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Targeting Systemic Innate Immune Cells as a Therapeutic Avenue for Alzheimer Disease

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***Abstract*——Alzheimer disease (AD) is the first progressive neurodegenerative disease worldwide, and the disease is characterized by an accumulation of amyloid in the brain and neurovasculature that triggers cognitive decline and neuroinflammation. The innate immune system has a preponderant role in AD. The last decade, scientists focused their efforts on therapies aiming to modulate innate immunity. The latter is of great interest, since they participate to the inflammation and phagocytose the amyloid in the brain and blood vessels. We and others have developed pharmacological approaches to stimulate these cells using various ligands. These include toll-like receptor 4, macrophage colony stimulating factor, and more recently nucleotide-binding oligomerization domain–containing 2 receptors. This review will discuss the great potential to take advantage of the innate immune system to fight naturally against amyloid β accumulation and prevent its detrimental consequence on brain functions and its vascular system.**

***Significance Statement*——The focus on amyloid β removal from the perivascular space rather than targeting CNS plaque formation and clearance represents a new direction with a great potential. Small molecules able to act at the level of peripheral immunity would constitute a novel approach for tackling aberrant central nervous system biology, one of which we believe would have the potential of generating a lot of interest.**

I. Alzheimer Disease

Alzheimer disease (AD) is the first progressive, neurodegenerative disease worldwide. The disease has no real effective treatment and no cure, for years researchers have tried to develop molecules to delay or slow the progression of AD in vain. The last decade has seen the emergence of molecules able to modify the pathology, especially in rodents. These compounds discussed in this review take advantage of the innate immunity, and can partly reprogram the latter to delay AD.

Clinically, AD is a multifactorial disorder manifested by a gradual decline in memory and other cognitive functions that leads to death within 8 to 10 years after diagnosis (Ballard et al., 2011). The decline is associated with the presence of specific neuronal loss, synapse alteration, neurofibrillary tangles, and senile plaques (Aarsland et al., 1996). AD progression is divided into

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different stages, namely early, moderate, and severe phases. The disease alters gradually short-term memory, behavior, verbal communication, and motor functions (Zvěřová 2019). The diagnosis is probabilistic, meaning that postmortem studies confirm initial diagnosis. The clinical evaluation is mainly based on personal and familial medical history, neurologic and physical examination, neuroimaging using PET scan associated with MRI, and laboratory tests (Dubois et al., 2016; Zvěřová 2019). Aging is the principal risk factor for AD. The incidence of the disease doubles every 5 years beyond age 65 (Querfurth and LaFerla 2010), meaning that 1/3 person aged 85 and older may have AD. Compared with obesity, diabetes, vascular, and cardiac conditions, age remains the principal risk factor. Noteworthy, the biologic sex has a direct impact on AD incidence; 2/3 of patients are women. This higher prevalence may be caused by the genetic and hormones (Fisher, Bennett, and Dong 2018). Estrogen isoform E2 and its receptor are found in the hypothalamus and hippocampus. This axis is of great interest, since studies revealed that E2 mediates sex-specific behaviors, regulate synaptic plasticity and neuronal survival, and has a neuroprotective role (Green and Simpkins 2000; Fisher, Bennett, and Dong 2018). E2 receptor β has also a direct role of the neuroinflammatory response by microglia (Gosselin and Rivest 2011). The decrease of E2 during the menopause has been proposed to be involved in the development of AD in women.

AD has multiple causes. Researchers have elaborated 3 main hypotheses explaining the origin of the disease: 1) amyloid hypothesis, by far the most studied, 2) τ hypothesis, and 3) the cholinergic hypothesis. For years, amyloid hypothesis was the principal explanation for AD, and this hypothesis states that amyloid aggregation starts a cascade of events such as hyperphosphorylation of τ protein, neuroinflammation, and neuronal dysfunction that ultimately lead to AD (Kametani and Hasegawa 2018). This hypothesis is reinforced by some evidence, such as the familial form of AD that is triggered by mutations leading to amyloid accumulation and in patients with Down syndrome, which have a marked and early amyloid deposition (Johannesson et al., 2021).

The τ hypothesis refers to an hyperphosphorylation of τ, a protein that participates to microtubule formation that is vital for axonal transport. Once hyperphosphorylated, τ tends to form neurofibrillary tangles that impairs neuronal functions and ultimately leads to axonal degeneration (Bennett et al., 2018). τ pathology is not restricted to AD, since hyperphosphorylated τ deposition could be found in healthy brain after a cellular stress or in Parkinson disease (Bloom 2014). Interestingly, under certain circumstances, amyloid deposition enhances τ pathology, although the link between both hypotheses is still debated (Arnsten et al., 2021). The last hypothesis states that the loss of cholinergic neurons is the main cause of dementia in AD, but the loss of cholinergic system is also found in Parkinson, Down syndrome, and amyotrophic lateral sclerosis (Ferreira-Vieira et al., 2016).

Intriguingly, amyloid is found in τ and cholinergic hypotheses, suggesting that amyloid-β (Aβ) has a central role in the pathology, but it is important to note that these hypotheses are not statics, and they evolve over the time. Moreover, they cannot explain the whole pathology, since AD is a very complex and multifactorial disease.

There are 2 main forms of AD, the sporadic form of AD; mainly due to the environment, lifestyle, and the genetic form of the disease named the familial form. The early onset of Alzheimer's Disease (EOAD) represents less than 1%–2% of cases, it is primarily caused by a mutation of Amyloid precursor protein (APP) on chromosome 21q21, Presenilin 1 (PSEN1) on chromosome 14 (14q24.2), and PSEN2 on chromosome 1 (1q42.13). These mutations are autosomal dominant; PSEN1 represents up to 80% of mutations, whereas PSEN2 accounts for 5%, resulting in an aberrant Aβ production and/or an increase in plaque formation. Also, APP accounts for 15% of modifications, it leads to a misfolded protein (Bekris et al., 2010). APP gene is alternatively spliced and named according to the length. Three isoforms are mainly involved in AD, APP695 is specifically expressed in the CNS, whereas APP751 and APP770 are found in CNS and peripheral tissues. So far, 32 different APP missense mutations are characterized; the vast majority of these mutations are found at the secretase cleavage domain or at the transmembrane domain (Bertram 2004). Mutations of APP seem to be specific to the EOAD form. In extreme cases, defects in PSEN1 can lead to the most severe form of AD, with an onset occurring as early as the age of 30. However, the mean age of the onset is over age 58 when PSEN1 is involved. 176 PSEN1 mutations have been identified, as for APP the majority are missense mutations (Sherrington et al., 1995). PSEN2 mutations differ from the clinical pattern of PSEN1-affected patients in that the age of the onset varies between 45 and 88 years. PSEN2 mutations, like

ABBREVIATIONS: Aβ:, amyloid beta; ABCB1, ATP-binding cassette B1; AD, Alzheimer disease; APOE, apolipoprotein; APP, amyloid precursor protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; BMDM, bone marrow–derived microglia; CAA, cerebral amyloid angiopathy; cMoP, common monocyte progenitor population; CNS, central nervous system; CR1, complement receptor type 1; CSF1R, macrophage-colony stimulating factor receptor; DAMP, damage-associated molecular patterns; EOAD, early onset Alzheimer disease; ERK, extracellular signal-regulated kinase; GMP, granulocyte and macrophages progenitor; HLA, human leukocyte antigen; IL, interleukin; IRF, interferon regulatory factor; LOAD, late-onset Alzheimer disease; LPS, lipopolysaccharide; mCSF, macrophage colony stimulating factor; MDP, muramyl dipeptide; MPL, monophosphoryl lipid A; NGF, nerve growth factor; NOD2, nucleotide-binding oligomerization domain–containing 2; PAMP, pathogen-associated molecular pattern; PICALM, phosphatidylinositol binding clathrin assembly protein; PRR, pattern recognition receptor; PSEN, presenilin; PU.1, purine-rich box 1; ROS, reactive oxygen species; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; TLR, toll-like receptor.

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others, are missense mutations and have a lower penetrance than PSEN1 gene modifications (Bekris et al., 2010).

Patients with EOAD tend to develop the pathology before the age 65. The other familial-like AD is named late-onset Alzheimer's disease (LOAD), this form is more common and complex. The complexity comes from the involvement of genetic, epigenetic, and environmental factors (Sun et al., 2017). The first discovered risk factor is the apolipoprotein E ε4 (APOE ε4), this allele represents 50% of LOAD cases. APOE gene is on chromosome 19q13.2, the protein plays a role in cholesterol transport, delivery, and distribution. The three isoforms differ in sequence by two single nucleotides, rs429358 and rs7412 (Sun et al., 2017). The alternative isoforms have a different impact on Aβ. Researchers from the genome-wide sequencing studies have identified dozens of additional genes as risk factors. In a nonexhaustive manner, we can cite the involvement of CD33, Clathrin Assembly Lymphoid Myeloid leukemia (CALM), human leukocyte antigen (HLA) DRB5/DRB1, and complement receptor type 1 (CR1), which are associated to the immune system. Further studies identified the amyloid transporter ABCA7 (ATP Binding Cassette Subfamily A Member 7) gene on chromosome 19 (19p13.3) as another risk factor. A single-nucleotide polymorphism rs3764650 is found in 64% of LOAD cases (Sun et al., 2017; Yu et al., 2015).

The EOAD has a different impact on patients than LOAD, since EOAD patients have a better memory compared with those with LOAD. However, they have a greater attention deficit, executive functions, and ideomotor praxis (Mendez 2017). Conversely, brain imaging reveals that EOAD patients have a greater atrophy of parietal cortex with a preserved hippocampal volume compared with LOAD patients (Kaiser et al., 2012). Both forms present an equivalent atrophy level of temporoparietal-pecuneus, a region involved in self-consciousness, episodic memory, and executive function. Finally, EOAD patients present more neuritic plaques and neurofilament τ in this region (Mendez 2017).

So far, there is no efficient treatment of AD. Few drugs are available, but their effects remain marginal. The first class of drug is acetylcholinesterase inhibitors (e.g., donepezil), which targets cholinergic neurons by inhibiting the degradation of acetylcholine, a neurotransmitter important for the short-term memory mainly found in hippocampus (Boncristiano et al., 2002; Schliebs and Arendt 2011). The other drug on the market is an antagonist of NMDA receptors called memantine. This molecule is used to decrease the neuronal excitotoxity provoked by the excess of glutamate (Acharjee et al., 2018). These neurotransmitter regulators are supposed to relieve symptoms for a short-term period, but they cannot delay the progression of AD (P. Liu et al., 2019).

Aβ is clearly a hallmark of AD. The amyloid hypothesis is the most tested, since it represents 22.3% of all clinical trials up to 2019, followed by the neurotransmitter hypothesis representing 19%. Treatment strategies focusing on the Aβ hypothesis targeted either β- and γ-secretase, 2 proteolytic enzymes responsible of APP cleavage (Golde 2014) or amyloid deposits, using monoclonal antibodies. The vast majority of immunotherapy based treatments failed in phase III as solanezumab (Eli Lilly), Gantenerumab (Roche/Genentech), and Crenezumab (Roche/Genentech/Ac Immune). Antibodies successfully reduced Aβ burden but failed to delay or improve the cognitive decline (P. Liu et al., 2019). Moreover, antibody-based therapies caused cerebral hemorrhages associated with the secretion of inflammatory factors. Lately, a novel antibody-based treatment showed promising results with fewer side effects. The antibody named HAE-4 targets APOE4 gene in the AD mouse model 5XFAD-APOE4$^{+/+}$. Xiong et al. (2021) demonstrated that HAE-4 does not exacerbate microhemorrhages and is efficient to decrease amyloid burden in the parenchyma and cerebral vessels (Xiong et al., 2021). Recently, Aducanumab (Biogen Idec) was partially approved by FDA not without debates. Indeed, the decision was based on results from a retrospective analysis made on a single trial (Ackley et al., 2021; Richard, den Brok, and van Gool 2021). Aducanumab, like other antibodies, has detrimental side effects (P. Liu et al., 2019; Walsh et al., 2021). This situation makes echo with the aforementioned therapies, namely acetylcholinesterase inhibitor and memantine, which were defunded in some countries since they failed to show evidence of clinical benefit (Walsh et al., 2021).

Other treatments aimed to inhibit β-secretase/BACE1 showed a reduction of Aβ in cerebrospinal fluid by 80%–90%. Here again, however, most of clinical trials failed in phase III, whereas some treatments even worsen cognitive decline and induced side effects (Doody et al., 2013; Honig et al., 2018; P. Liu et al., 2019). Antibody-based therapies allow to remove a great percentage of Aβ, suggesting that innate immunity can play a great role in AD and a direct modulation of immune cells could lead to better outcomes in regulating inflammation and Aβ phagocytosis.

II. Cerebral Amyloid Angiopathy

Aβ can aggregate into various forms, as oligomers, protofibrils, and amyloid fibrils which can assemble into amyloid plaques (G. Chen et al., 2017). The role of amyloid plaques in the cognitive decline and the etiology of AD is now highly controversial, and recent studies suggest that they may just be a reservoir of amyloid peptides (Murphy and LeVine 2010; Esparza et al., 2018). Consequently, solely targeting them is not a good therapeutic strategy. AD is also

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characterized by an accumulation of amyloid in cerebral vasculature, named cerebral amyloid angiopathy (CAA) (Brenowitz et al., 2015). In 2002, Jellinger estimated that 78%–98% of AD patients suffer of CAA (Jellinger 2002). Amyloid accumulation is found within the small- and medium-sized vessels, the Aβ deposition weakens the wall of vessels and leads to intracerebral hemorrhages and microbleeds, and these events accelerate AD (Pimentel-Coelho and Rivest 2012). Many factors may also cause changes in neurovasculature, such as hyperlipidemia. This condition is one of the most important since hypercholesterolemia increases the risk of AD by 3-fold. Moreover, a high level of cholesterol is correlated with a lower Mini-Mental State Examination (MMSE) score (Proitsi et al., 2014). It is interesting to note that, in the obesity context, adipose tissue is a source of inflammatory factors such as tumor necrosis factor (TNF-α), interleukine-1 and 6 (IL-1 and IL-6). Inflammation can lead to Aβ accumulation and τ phosphorylation (Letra, Santana, and Seiça 2014). Additionally, hypertension has been identified as an aggravating factor in AD, it is associated with a degradation of cognitive function (Moonga et al., 2017). Several clinical trials have been conducted using (1) statins, these molecules are used to lower the blood cholesterol level or (2) antihypertensive medication as ramipril a specific angiotensin-converting enzyme inhibitor; all of them failed to improve patient conditions (Wharton et al., 2012; Moonga et al., 2017).

Targeting amyloid deposits within vasculature remains interesting; the principal amyloid species accumulated in cerebral vessels is Aβ_{40} (Davis and Van Nostrand 1996). The balance between A$\beta_{40–42}$ may help to predict where amyloid will be located. High 40/42 ratio determines a greater accumulation in cerebral blood vessels, whereas low ratio leads preferentially to the formation of parenchymal plaques (Herzig et al., 2006). In the 90s, Calhoun et al., (1999) proposed that a neuronal source of APP can induce a prominent amyloid deposition in cerebral blood vessels, although the exact mechanism remains elusive. Two hypotheses were proposed to explain such a phenomenon. The first one postulates that amyloid is transported through interstitial fluid efflux (Carare et al., 2013; Hawkes et al., 2014), and the origin of Aβ in blood vessels and parenchyma is the same. The second is proposing that Aβ is transported by cerebrospinal fluid influx and/or through specific transporters at the blood-brain barrier (BBB). The latter is clearly the most interesting, since the brain has transporter mediating the efflux of Aβ and results from other studies seem to corroborate it (Herzig et al., 2006; Yuan et al., 2020).

For this section, we will focus on two major transporters, namely ATP-binding cassette B1 (ABCB1) and low-density lipoprotein-related protein-1. In physiologic conditions, neurons produce amyloid, which is removed by different mechanisms such as phagocytose by glial cells, enzymatic degradation, and transport through the BBB. In AD, these mechanisms are impaired. ABC transporters are using ATP as a source of energy; the subfamilies B, C, and G can remove toxic molecules from the brain to the blood (Qi and Ma, 2017). One of the most studied is ABCB1, also known as multi-drug resistance gene (MDR) 1/P-gp. Its expression decreases with aging and CAA conditions. Some reports revealed that ABCB1 is involved in Aβ removal. The mode of interaction between amyloid and ABCB1 is unclear, different possibilities have been elaborated the past years: 1) ABCB1 can directly bind Aβ and transport it, or 2) ABCB1 interacts with amyloid but is not involved in its transport. The latter case raises the possibility that MDR1 may anchor the Aβ preventing uptake into endothelial cells, or ABCB1 can transport degradation products of amyloid (F. C. Lam et al., 2001; Sita et al., 2017). It is well established that expression of ABCB1 is sensitive to amyloid. In vitro models have shown that A$\beta_{40 \text{ and } 42}$ downregulates ABCB1 in the vasculature. Amyloid induces the ubiquitination of the transporter leading to its internalization and degradation by the proteasome (Hartz et al., 2016). Depending on the mechanism, ABCB1 is crucial to transport Aβ out of the brain, since the pharmacological blockade of this transporter drastically decreases the amyloid efflux (F.C. Lam et al., 2001; Hartz, Miller, and Bauer 2010; ElAli and Rivest 2013; Sita et al., 2017).

Reactive oxygen species (ROS) are common to many CNS disorders, and ABCB1 is also sensitive to oxidative stress. However, the impact of ROS on ABCB1 expression is controversial, and some studies reported that ROS may promote endothelial cell survival by increasing ABCB1 expression. On other hand, ROS may lead to lipid peroxidation, and the latter is involved in BBB degradation, resulting in a decrease in ABCB1 expression (Sita et al., 2017, 1; Hartz, Miller, and Bauer 2010).

The other transporter is LRP1, a fast endocytic receptor mediating the trafficking and the degradation of more than 40 ligands, including Aβ (Shinohara et al., 2017). As ABCB1, its expression is decreased with aging and AD (Kang et al., 2000). However, LRP1 functions seem complex, the signaling downstream might impact the phagocytic abilities of cells. It has been reported that LRP1 is a modulator of cytoskeleton dynamic via the focal adhesion kinase/paxillin/phosphoinositide 3-kinase and extracellular signal-regulated kinase (ERK) pathways (Dedieu and Langlois 2008; Shinohara et al., 2017). To further understand the role of this receptor, researchers developed a selective deletion model of LRP1 within brain endothelial cells in 5xFAD mice exploiting the specific expression of thyroxine transporter Slcolcl in brain endothelial cells by engineering a

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Cre/lox mouse (Slcolcl-CreER^{T2} LRP1$^{fl/fl}$). The knockout of LRP1 in AD mice is associated with a decrease in plasmatic Aβ, an increase in soluble brain amyloid and a greater cognitive decline (Storck et al., 2016). These results highlight the importance of LRP1 in the Aβ clearance through the BBB.

Interestingly, Storck et al. (2018) proposed that amyloid removal by LRP1 and ABCB1 is linked by PICALM. Using immunoprecipitation experiments and inhibition of both ABCB1 and LRP1, they have shown that both transporters are functionally linked, meaning that the expression of one transporter influences the other. Indeed, a knockout of LRP1 in brain endothelium leads to a drastic diminution of ABCB1 expression. Moreover, the LOAD risk factor PICALM (Phosphatidylinositol Binding Clathrin Assembly Protein) is also associated with ABCB1 and LRP1 expression. It plays a functional link is guiding both proteins through brain endothelium. These results provide a better comprehension on the mechanisms mediating the Aβ transport across the BBB.

Many studies have documented the strong association between CAA and AD. CAA is thought to have a greater clinical impact than AD alone (Jellinger 2002; Thal et al., 2003; Brenowitz et al., 2015). However, the exact mechanism underlaying the CAA onset remains elusive, and further studies are required to better understand it. After more than a decade of clinical trials, a treatment remains far ahead, and the pathology is still not well understood. The therapeutic strategy has now changed, and scientists are now focusing their efforts on the innate immune system. A growing number of evidence shows that the modulation of such cells could be a more effective therapy against AD than the previous ones. Indeed, monocytes and microglia are of great interest and we and many others believe that a proper stimulation of these cells with specific ligands targeting three families of receptors could have promising therapeutic properties to prevent and delay AD.

III. Innate Immune System

The innate immune system is a well conserved host defense system. Leukocytes act as sensor and effector cells. They can initiate the immune response and therefore becoming activated in response to tissue injury, infection, or stress (Gasteiger et al., 2017). This immune system comprises a broad range of cells originating from the hematopoietic system, such as monocytes and monocyte-derived cells, natural killer cells, and granulocytes. Innate immune cells can recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) via evolutionarily conserved structures named pattern recognition receptors (PRRS) (Akira 2006). PRRs family is composed of toll-like receptors family (TLRs), C-type lectin receptor, NOD-like receptors, retinoic acid-inducible receptors, I-like receptors and DNA sensors. Once activated, PRRs mediate proinflammatory signals (Mogensen 2009). Signalization through TLRs activates a complex intracellular signaling cascade leading to the activation of transcription factors such as AP-1, NF-κB or IRF3. Some DAMPs and PAMPs can be recognized by one PRR, e.g., TLR4, suggesting similarities between DAMPs and PAMPs regarding the inflammatory response (L. Chen et al., 2017).

Monocytes and microglia belong to the innate immune system, but they do not have the same common progenitors. Indeed, three distinct hematopoietic programs drive the development of microglia, tissue-resident MP, and monocyte-derived MP (Hoeffel and Ginhoux 2018). Both types of immune cells are deeply involved in AD onset and progression (Rossi et al., 2021; Heneka 2020; Ní et al., 2020). The last decade, inflammation was thought to be the main cause of AD, but neuroinflammation is now seen as a consequence of AD rather than a cause (Kinney et al., 2018).

IV. Development of Monocytic Lineage

Monocytes are innate immune cells that are produced in the bone marrow. They have multiple roles and participate to tissue development, defense, and homeostasis. They also initiate and resolve the inflammatory reaction (Wolf et al., 2019). Monocytes arise in the fetal liver from the late yolk sac-derived erythromyeloid progenitors during the last wave of hematopoiesis (Hoeffel and Ginhoux 2018). Immature hematopoietic stem cells colonize and settle into the fetal liver. The latter is a major hematopoietic organ for the development of the immune system. Then, hematopoietic stem cells invade the bone marrow and become fully functional after birth (Wolf et al., 2019). Monocytic lineage formation and differentiation are under the control of transcription factors such as runt-related transcription factor 1 (RUNX1), C/EBPβ, PU.1 (purine-rich box 1), and interferon regulatory factor 8 (IRF8) and the cytokine IL-34 and macrophage colony stimulating factor (mCSF) (Dahl et al., 2003, 1). PU.1 is a major regulator of cells of myeloid lineage (Friedman 2007). It binds to the DNA site 5′-AAAG(A/C/G)GGAAG-3′ via the C-term domain and activates the transcription through the N-term domain and acidic domain (Klemsz et al., 1990). PU.1 is required to induce the development of microglia and monocytes. PU.1 influences the fate of progenitor cells in a dose-dependent manner. Dahl et al. (2003) have found that a higher expression of PU.1 favors monocytic over granulocytic development, whereas PU.1$^{+/-}$ favors neutrophil lineage. The phosphorylation of PU.1 allows interaction with IRF8, then the molecular complex binds to an Ets/IRF element containing a GGAA PU.1 site and induces the monocyte lineage gene program (Yáñez and Goodridge 2016). IRF8$^{-/-}$ or PU.1$^{-/-}$ mice present a drastic diminution of

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macrophages, resident macrophages and monocytes (Friedman 2007).

The classic model of myeloid cell production in the bone marrow follows different stages; multipotent hematopoietic stem cells, a subgroup of hematopoietic stem cells give rise to clonogenic progenitors named common lymphoid progenitors and common myeloid progenitors. The latter are under control of runt-related transcription factor 1 (RUNX1), PU.1, and IRF8 and give rise to megakaryocyte-erythrocyte progenitors and granulocyte and macrophages progenitors (GMPs). MDPs derive from GMPs, the latter are critical for monocyte production. The maturation of GMPs to MDPs is under the control of PU.1, IRF8, and GATA (guanine-adenine-thymine-adenine) 2 (Y. P. Zhu, Thomas, and Hedrick 2016). Lately, the common monocyte progenitor population (cMoP) has been discovered. These cells arise from MDPs driven by PU.1 and IRF8. cMoP is the last stage before fully functional monocytes. This ultimate maturation is driven by PU.1, IRF8, KLF4, and C/EBPβ that give rise to the classic monocyte subset. Within the three different populations, classic monocytes are the most abundant subset in blood. The two others are nonclassic also named patrolling monocytes and intermediate monocytes. cMoP and MDPs can give rise to patrolling monocyte subset, but the exact mechanism remains unclear. Of interest, classic monocytes can switch to patrolling monocytes and such a transformation involves the transcription factor Nr4a1/Nur77, C/EBPβ, c-Jun. These factors interact with AP-1 and binds to the DNA site 5′-TGA(C/G)TCA-3,' although further studies are needed to unravel the exact transcriptional processes involved in monocyte conversion (Wolf et al., 2019; Y. P. Zhu, Thomas, and Hedrick 2016).

V. The Role of Monocytes

Monocytes are very plastic and potent cells; they respond to stress, injury, and infection by bacteria or viruses since they express a large variety of cell surface molecules such as PRRs. The expression of these markers varies depending on monocyte subsets (Thériault, ElAli, and Rivest 2015; Kapellos et al., 2019). Different phenotypes have been identified so far using flow cytometry and intravital microscopy approaches. Populations differ from each other by the level expression of surface markers such as CD115, CD14, and CD16 in human and CD115, CD45, CCR2, CX3CR1, and Ly6C in mouse (Ginhoux et al., 2013). Human classic monocytes are defined by the expression of $CD14^{++}CD16^{-}$, the intermediate $CD14^{+}$, $CD16^{+}$ $HLA\text{-}DR^{+}CD86^{+}CD11c^{+}$ with a distinct transcriptomic profile (LYZ, S100A8, CD14, CD74, HLD-DRA, $HLA\text{-}DPB_1$ and CPV), and the nonclassic $CD14^{+/-}CD16^{++}$ (Ginhoux and Jung 2014). In mice, the distinction between populations is based on Ly6C expression level. Proinflammatory/classic monocytes $CX3CR1^{-}CCR2^{+}Ly6C^{+}$ contribute to inflammatory response and can infiltrate the tissue. The patrolling/nonclassic subset $CX3CR1^{+}$, $CCR2^{-}$, $Ly6C^{-}LFA\text{-}1^{+}$ patrols into vasculature are able to phagocyte amyloid peptides, regulate the inflammation, and stimulate tissue repair (Rossi et al., 2021). We can also distinguish an intermediate monocyte population in mice characterized by $Ly6^{int}$, however, this population has not been fully characterized yet (Sprangers et al., 2016). Classic and patrolling monocytes in human and mouse functions are quite similar.

Classic monocytes are well known to respond rapidly to infection or injury. They arise from the bone marrow and are released to the circulation in a CCR2-dependent manner. They can infiltrate different tissues, which then differentiate into macrophages or dendritic cells. They participate actively to the inflammatory response and the production of a wide range of cytokines, chemokines, adhesion molecules, and many other secreted molecules. They have the ability to do so since they express at a high-level critical innate immune receptor namely TLR4, TREM1, CCR2, NLRP3, and many others (Anbazhagan et al., 2014).

Patrolling monocyte subset is of great interest, since they can modulate the inflammation, scan the vasculature, and scavenge particles. The unique patrolling behavior of nonclassic monocytes highly depends on the interaction of LFA-1 with the wall of blood vessels (Narasimhan et al., 2019). TLR7 activation seems to increase the retention time of these monocytes on the endothelium (Imai and Yasuda 2016). Patrolling monocytes have a different gene signature compared with inflammatory monocytes. Indeed, patrolling monocytes express a high level of genes involved in cytoskeletal dynamics CDC42 effector protein-4, creatine kinase B and EML4 as well as corresponding receptors, such as CX3CR1, CD115, and Siglec10. Intriguingly, nonclassic monocytes do not produce ROS suggesting that they do not directly participate to the inflammation.

VI. Microglia Development and Role

Microglia are the resident macrophages of the CNS, they originate from the yolk sac, and are derived from the peripheral mesodermal tissue, the mechanisms underlying the microglia colonization, and differentiation has been recently unraveled (Prinz and Mildner 2011; Baufeld et al., 2018). In rodents, $CD45^{-}CD117^{+}$ erythromyeloid precursors from the yolk sac through the blood circulation settle and colonize the mesenchyma surrounding the neural tube at E8. Around E9.5, progenitor cells repress the expression of CD117 and express CX3CR1 (Lenz and Nelson 2018). The latter is involved in the communication between microglia and neurons. At this point, microglia

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progenitors infiltrate the neuroectoderm using metalloproteinases, a family of enzymes involved in the remodeling of extracellular matrix components (Kierdorf et al., 2013). As their monocyte counterparts, the development and the survival of microglia progenitors depend on CSF1R, PU.1, and IRF8 (Kierdorf et al., 2013; Lenz and Nelson 2018). CSF1R can bind two ligands, namely mCSF and IL-34, and it has been demonstrated that IL-34 is the predominant ligand of CSF1R during the development (Boulakirba et al., 2018). The cortex in mouse is colonized by microglia at E11.5, the first aggregate is seen at the pial surface and within the lateral ventricles (Swinnen et al., 2013). Then, microglia spread throughout the cortical wall (Low and Ginhoux 2018). The colonization of brain by microglial cells is a multiple-step process, this progression is similar in both mouse and human. The first phase is called tangential migration, ameboid microglia move parallel to the brain surface, the second phase is named radial migration, during this step microglia change direction to move into regions of parenchyma (Cuadros and Navascués 2001). After the brain colonization, microglia maturate and proliferate; the shape of microglial cells changes from ameboid to ramified, which is partly dependent on astrocyte-derived factors, namely mCSF/IL-34, TGF-β2, and cholesterol (Bohlen et al., 2017). Microglia proliferate until the fourteenth postnatal day in rodents, and after having reached the peak of proliferation, the number of microglia slowly decreases to adult levels (I. Kim et al., 2015). Importantly, neither CX3CR1, CCR2, CCR1, CX3CR3, or their ligands or DAP12 are essential for the survival and the development of embryonic microglia. However, DAP12 is crucial during adulthood for survival and homeostatic functions of microglia in several brain regions (Kierdorf et al., 2013).

Microglia signature differs from a healthy and a pathologic CNS. In the last decade, microglial phenotypes were characterized according to the differential expression of cell surface receptors, or the expression of cytokines. The nomenclature has distinguished different phenotypes. M1, a proinflammatory/neurotoxic profile, and the M2, which was described as an anti-inflammatory phenotype participating in the resolution of inflammation, although this is a simplistic view of the complex physiology of microglia (Ransohoff 2016). Newly developed technics, including RNA-sequencing, epigenetic studies, bioinformatics, and quantitative proteomics helped to better understand and characterize microglial diversity in rodents and humans (Hickman et al., 2013; Gosselin et al., 2017; Butovsky and Weiner 2018; Olah et al., 2018).

Interestingly, there is a unique transcriptional signature in microglia of healthy adult mouse with the main expression of purinoreceptor P2ry12, Tmem119, sialic acid binding Ig-like lectin H, suppressor of cytokine signaling 3, olfactomedin-like protein 3 and Fc receptor-like S a scavenger receptor (Satoh et al., 2016; C. Zhu et al., 2017; Zrzavy et al., 2017). A similar transcriptional signature has been observed in the human brain, especially for P2yr12 and Tmem119 (Prinz et al., 2017). Microglia are essential for synaptic pruning during the development and adulthood, and they are required for shaping neuronal networks (Szepesi et al., 2018). As immune cells, they are capable of phagocyting synapses, and synaptic pruning involves complement protein C1q and CR3. Inhibition of complement molecules reduces the number of phagocytic microglia and triggers synaptic loss (Butovsky and Weiner 2018; Rivest 2018). The synaptic loss is associated with the cognitive decline in AD, which may also depend on the complement cascade together with amyloid plaques (Hong et al., 2016). Microglia reactivity changes during the progression AD and such a dysregulation could contribute to the physiopathology of the disease.

Microglia serve as a trophic support for brain cells, since they have the ability to produce brain-derived neurotrophic factor (BDNF), neurotrophin 3, nerve growth factor (NGF) and insulin-like growth factor 1 (IGF-1) (Pons and Rivest 2020). Interestingly, the latter is produced by an ITGAX-expressing microglial subset in the developing brain (Wlodarczyk et al., 2017). These neurotrophic factors are essential for the brain development and repair, and it was shown that microglia promote learning-dependent synapse formation through BDNF (Parkhurst et al., 2013). The presence of Aβ alters the homeostatic phenotype of microglial cells and the inflammatory environment interferes with memory consolidation and secretion of neurotrophic factors (Giuffrida, Copani, and Rizzarelli 2018). Further studies have demonstrated that patients become resistant to IGF-1, which may contribute to the cognitive decline (Talbot et al., 2012; Westwood et al., 2014; Galle et al., 2019). Expression levels of NGF and TrkA are increased in mild cognitive impairment and mild AD patients, although a reduction of both molecules is observed in severe AD. As NGF and despite conflicting reports, BDNF level is also decreased in AD (Buchman et al., 2016; Crispoltoni et al., 2017; Sampaio et al., 2017). In conclusion, microglia have the ability to secrete numerous growth factors in the brain of healthy individuals, but they seem to lose such properties in the course of AD.

VII. Modulation of the Innate Immune System in AD

In the past two decades, a large body of evidence has underlined a critical role of the innate immune system in AD. Years ago, the research was focused on understanding the contribution of inflammatory response to

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the disease process, whereas the past decade was dedicated to take advantage of such a system to delay AD progression and to treat patients. In the following sections, we will focus on the powerful neuroprotective effects of a series of molecules that can trigger the immune response in AD. Some of them may soon be used in AD patients and individuals at risk of developing the disease.

VIII. Targeting the mCSF/CSFS1R Axis

Microglia interact directly with Aβ via PRRs. On the front line, microglial cells use class A scavenger receptor, CD36, CD14, CD47, TLR2-4-6, and 9. Upon binding amyloid, receptors initiate cell activation and phagocytic pathways (Bloom 2014; Fan et al., 2019). Once internalized, amyloid peptides trigger endosomal and lysosomal pathways. However, a question remains controversial about the intracellular degradation of amyloid. Contradictory studies showed that, in one hand, cultured primary mouse microglia release fibrillary amyloid after internalization (Chung et al., 1999), whereas in other, they can keep Aβ for weeks without degrading it (Paresce, Chung, and Maxfield 1997). In 2007, Majumbar et al. (2007) proposed that microglia have to be properly activated to efficiently degrade amyloid. They showed that mCSF-stimulated microglia are prone to degrade Aβ due to the lysosomal acidification induced by the cytokine. CSF1R also named CD115 is a tyrosine kinase receptor encoded by c-fms proto-oncogene (Chitu and Stanley 2006). The receptor is highly expressed by myeloid lineage cells and is involved in the development, activation, and survival of these cells. Recently, genetic variants of CD115 have been identified in AD patients, and these mutations are strongly associated with LOAD (Sassi et al., 2018; Martin-Estebane and Gomez-Nicola 2020). Boissonneault et al. (2009) confirmed in 2013 in vivo the results found by Majumbar et al. They administered mCSF weekly in $APP_{swe/PSEN1}$ mice from 3-month-old to 6 or 9-month-old and found a powerful effect of mCSF on the progression of AD. mCSF-treated animals displayed a reduced cognitive decline and less amyloid burden (Fig. 1).

On the clinical side, the cytokine is promising, because animals did not exhibit noticeable side effects despite the repeated injections. The cytokine acts on microglia and monocytes by stimulating their proliferation in the cortex and hippocampus followed by a massive infiltration of $CCR2^+$ monocytes. However, there is no evidence that CSF1R is directly involved in the recruitment of monocytes (Pons et al., 2020). Interestingly, breeding CCR2-deficient mice with APP animals exacerbated amyloid deposition, worsened the cognitive decline, and reduced the number of infiltrating monocytes (El Khoury et al., 2007). Further studies showed that CCL2/CCR2 axis is impaired in

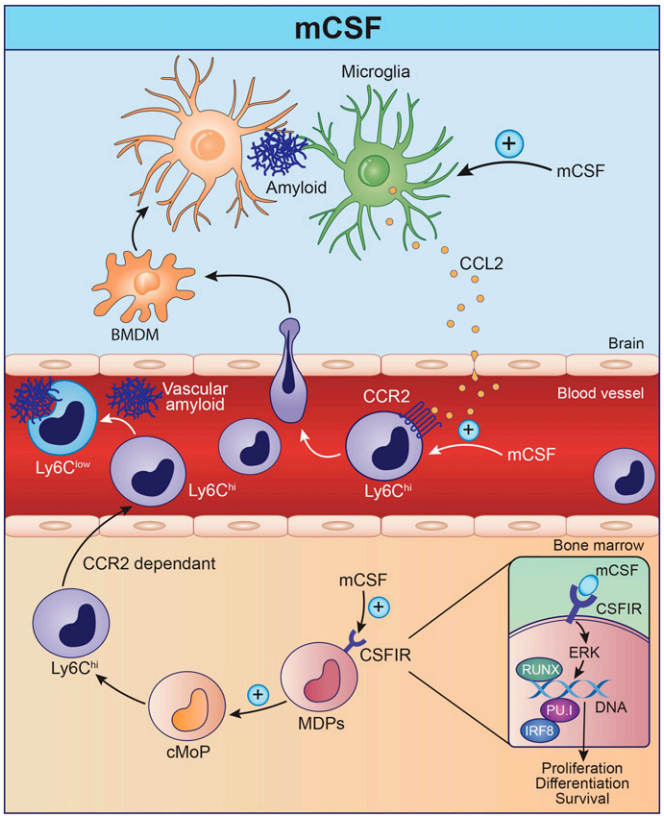

Fig. 1. Action of mCSF on innate immune cells in Alzheimer's disease. In the brain, mCSF stimulates proliferation of microglia and their phagocytic abilities toward amyloid peptides. The cytokine also stimulates the production of CCL2, which recruits monocytes from the blood stream. Monocytes infiltrate the brain on a CCR2-dependent manner and differentiate into microglia-like cells once into brain. The latter then helps to phagocyte amyloid peptides.

monocytes from AD patients resulting in a lack of migration toward the parenchyma, suggesting an important role of classic monocytes in AD (Guedes et al., 2015). Moreover, some studies reported that bone marrow–derived cells (BMDM) are more efficient to clear amyloid than resident microglia. mCSF-stimulated microglia secrete CCL2 to recruit monocytes, which involves adhesion factors such as VLA-4 and LFA-1 and their counterparts on the endothelium, VCAM-1 and ICAM-1 (Li, Chen, and Zhang 2020). Once into the parenchyma, monocytes differentiate into microglia-like cells. BMDM and resident microglia are slightly different, however, the mechanism of differentiation need to be determined. BMDM express higher levels of MHC class II, a greater ability to clear Aβ and a reduced production of ROS (Jin et al., 2017). BMDM can be distinguished from microglia by the expression of CCR2, since this receptor is absent in all CNS cell types (Mizutani et al., 2012). In the same line, Kawanishi et al. (2018) have demonstrated that mCSF-treated BMDM once injected within the mouse hippocampus migrate toward amyloid and phagocyte Aβ, resulting in decreased number of

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amyloid plaques compared with their littermate-controls. These results show that the stimulation of CSF1R in AD triggers microglia activation and monocyte differentiation toward amyloid deposits and ameliorate the physiopathology of AD in mice. Further study by Delaney et al. (2021) showed that depletion in CSF1R signaling induces BBB disruption and decreases the phagocytic capacity of peripheral macrophages, whereas it has no effects on microglia. Our laboratory has also demonstrated such effect on microglia after CSF1R deletion in a recent study. We have reported in APP mice after the conditional deletion of CSF1R a decrease in the volume of amyloid plaques in hippocampus and cortex associated with a cognitive improvement in APP-CSF1R$^{-/-}$ mice compared with the APP control mice. Besides, our study also confirmed results found by Delaney et al. regarding the impairment of the peripheral immunity. We observed a maintained expression of ABCB1 in knockout mice associated with an increased number of Aβ-positive vessels and a higher concentration of Aβ_{40} into the vasculature suggesting an exacerbation of CAA at 8-month-old in APP-CSF1R$^{-/-}$ mice, probably caused by a monocyte defect (Pons et al., 2021). Interestingly, we have also observed in CSF1R$^{-/-}$ mice an upregulation of IL-34 at 6-month-old suggesting a potential role of this cytokine in AD.

IL-34 is the second ligand binding to CSF1R and has a great interest regarding the modulation of innate immunity (Ma et al., 2012). The cytokine was first shown to be important for the maintenance and differentiation of adult microglia. Mizuno et al. (2011) showed that IL-34–treated microglia decreased the neurotoxic effect of Aβ and promoted phagocytose and degradation of amyloid peptides in a neuron-microglia coculture system. The neuroprotective effect of IL-34 treatment appears to be driven by the upregulation TGF-β1. The latter prevents microglia activation and proliferation in vitro and in vivo. It is important to mention that blocking the anti-inflammatory cytokine TGF-β was also found to exacerbate AD-like symptoms through inhibiting the phagocytic properties of microglia and monocytes (Town et al., 2008). The exact mechanism is partially understood, some studies reported that TGF-β1 suppresses interferon-γ signaling by reducing STAT1 phosphorylation via the overexpression of MAPK phosphatase-1, thereby negatively regulating ERK and p38 (Takaki et al., 2006; Herrera-Molina et al., 2012; Kaplan 2013; Zhou et al., 2015). IL-34 signaling pathways are complex, some actions are overlapping with mCSF, notably its action on immune cells. The main difference resides on the production of chemokines. IL-34–stimulated cells express less ICAM-1, MCP-1, and more HLA-DR and eotaxin-2 (CCL24), a molecule that binds CCR3 to stimulate the recruitment of eosinophils and neutrophils (Chihara et al., 2010; Guillonneau, Bézie, and Anegon 2017). Additionally, IL-34 can bind 3 receptors, namely CSF1R, Syndecan-1, and PTP-ζ that complexify the study and the understanding of this cytokine. Further studies are needed to understand the basic mechanisms mediating the great therapeutic potential of CSF1R ligands in AD.

It is interesting to note similar outcomes by either impeding or enhancing CSF1R signaling in AD, it appears to be contradictory, and both seem to be beneficial for the disease for different reasons (Majumdar et al., 2007; Boissonneault et al., 2009; Mizuno et al., 2011; Chitu et al., 2016; Kawanishi et al., 2018; Delaney et al., 2021; Pons et al., 2021). We deliberately omitted to talk about the supposedly beneficial effect of CSF1R small-molecule inhibitors named PLX on AD. The debate is vivid between researchers about the interpretation of results. Some argue that PLXs affect solely microglia and have a minimal effect on peripheral cells, although a growing number of evidence shows that molecules impact the periphery even in on a short period (Lei et al., 2021, 2020; Delaney et al., 2021).

IX. Triggering Patrolling Monocytes to Clear Vascular Aβ

The nucleotide-binding oligomerization domain 2 (NOD2) belongs to the PRRs subfamily NOD-like receptors (Negroni et al., 2018). It is a cytosolic receptor able to detect a component of the bacterial wall, namely muramyl dipeptide (MDP) (Kawai and Akira 2009). A NOD2 mutation or altered expression is involved in chronic inflammatory disorders, such as Crohn disease, Blau syndrome, and early onset sarcoidosis (Ogura et al., 2001; Kanazawa et al., 2005; Dugan et al., 2015). Upon MDP liaison to NOD2, the latter undergoes an oligomerization and recruits downstream molecules, such as RIP2 (also known as RICK), Ripk2, and CCK. Once activated, RIP2 leads to the ubiquitination of NF-κB, followed by the activation of IKK, then IKK complex phosphorylates the inhibitor of NF-κB, resulting in the translocation to the nucleus of NF-κB (Park et al., 2007). NF-κB participates in the control of transcription of over 150 target genes (Pahl 1999). The last decade, a vivid debate animated the scientific community about the potential role of MDP-activated NOD2 on inflammation (Ogura et al., 2001; G. Kim et al., 2011; Coulombe et al., 2012; Philpott et al., 2014). Lately, Lessard et al. (2017) have demonstrated that MDP-stimulated NOD2 converts inflammatory monocytes into patrolling monocytes in a Nr4a1 (Nur77)-dependent manner. Nur77 is an orphan nuclear receptor belonging to Nur77 family containing Nurr-1 and Nur77 is involved in various biologic processes such as apoptosis, brain development, and metabolism (Yoon and Lau 1993). So far, no ligand has been identified for this family. The expression of

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Nur77 is regulated by CREB, and Nur77 gene contains four copies of a CRE that bind CREB and two sites for MEF2 factors. Mechanistically, AP-1 and CREB transcription factors bind and activate Nur77 (B. Y. H. Lam et al., 2010). The monocytic switch from classic to nonclassic phenotype after NOD2 stimulation is not fully understood, several studies used Nur77$^{-/-}$ mice to decipher the role of the transcription factor. The most interesting study is from Hanna et al. (2011). They have demonstrated that mice lacking Nur77 have a defect in production of patrolling monocytes. The poor number of patrolling monocytes that remains in the bone marrow seems to be enabled to proliferate properly. They also showed that Nur77-deficient patrolling monocytes are blocked in the S phase of the cell cycle and undergo apoptosis, suggesting Nr4a1 is absolutely needed for the production of patrolling monocytes (Hanna et al., 2011).

Little is known about the migration, the transformation, and the recruitment of nonclassic monocytes to the vascular amyloid. CCR5 might be partially involved in the recruitment of Ly6C^{-}. The blockade of CCR5 leads to a 40% reduction in the number of patrolling monocytes at the site in a model of atherosclerosis. However, CCR5 is poorly expressed on these monocytes raising the question about the real impact of such receptor on the recruitment of Ly6C^{-} monocytes (Thomas et al., 2015). Despite the little number of studies on the role of patrolling monocytes in AD, it seems important to highlight the strong therapeutic potential of this subset. Michaud et al. (2013) used intravital two-photon microscopy to functionally assess the role of Ly6C^{-} monocytes in the brain vasculature of APP mice. They have demonstrated that patrolling monocytes are specifically attracted onto the luminal wall of Aβ-positive veins and, interestingly, these monocytes are not active in Aβ-positive arteries or Aβ-free blood vessels. The specific removal of vascular Aβ by Ly6C^{-} leads to a significant decrease of amyloid plaques in hippocampus and cortex area. This study shed the light on the role of such monocytes, suggesting that the increase of the latter in AD could be an interesting therapeutic avenue (Michaud et al., 2013). Patrolling monocytes have a greater ability to phagocyte compared with classic monocytes, and they produce fewer proinflammatory cytokines upon stimulation with LPS, as they express lower levels of CD14 (a coreceptor of TLR4) (Cros et al., 2010). The phagocytic mechanism seems to be dependent on LFA-1-ICAM-1/VCAM-1, since antibodies against them block the uptake of altered red blood cells (Y. Liu et al., 2019).

Increasing the number of patrolling monocytes into the vasculature is quite interesting in AD, since clearing the amyloid associated to blood vessels could lead to an amyloid efflux from the brain to the vasculature, a mechanism called the sink effect (Fig. 2). It rests on the hypothesis that amyloid in the brain and periphery are

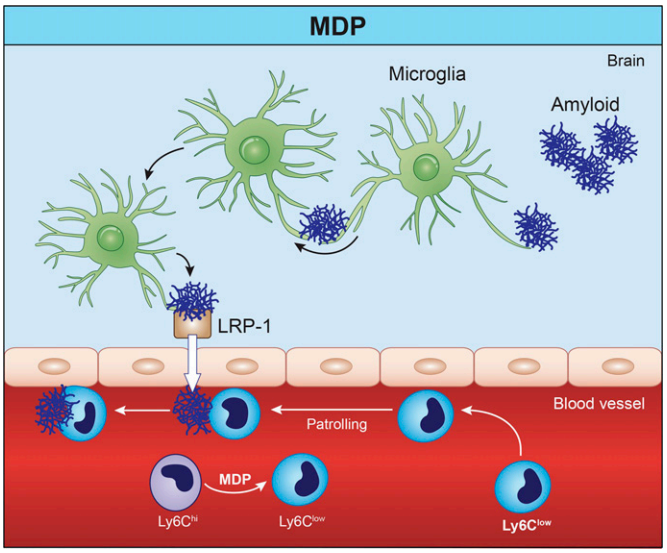

Fig. 2. The effect of MDP on innate immunity: MDP induces the switch from inflammatory monocytes to patrolling monocytes into blood vessels. The latter cells scavenge vascular amyloid. The transport of Aβ across the BBB is partly done by LRP1. Perivascular microglia could be the cells transporting amyloid peptides from the parenchyma to LRP1 at the abluminal side of the BBB.

in equilibrium, meaning that removing Aβ into blood vessels could lead to a passive or active diffusion of amyloid from the brain to the vasculature (Bell 2012; DeMattos et al., 2001). As far as we know, the only study using MDP as a treatment of AD has been done by our team. Fani Maleki and colleagues injected mice with MDP to increase patrolling monocytes in blood vessels, as they wanted to prove that the switch of monocytic population from inflammatory to patrolling improves the condition of APP mice. The treatment started at 3 months of age before the appearance of symptoms to 6-month-old. We proved that repeated injections of MDP can maintain a high level of patrolling monocytes for at least 3 months, without any harmful effects on mice. We showed an improvement in memory function associated with a delayed synaptic loss. Of interest, expression of the amyloid transporter LRP1 was increased, suggesting that Aβ is transported to the blood vessels, where patrolling monocytes can scavenge it (Fani Maleki et al., 2020). Further studies have to be made to fully understand the mechanism underlaying these encouraging results. Patrolling monocytes are of interest due to their capacity to phagocyte amyloid and by their abilities to mediate neuroprotection in an excitotoxic environment after sterile inflammation triggered by kainate, a conformational analog of glutamate. Monocytes migrated toward CNS and accumulated specifically near the excitotoxic injury. Monocytes underwent a differentiation into microglia-like cells and strongly expressed Iba1 and CD68 7 days postinjury. Authors deleted CX3CR1 in mice and they observed a diminution in level of patrolling monocytes

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in the blood 24 hours postinjection of kainite. Additionally, they also found a specific elimination of patrolling monocytes using Nur77$^{-/-}$chimeric mice, suggesting a protective role of nonclassic monocyte subset in this mouse model of neuronal injury (Bellavance et al., 2015).

Interestingly, besides the beneficial effect of patrolling monocytes on inflammation, tissue repair and phagocytose, monocytes can recruit neutrophils under some circumstance. Neutrophils are an emerging player in AD. This population of immune cells are highly reactive, and they can adapt their phenotype and function in response to environmental stimuli (Ng, Ostuni, and Hidalgo 2019; Rossi et al., 2021). New evidence show that patrolling monocytes can recruit and retain neutrophils, since CX3CR1- and Nr4a1-deficient mice display a reduced number of neutrophil recruitment (Carlin et al., 2013). Neutrophils are involved in AD pathology, and they are recruited to the vasculature and the brain. A selective inhibition of these cells leads to a cognitive improvement and a decrease of neuropathological features of AD (Pietronigro et al., 2017). Neutrophils are potentially harming the BBB and neural cells via extracellular traps in the brain and blood vessels of AD mice. A recent study has found that accumulation of such leukocyte subset into the brain vasculature alters the blood flow in different AD mouse models, namely APP/PS1 and 5xFAD (Cruz Hernández et al., 2019). A study has shown that cell-cell contacts can promote intravascular activation and exacerbates the production of inflammatory molecules during acute inflammation (Finsterbusch et al., 2016).

However, the interaction between patrolling monocytes and neutrophils and the role of such interaction is not clear in AD, and it will require further studies to elucidate whether patrolling monocytes can drive the neutrophil response and how this is done.

X. Targeting TLR4

TLRs are a family of surface receptors on innate immune cells, specialized in the detection of PAMPs and DAMPs able to trigger cell activation (Akira 2006). TLR4 was the first PRR of the family to be identified in humans. The latter can sense PAMPs such as lipopolysaccharide (LPS) and a large variety of DAMPs like $HMGB_1$, metabolites from ROS, extracellular matrix destruction products, and amyloid (Cruz Hernández et al., 2019). TLR4 signaling pathways are complex and have been thoroughly reviewed by (Akira 2006). Briefly, MD-2 and CD14 are two extracellular molecules required to mediate the signal. Upon TLR4 activation, MyD88 mediates the activation of IL-1 receptor–associated kinases (IRAKs) and TNF receptor–associated factor 6 (TRAF6). This is followed by the activation of the IKK complex and the translocation of NF-κB into the nucleus leading to the transcription of numerous inflammatory genes (Kawai and Akira 2009). Additionally, TRAF6 activates ERK, JNK and p38, which participate to the inflammatory response and phagocytose, since TLR4 can induce the expression of the scavenger receptor SR-A, MARCO and LOX-1 in a MyD88-IRAK4 and p38-dependent manner (Doyle et al., 2004).

In the brain, TLR4 is mainly expressed by microglia, although other cell types have been shown to respond to LPS and endogenous TLR4 ligands. Microglial cells strongly express TLR4 when surrounding amyloid plaques in mouse models of AD and AD patients, which also exhibited higher expression levels of several inflammatory mediators compared with healthy controls (Fig. 3) (Minoretti et al., 2006; Walter et al., 2007; Calvo-Rodriguez et al., 2020). Of interest, both detrimental and beneficial roles of TLR4 have been reported in AD (Fiebich et al., 2018). A defect in TLR4 activation has been identified as a risk factor for AD in humans. Indeed, Asp299Gly polymorphism or mutations are associated with a reduced inflammatory response and a more pronounced pathology (Minoretti et al., 2006; Tahara et al., 2006; Paudel et al., 2020). These results were reproduced in AD mice lacking TLR4, as these animals presented a reduced microglial activation associated with a greater cognitive decline and an increased level of amyloid (Song et al., 2011). These data suggest a central role of TLR4 in AD and amyloid uptake. However, a conflicting study reports that a selective TLR4 antagonist or a knockout had no effect on memory loss or microglia activation after intracerebral injection of amyloid (Balducci et al., 2017). LPS-induced different outcomes depending on the route of administration, the

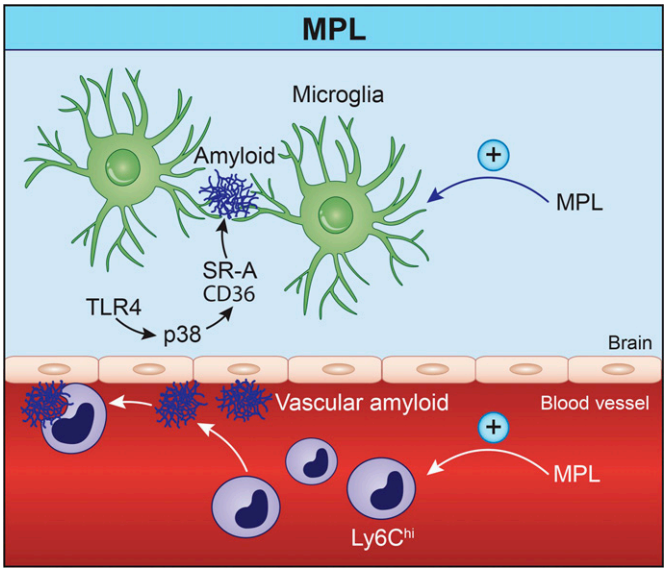

Fig. 3. The effect of MPL on the immune system in AD. MPL activates the microglial phagocytosis via p38 and CD36/SRA. In blood vessels, MPL stimulates the proliferation of monocytes.

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dose, the duration, and the age (Nazem et al., 2015; Zhao et al., 2019), underling the importance of the model and treatment in the interpretation of the data (Bardou et al., 2014).

LPS injections exacerbated the physiopathology in APP sweTg and 3xTg-AD mice, as authors found an increase in amyloid production and tau hyperphosphorylation (Sheng et al., 2003; Kitazawa et al., 2005; Zhan, Stamova, and Sharp 2018). Chronic exposure to LPS is also detrimental in patients and AD mouse models, since it leads to an overproduction of inflammatory cytokines, and these molecules were proposed to mediate the increase of Aβ deposits along with BBB disruption (Y. Wang et al., 2015; Chang, Yee, and Sumbria 2017; Martini et al., 2019; Zhao et al., 2019).

Monophosphoryl lipid A (MPL) is a TLR4 agonist derived from LPS, both molecules share many immunomodulatory properties exception made on the induction of a strong proinflammatory response. MPL is 100-fold less pyrogenic than LPS and is a weak inducer of TNF-α, IL-1β and CCL2 (Rego et al., 2016). Importantly, MPL is safe for humans, since it is used as adjuvant in several vaccines, e.g., Cervavix and Fendrix, (Q. Wang et al., 2020; Baldrick et al., 2002). LPS-activated TLR4 drives the immune response via MyD88 and TRIF. MyD88 pathway is activated at the plasma membrane, whereas TRIF-dependent pathway is activated when TLR4 is internalized into endosomes (Kagan et al., 2008; Tanimura et al., 2008). Conversely, MPL barely stimulates TLR4, this altered activation is correlated with a decrease of CD14-dependent TNF-α production, IFNβ induction and an upregulation of CD86. Tanimura et al. (2014) have suggested that MPL fails to induce a proinflammatory signal due to a lack of CD14/MyD88 response at the plasma membrane.

Our laboratory was the first to use MPL as a preventive therapeutic tool against AD, and in this study, we have demonstrated the beneficial role of MPL in a mouse model of AD. Michaud et al. (2013) have administered MPL once a week for 12 consecutive weeks in AD mice from 3 months old to 6 months old. They have reported that MPL-stimulated microglia and monocytes displayed a greater ability to phagocyte amyloid compared with LPS, this is mainly due to a better activation of p38/SR-A in microglia and monocytes by MPL. The reactivation of this pathway by MPL seems to be important in the disease since SR-A expression is altered in AD patients and APP mice (Michaud et al., 2013; Cornejo et al., 2018). Additionally, MPL triggers a robust monocytopoiesis. Consequently, the production of monocytes, a restored phagocytic ability and a weak induction of inflammatory response is beneficial for AD mice (Michaud et al., 2013). These results suggest that a proper activation could lead to improve the physiopathology of AD (Shaftel et al., 2007; Birch, Katsouri, and Sastre 2014; Chakrabarty et al., 2015; Businaro et al., 2018).

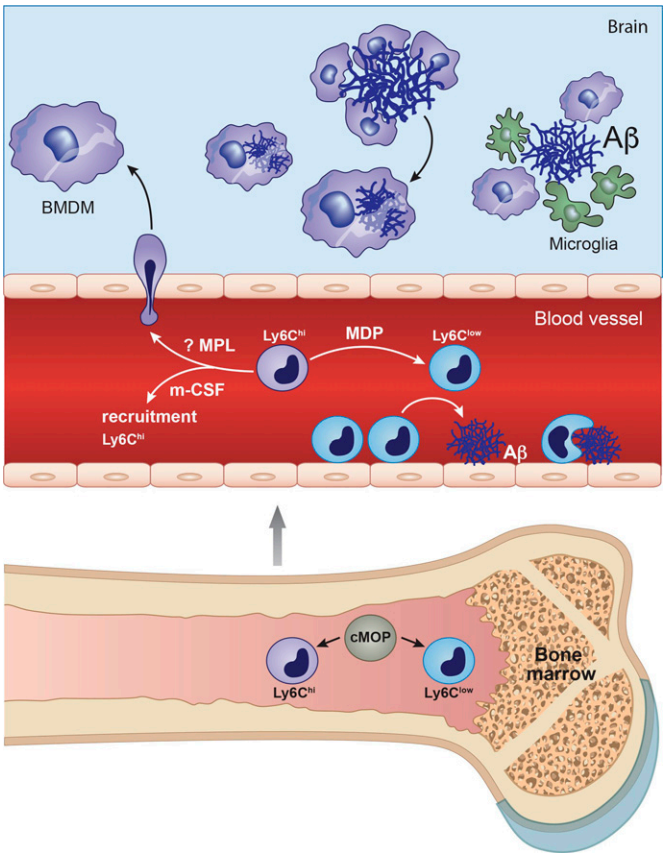

Fig. 4. Action of mCSF, MDP, and MPL on the immune system in AD. mCSF stimulates monocyte precursors in the bone marrow to trigger the recruitment of Ly6C^{hi} monocytes in the blood vessels where they may infiltrate into the brain to phagocyte amyloid plaques. MPL induces the proliferation of monocytes and activates the phagocytic response by microglia. MDP injections lead to the conversion from Ly6C^{hi} to Ly6C^{low} monocytes in blood vessels and patrol the cerebrovascular system and clear amyloid peptides on the luminal side of the blood-brain barrier.

Lately, Pourbadie et al. (2018) used a low dose of either LPS or MPL to properly prime myeloid cells. They found that priming microglia with low dose of TLR4 agonists abolished the tolerance of microglia toward amyloid and prevented impairment of cognition and reduced amyloid burden in brain. Agonist-stimulated microglia displayed a mild inflammatory response with a downregulation of TNF-α expression in the group injected with LPS, but not in MPL-treated rats. Such a modulation is associated with an increase in IL-10, arginase-1 and TGF-1β expression in all groups. Interestingly, MPL and LPS have different outcomes regarding the plaque number since authors have found a lower number of plaques in MPL-treated animals (Pourbadie et al., 2018). These results suggest that different effects of agonists on the cellular response may be due to the different TLR4 signaling pathways triggered by both analogs.

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In the same line, Yousefi et al. (2019) found that the pretreatment in vivo and in vitro with a low dose of LPS or MPL increases the expression of the neuroprotective cytokine IFN-β. The latter seems necessary to modulate the inflammatory reaction (Tarassishin, Suh, and Lee 2011), since it stimulates the transcription of SIRP-β1. This protein can complex with TREM2/DAP12 complex, which is strongly involved in the phagocytic response and the regulation of inflammation (Hayashi et al., 2004; Lanier 2009; W. Liu et al., 2020; Butler et al., 2021). TREM2 plays a pivotal role in AD and recent findings revealed that TREM2 and TLR4 expressions are negatively correlated. Long and colleagues have shown that TREM2 attenuates amyloid-mediated neuroinflammation by repressing TLR2, 4 and 6 downstream in vitro (Long et al., 2019). This group proposed that TREM2 may regulate the translocation of NF-κB and then suppress p-ERK/p-p38 and p65 signaling pathway (Long et al., 2019). However, the exact mechanism linking TREM2 and TLR4 remains to be elucidated.

XI. Final Remarks

Modulating the innate immune response constitutes a promising therapeutic avenue for AD, especially in targeting three families of receptors, e.g., CSFR1, NOD2 and TLR4 (Fig. 4). In the last decade, specific ligands for these receptors have shown interesting outcomes on the AD physiopathology and this both in vitro and in vivo contexts. MDP, mCSF, and MPL are able to modulate the immunity, delay the cognitive decline and reduce the amyloid burden. It raises interesting questions about the real effect of these molecules on cells and the disease. What are the mechanisms involved and do they last? What are the roles and the functions of patrolling and intermediate monocytes? Finally, whether the signaling pathways initiated by MDP, mCSF, and MPL interact together on monocytes and resident microglia? Advances in understanding the proper way to activate of innate immune cells are primordial to develop effective therapeutic strategies in AD and we may be closer to propose something to patients and those at risk of developing this disease at the end of the day.

Acknowledgments

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