, PCSK9, or SREBPs). Those natural products may be working in a similar ways to some nutraceuticals (such as polyunsaturated fatty acids) or current lipid-modulating therapies (Sahebkar et al., 2016a,b;

Serban et al., 2016; Cicero et al., 2017; Momtazi et al., 2017; Ursoniu et al., 2017; Banach et al., 2018; Patti et al., 2018). Another important consideration in future research is to verify whether the anti-foam cell formation effects of natural products directly contribute to their antiatherosclerotic effects, since the progression of atherosclerosis is a complex process. In the light of recent observations that impaired ABCA1-dependent cholesterol efflux associates with markers of inflammasome activation in mouse and human patients with loss-of-function mutations in ABCA1 (Tangier disease) (Westertorp et al., 2018), it is possible that the vicious cycle of “foam cell formation-inflammation/inflammasome-foam cell formation-atherosclerosis” could perpetuate the pathogenesis of atherosclerosis. Some of the natural compounds exhibit very strong inhibitory effects on foam cell formation in vitro, in vivo, and in small clinical trials. It is very valuable to conduct large and multi-ethnic population cohorts to confirm their therapeutic effect on atherosclerosis.

- Improvement of druggability of promising natural products. Some of the natural products with cardiovascular potential have the disadvantage of low oral bioavailability and low efficacy and have systemic and complex pharmacological effects in vivo. Further structural modification of these promising compounds can lead to antiatherosclerotic drug candidates with higher efficacy and less toxicity/nonspecific effects. In addition, the use of nanotechnology, for example, nanoencapsulation can significantly enhance the stability and anti-atherogenic efficacy of natural products, as shown for EGCG in macrophages (Zhang et al., 2013, 2016a; Hong et al., 2014). In the future, it is feasible to design nanomedicines by coupling natural products with macrophage specific marker proteins to achieve targeted delivery of drugs to foam cells in atherosclerotic plaques in vivo.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Wang, Yang, Lei, Tzvetkov, Liu, Yeung, Xu, Atanasov.

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