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***Abstract*——Retinoid is a term for compounds that bind to and activate retinoic acid receptors (RARα, RARβ, and RARγ), members of the nuclear hormone receptor superfamily. The most important endogenous retinoid is all-*trans*-retinoic acid. Retinoids regulate a wide variety of essential biological processes, such as vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, differentiation and apoptosis, and homeostasis, as well as their disorders. This review summarizes the considerable amount of knowledge generated on these receptors.**

Introduction

The retinoic acid receptors (RARs[1]) mediate both organismal and cellular effects of retinoids. "Retinoids" is a generic term that covers compounds including both naturally dietary vitamin A (retinol) metabolites and active synthetic analogs (Sporn et al., 1976; Chambon, 2005). Both experimental and clinical studies have revealed that retinoids regulate a wide variety of essential biological processes, such as vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, differentiation and apoptosis, and homeostasis, as well as their disorders (Sporn et al., 1976; Blomhoff, 1994; Sporn et al., 1994; Kastner et al., 1995; Chambon, 2005). All-*trans*-retinoic acid (ATRA), the most potent biologically active metabolite of vitamin A, can both prevent and rescue the main defects caused by vitamin A deficiency (VAD) in adult animals (Kastner et al., 1995). As early as 1925 preclinical studies demonstrated that VAD correlated with the development of squamous metaplasia in rodents (Wolbach and Howe, 1925). This and subsequent studies anticipated a strong rationale for the use of retinoids in the treatment and prevention of cancer (Hong and Sporn, 1997). The most impressive example of retinoid anticancer activity is the treatment of patients with acute promyelocytic leukemia (APL), a subtype of acute myelogenous leukemia, since upon addition of ATRA to the therapy approximately 72% of patients with APL can be cured (de The et al., 1990a; Degos and Wang, 2001; Lin et al., 1999).

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[1] Abbreviations: RAR, retinoic acid receptor; ATRA, all-*trans*-retinoic acid; VAD, vitamin A deficiency; APL, acute promyelocytic leukemia; RARE, retinoic acid response element; RXR, retinoid X receptor; DR, direct repeat; NCoR, nuclear receptor corepressor; SMRT, silencing mediator for retinoid and thyroid hormone receptors; CRABP, cellular retinoic acid-binding protein; HCAC, histone deacetylase; AF, activation function; AP-1, activator protein-1; 9CRA, 9-*cis* retinoic acid; RA, retinoic acid; PML, promyelocyte leukemia protein; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; PLZF, promyelocytic leukemia zinc finger.

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RARs

Retinoids exert their pleiotropic effects through the three RAR subtypes [RARα (NR1B1), first identified in 1987 independently by Pierre Chambon's and Ron Evans's groups, RARβ (NR1B2), and RARγ (NR1B3)] that originate from three distinct genes (Giguere et al., 1987; Petkovich et al., 1987; Chambon, 1996). For each RAR subtype, several isoforms exist that differ from one another in their N-terminal region A. These isoforms arise from the differential usage of two promoters and alternative splicing. The downstream promoters, referred to as P2, are induced by retinoids owing to the presence of a retinoic acid response element (RARE, see below). There are two major isoforms for RARα (α1 and α2) and for RARγ (γ1 and γ2) and four major isoforms for RARβ (β1 and β3 initiated at the P1 promoter and β2 and β4 initiated at the P2 promoter). RARs function as

heterodimers with the three retinoid X receptors [RXRα (NR2B1), RXRβ (NR2B2), and RXRγ (NR2B3)] (Mangelsdorf and Evans, 1995; Kastner et al., 1997; Mark et al., 1999). In vitro studies demonstrated that RXR-RAR heterodimers act as ligand-dependent transcriptional regulators by binding to the specific RARE DNA sequences found in the promoter region of retinoid target genes. RAREs correspond to direct repeats of polymorphic arrangements of the canonical motif 5′-PuG(G/T)TCA separated by five (generally referred to as DR5) or one (DR1) or two (DR2) nucleotides (Leid et al., 1992; Mangelsdorf and Evans, 1995). In DR5 and DR2 elements, RXRs occupy the 5′ element, whereas RARs occupy the 3′ element (5′-RXR-RAR-3′). In contrast, the polarity of heterodimers is reversed in DR1 elements (5′-RAR-RXR-3′) (Kurokawa et al., 1994; Rastinejad et al., 2000; Rastinejad, 2001). Strikingly, and contrary to DR2 or DR5 context (see below), specific RAR agonists do not induce the dissociation of corepressors from the RAR-RXR heterodimer bound to a DR1 leading to repressive activity (Kurokawa et al., 1995). DR5 elements were identified in the promoters of genes such as the *RARβ2* gene (de The et al., 1990b), several *Hox* genes that are key players in the specification of the anteroposterior axis during development (Boncinelli et al., 1991; Tabin, 1995; Dupe et al., 1997), and the cytochrome P450RAI (*CYP26*) gene whose product is implicated in the catabolism of ATRA (Loudig et al., 2000). DR2 elements were found in the promoters of the cellular retinol binding protein I (Smith et al., 1991) and *CRABPII* (Durand et al., 1992) genes, CRABPs functioning in retinoid storage and intracellular transport (for other retinoid target genes, see McCaffery and Drager, 2000; Laudet and Gronemeyer, 2002).

A molecular mechanism by which RXR-RAR heterodimers regulate transcription of target genes has been proposed (Glass and Rosenfeld, 2000). In the absence of RAR agonist, the RXR-RAR heterodimer recruits the corepressor proteins NCoR or SMRT and associated factors such as histone deacetylases (HDACs) or DNA-methyl transferases that may lead to an inactive condensed chromatin structure, preventing transcription. Upon RAR agonist binding, corepressors are released, and coactivator complexes such as histone acetyltransferases or histone arginine methyltransferases are recruited to activate transcription (Nagy et al., 1997; Hu and Lazar, 2000; Aranda and Pascual, 2001; Privalsky, 2001; McKenna and O'Malley, 2002; Perissi and Rosenfeld, 2005). Recently, poly(ADP-ribose) polymerase 1, which can interact directly with RARα, has been shown to be indispensable to RAR-mediated transcription from the RARβ2 promoter (Pavri et al., 2005).

Whereas RAR agonists can autonomously activate transcription through such heterodimers, RXRs are unable to respond to RXR-selective agonists (rexinoids) in the absence of RAR ligand. The molecular basis of this phenomenon, referred to as RXR subordination or silencing, has been dissected. Agonist binding to RXR is unable to induce the dissociation of corepressor from the RXR-RAR heterodimers, preventing coactivator recruitment (Westin et al., 1998; Germain et al., 2002). A synergistic transcriptional activation is observed when RAR and RXR partners are simultaneously bound to agonists, indicating that RXRs are not transcriptionally silent partners in RXR-RAR heterodimers (Lotan et al., 1995b).

The essential role of gene silencing by RARs has been demonstrated for two developmental processes, namely the skeletal development in the mouse and head formation in *Xenopus* (for a review, see Weston et al., 2003), and is underscored by the pathogenesis of APL in which an inappropriate repression by oncogenic RARα fusion proteins blocks myeloid differentiation leading to APL. The repressive model of unliganded heterodimers is based mainly on studies involving RARα, which can strongly interact with corepressors. However, recent findings suggest differences in cofactor stoichiometry and patterns of interactions among the distinct RAR subtypes, as unliganded RARβ was shown to poorly associate corepressors and to be a significant transcriptional activator, contrasting with the strong repressing activity of unliganded RARα (Germain et al., 2002; Farboud et al., 2003; Hauksdottir et al., 2003).

RARs also integrate a variety of signaling pathways, notably through posttranslational modifications (Rochette-Egly and Chambon, 2001; Laudet and Gronemeyer, 2002; Rochette-Egly, 2003). Among these modifications, phosphorylation of RARs has been shown to play a critical role in the retinoid response. Both AF-1 domains and LBDs of RARs are substrates for various kinases activated by a variety of signals (Bastien and Rochette-Egly, 2004). Another particularly interesting feature of RARs has been revealed by the studies of several genes such as osteocalcin or collagenase showing the inhibition of the transcription factor complex activator protein-1 (AP-1)-driven transactivation by liganded RARs (Lafyatis et al., 1990; Nicholson et al., 1990; Schule et al., 1990; Chen et al., 1995; Resche-Rigon and Gronemeyer, 1998). However, the mechanism of this cross-talk remains elusive.

Expression and Function of Retinoid Acid Receptors

In situ hybridization revealed the expression of all three RARs during mouse embryonic development. Whereas RARα is present in most tissues, both RARβ and RARγ expressions are more selective (Dolle et al., 1990). These differences in tissue distribution suggest that RARs have distinct physiological functions.

The specific role of each RAR has been studied in great detail in the RA-responsive F9 murine embryonal carcinoma cell line. Interestingly, F9 cells represent a simple

cell-autonomous model system for analyzing RAR signaling under in vitro conditions that mimics, at least to some extent, physiological processes occurring during early embryogenesis (for a review, see Rochette-Egly and Chambon, 2001). Both synthetic RAR isotype-selective ligands and knockouts of the individual RARs through homologous recombination followed by re-expression of wild-type or mutant RARs have been used. Overall these experiments revealed important insights regarding the complexity and the selectivity of retinoid signaling. In F9 cells RXR-RAR heterodimers are the functional units that selectively mediate the target gene expression and the differentiation and the growth arrest controlled by retinoids, and the AF-2 ligand-dependent transcriptional activity of RXRs is subordinated to their RAR heterodimeric partner. More specifically RXRα-RARγ heterodimers are necessary for growth arrest, visceral endodermal differentiation, and primitive endodermal differentiation, whereas RXRα-RARα is required for parietal endodermal differentiation in the presence of cAMP. In addition the different roles of RAR phosphorylations have been revealed in the context of the differentiation induction in F9 cells. For instance, phosphorylation within the RARγ AF-1 activation domain is required for primitive endodermal differentiation and for induction of retinoid target genes, but in a differential promoter-dependent manner, and for degradation of RXRα-RARγ heterodimers by the ubiquitin-proteasome system (Taneja et al., 1997) (for reviews, see Rochette-Egly, 2003; Bastien and Rochette-Egly, 2004). Furthermore, the RARβ2-null F9 cell line exhibits no growth arrest in response to retinoids in contrast to wild-type, RAR$\alpha^{-/-}$, and RAR$\gamma^{-/-}$ F9 cell lines (Faria et al., 1999). However, RAR knockouts may generate artifactual functional redundancies between individual RARs that do not exist under wild-type conditions (Taneja et al., 1996). Overall these investigations with the F9 cells and previous gene transfection studies demonstrated that the individual RAR subtypes can have distinct activities even within the same cell line. In the same line, in vitro studies have shown that, even though other RAR subtypes are also expressed, RARα agonists induce the inhibition of proliferation of some breast cancer cell lines and the differentiation of leukemic cells (Dawson et al., 1995; Chen et al., 1996).

The above studies on F9 were complemented by genetic strategies in the mouse to determine the function of RARs under physiological conditions. This was mainly performed by Pierre Chambon's laboratory by knockout of the three RAR subtypes as well as the eight RAR isoforms (see above) through homologous recombination in embryonic stem cells. In combination with pharmacological approaches using RAR antagonists to block the retinoid signaling pathway, the generation of such germline mutations has provided many valuable insights on the developmental functions of RARs (for comprehensive reviews, see Mark et al., 2004, 2005). However, because of the functional redundancies observed between RARs artifactually generated by knockouts, the number of organs that need retinoids for their development might be underestimated, and these studies have failed to reveal many of the physiological functions of RARs, notably in adult animals. Despite this fact, they provided the genetic evidence that RARs transduced retinoid signals in vivo and revealed that the various RAR subtypes have distinct functionalities during embryogenesis. Briefly, all RAR single-null mutant mice are viable and altogether display some aspects of the postnatal and fetal VAD syndromes. Specifically, RARα-null mutant males are sterile as a result of a degeneration of the seminiferous epithelium that inhibits spermatogenesis (Li et al., 1993; Lufkin et al., 1993). RARβ-null mice display abnormalities in the vitreous body in eyes (Grondona et al., 1996) and impaired abilities in locomotion and motor coordination (Krezel et al., 1998). RARγ inactivation causes both skeletal and epithelial defects (Lohnes et al., 1993; Ghyselinck et al., 1997; Chapellier et al., 2002). In contrast to RAR single-null knockout mice, mutants lacking a pair of RAR subtypes (double-null mutants) or two or more isoforms belonging to distinct subtypes exhibit a number of defects leading to a dramatically reduced viability and all the known manifestations of the VAD syndrome. Also such genetic studies have revealed that retinoid signals are transduced by specific RXRα-RAR(α, β, or γ) heterodimers during development.

Natural Retinoids and Synthetic Analogs

Natural retinoids are produced in vivo from the oxidation of vitamin A. Synthesis of retinoic acid from retinol is a two-step process in which alcohol dehydrogenases perform the oxidation of vitamin A to all-*trans*-retinaldehyde, followed by oxidation of the latter to ATRA by retinaldehyde dehydrogenases (of which four have been characterized, RALDH1–4), which is the rate-limiting step in its production. ATRA is in turn metabolized by CYP26 to hydroxylated metabolites that can also activate all three RARs (Fujii et al., 1997; White et al., 1997). However, genetic approaches using the RALDH1a2 null mutation and the CYP26 null mutation demonstrated that the main function of CYP26 is to degrade endogenous ATRA and to protect cells from excess ATRA rather than to synthesize active hydroxylated retinoids (Niederreither et al., 2002). RARs bind with high affinity not only ATRA but also 9-*cis* retinoic acid (9CRA), an isomerization product of ATRA. Whereas ATRA can bind only to RARs, 9CRA can bind to both RAR and RXR. However, because 9CRA has not been consistently detected in mammalian cells unless the medium contained ATRA, the consideration of 9CRA as a natural bioactive retinoid remains controversial (see "LXIII. Retinoid X Receptors" on page 760 of this issue).

Given the importance of the retinoid signaling pathway, a major research effort has been directed to the identification of potent synthetic retinoids leading to the generation of a panel of modulators with activities ranging from agonists to inverse agonists (Klein et al., 1996; Thacher et al., 2000; Kagechika and Shudo, 2005). Such configurationally and/or conformationally restricted analogs of ATRA are valuable tools for dissecting the role of each RAR in several processes. Retinoids were also used as therapeutic agents for the treatment and prevention of cancer and hyperproliferative diseases (see below) (Thacher et al., 2000; Altucci and Gronemeyer, 2001; Clarke et al., 2004a; Dawson, 2004; Vivat-Hannah and Zusi, 2005). The crystal structures of the LBDs of all three RARs bound to various ligands have been solved, providing molecular details of the determinants of both subtype selectivity and the agonist/antagonist-induced structural changes (Renaud et al., 1995; Bourguet et al., 2000; Germain et al., 2004). These 3D structure determinations together with comparison of RAR sequences revealed only three divergent residues into the ligand-binding pockets of all three RARs that are critical for the recognition of subtype-specific ligands. This finding has been confirmed by swapping of these residues (Gehin et al., 1999). Accordingly, it has been possible to generate entirely subtype-selective ligands but also molecules that have complex activities such as ligands that are RARα and RARγ antagonists and RARβ agonists (Chen et al., 1995; Germain et al., 2004). Interestingly, selective retinoids that dissociate the inhibition of AP-1 activity from the classic RARE-dependent activation of transcription have been identified (Fanjul et al., 1994; Chen et al., 1995). Such compounds are promising therapeutic agents and provide valuable tools to address the mechanism of the RAR/AP-1 cross-talk, the importance of which for growth control and cancer is now established.

Diseases, Treatments, and Chemoprevention

The RARs have been associated with several diseases such as cancer or skin disorders on the basis of epidemiological, clinical, and experimental investigations in human and animals. Then retinoids are used in a variety of chemopreventive and chemotherapeutic settings. The recognized potential of the retinoids in skin disorders is demonstrated by the clinical use of ATRA, 9CRA, and 13-*cis*-retinoic acid for dermatological indications including acne, psoriasis, or photoaging (for reviews, see Thacher et al., 2000; Zouboulis, 2001; Dawson, 2004). In addition to these RA isomers, two synthetic retinoids are available for the treatment of stable plaque psoriasis [the RARβ/γ-selective agonist tazarotene (AGN190168)] (Marks, 1997; McClelland, 1998) and for acne [adapalene (CD271)] (Galvin et al., 1998; Zhu et al., 2001).

Aberrant retinoid signaling mechanisms have been linked to cancer. The most direct implication of RAR in human disease is given by APL, which is caused by a reciprocal chromosomal translocation between *RAR*α and promyelocyte leukemia protein (*PML*) human genes, leading to the alteration of the signaling of both RARα and PML (de The et al., 1990a). The resulting fusion protein PML-RARα displays increased binding efficiency to the transcriptional corepressors NCoR and SMRT compared with RARα, inducing the recruitment of HDAC complexes and the silencing of RAR target genes. This process, in turn, arrests myelopoiesis at the promyelocyte stage and prevents the differentiation of APL cells, which might normally occur in the presence of endogenous ATRA. Importantly, the use of supraphysiological doses of ATRA has led to remission in patients with APL, revealing the potential of retinoids for chemotherapeutic applications. This successful therapy is supposed to overcome the negative effects of PML-RARα by inducing the dissociation of silencing complexes from PML-RARα and then the activation of differentiation processes. In addition, high concentrations of ATRA can induce postmaturation apoptosis through the induction of the tumor-selective death ligand tumor necrosis factor-related apoptosis-inducing ligand (TRAIL, also called Apo2L), a most promising molecule in cancer research (Altucci and Gronemeyer, 2001). However, with this therapy some patients with APL have a relapse and become resistant to ATRA. Interestingly, the RARα-selective agonist Am80 can induce complete remission in patients previously treated by ATRA who have had relapses, highlighting interest on the generation of even more selective retinoids (Kagechika et al., 1988; Tobita et al., 1997; Takeuchi et al., 1998).

The *RAR*α gene can translocate with other genes, such as the promyelocytic leukemia zinc finger (*PLZF*) gene product, that are insensitive to ATRA. In the case of the PLZF-RARα fusion protein, the PLZF moiety is constitutively associated to corepressor complexes independently of ATRA, which is supposed to lead to the ATRA insensitivity.

Strong evidence supports the idea that retinoids pharmacologically prevent carcinogenesis in a variety of tissues. Retinoids are used as chemopreventive agents for the treatment of preneoplastic diseases such as oral leukoplakia, cervical dysplasia, and xeroderma pigmentosum (Lotan, 1996; Lippman and Lotan, 2000; Sun and Lotan, 2002). However, the promises of preclinical studies demonstrating the efficacy of retinoids did not consistently translate into clinical response for the treatment of other solid tumors. Interestingly, both experimental investigations and analyses of the natural course of solid human tumor development suggest that RARβ may act as a potential tumor suppressor. Indeed, its expression is selectively lost in many neoplastic tissues, including non-small cell lung cancer, squamous cell carcinomas of the head and neck, and breast cancer (Castillo et al., 1997; Widschwendter et al., 1997; Xu et al., 1997a,b; Picard et al., 1999). The restoration of

RARβ expression with concomitant retinoic treatment was associated with a clinical response of oral leukoplakia (Lotan et al., 1995a). Furthermore, a recently identified novel RARβ isoform, referred to as RARβ1′, which apparently arises from an alternative splicing of RARβ1, may function as a tumor suppressor gene in the lung with biological functions distinct from those of previously known RARβ isoforms (Petty et al., 2005).

Ongoing Research

Despite their promising therapeutic value for various indications, the administration of retinoids is strongly limited by severe associated toxic side effects due to the pleiotropic functions of these agents. These effects include teratogenicity, increases in serum triglycerides, mucocutaneous cytotoxicity, headache, and bone toxicity. Therefore, research in progress on retinoid therapy is focused on overcoming both the unwanted side effects of currently used retinoids in the clinic and intrinsic or acquired ATRA resistance in patients and their consequences (Freemantle et al., 2003). First, more work is required to understand better the molecular pathways induced by RARs, notably those underlying the antiproliferative and anticancer activities of retinoids, even though multiple mechanisms that modulate the complex retinoid signaling pathways and their cross-reactions are gradually being elucidated. For instance, the increased understanding of the regulation of RAR activities through phosphorylation should provide new insights in the developmental processes and in cancer (Bastien and Rochette-Egly, 2004).

Second, combinations with other chemopreventive agents that may also enhance the clinical efficacy of retinoids are increasingly sought. Indeed, increased understanding of epigenetic dysregulations that occur during the development of carcinogenesis suggest that ATRA resistance might be combatted by the use of epigenetic modifying agents such as HCAC inhibitors or DNA methyl transferase inhibitors in combination with retinoids, some of which are in clinical trials (Bachman et al., 2003; Egger et al., 2004; Feinberg and Tycko, 2004; Altucci et al., 2005). Several studies revealed other candidates for combinations treatment such as tumor necrosis factor or TRAIL (Altucci and Gronemeyer, 2001; Zusi et al., 2002). Interestingly the recent demonstration of retinoid-induced tumor suppression activities through a network involving the tumor suppressor interferon-regulator factor 1 and TRAIL provides new avenues for the therapeutic combination of retinoids and interferons that is already being tested clinically (Lippman et al., 1997; Clarke et al., 2004b, 2005).

Lastly, the improved use of retinoids in therapy will require the generation of novel synthetic RAR ligands harboring increased selective properties both to decrease the adverse effects associated with retinoid treatments and to overcome resistance to retinoids. Among the novel compounds, atypical retinoids, such as *N*-(4-hydroxyphenyl) retinamide or CD437, have emerged as potential anticancer agents because of their antiproliferative and apoptotic actions with little toxicity compared with classic retinoids (Ortiz et al., 2002; Dawson, 2004). Despite these compounds being classified as retinoids because of their binding to RARs, their antitumoral effects, at least in part, seem to be independent of the RXR-RAR heterodimer function (Holmes et al., 2000). Furthermore, the development of RARβ-selective ligands will be of prime importance because of the tumor-suppression potential of RARβ.

Tables 1 through 3 summarize the major molecular, physiological, and pharmacological properties of RAR subtypes.

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TABLE 1
RARα

Receptor Nomenclature	NR1B1
Receptor code	4.10.1:RA:1:B1
Molecular information	Hs: 462aa, P10276, chr. 17q21.1[1,2] Rn: 459aa, chr. 10[1,3] Mm: 462aa, P11416, 11 D[1,4–6]
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	PuG(G/T)TCA (DR1, DR2, DR5)
Partners	Cyclin H/cdk7/TFIIH (physical, functional): TFIIH phosphorylates RARα1 in its A/B region (Ser^{77}) by cdk7 subunit[7–9]; AP-1 (physical, functional): RAR inhibits AP-1-driven transactivation, and AP-1 represses RAR-mediated transcription[10–14]; CRABPII (physical, functional): can enhance the transactivation by RARα-RXR on DR5 element[15]; PARP-1 (physical, functional): indispensable to RARα-mediated transcription from the RAR α2[16]
Agonists	9-*cis*-Retinoic acid (0.3 nM),* all-*trans*-retinoic acid (0.4 nM),* AGN195183 (3 nM) [K_d][17–22]; Am580 (36 nM), TTNPB (36–72 nM), Am80 (124 nM) [IC_{50}][19–23]; BMS753[24]
Antagonists	BMS614 (2 nM), BMS493 (4.2 nM), AGN193109 (2–16 nM), Ro-41-5253 (60 nM) [IC_{50}][19,22,24–28]
Coactivators	NCOA1, NCOA2, NCOA3, PPARBP, CREBBP, p300[12,29–39]
Corepressors	NCOR1, NCOR2[40–44]
Biologically important isoforms	RARα1 {Hm, Mm}: transcribed from the promoter P1 and differs from RARα2 in the A domain—RARα1 is phosphorylated by cdk7/TFIIH (Ser^{77})[5,45,46]; RARα2 {Hs, Mm}: in contrast with the RARα1 isoform, RARα2 is transcribed from downstream promoter P2, which contains a DR5 and is inducible by retinoid[5,47]
Tissue distribution	Majority of tissues {Hs, Mm, Rn} [Northern blot, in situ hybridization, Western blot][6,48–54]
Functional assays	Inhibition of cellular proliferation of the MCF-7 breast cancer cell line expressing the estrogen receptor {Hs}[55]; induction of maturation of acute myeloid leukemia cell lines (NB4, PBL985, U937, HL60) using the histological nitro blue tetrazolium reaction and analysis of CD11c integrin expression by direct immunofluorescence {Hs}[21,32,56,57]; parietal endodermal differentiation in the presence of cAMP of F9 murine embryonal carcinoma cell line {Mm}[58]
Main target genes	Activated: CYP26 {Hs, Mm, Rn},[59] RARβ2 {Hs, Mm, Rn}[26,57,60,61], Hoxa-1 {Mm}[51,60,62], CRBP1 {Mm}[60,63], CRABPII {Mm}[60,64]
Mutant phenotype	Abnormalities observed: growth retardation, male sterility, impaired alveolar formation; congenital defects observed: webbed digits, homeotic transformations and malformations of cervical vertebrae, pterygoquadrate cartilage, malformations of the squamosal bone; note that both the specific RARα1-null and RARα2-null mutants are apparently normal {Mm} [knockout][34,65–67]
Human disease	APL, a subtype of acute myelogenous leukemia: caused by several translocations that implicate the human *RARα* gene; the reciprocal chromosomal translocation between *RARα* and *PML* human genes produces a fusion protein PML-RARα; the use of supraphysiological doses of ATRA lead to remission in patients with APL; in contrast, the fusion protein resulting from the translocation between *RARα* and the *PLZF* is insensitive to ATRA treatment[68–70]

aa, amino acids; chr., chromosome; HRE, hormone response element; PARP-1, poly(ADP-ribose) polymerase 1; TTNPB, 4-[(*E*)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid; PPARBP, peroxisome proliferator-activated receptor binding protein; CREBBP, cAMP response element-binding protein-binding protein.

* Radioligand.

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TABLE 2
RARβ

Receptor Nomenclature	NR1B2
Receptor code	4.10.1:RA:1:B2
Other names	Hap
Molecular information	Hs: 455aa, P10826, chr. 3p24[1,26] Rn: chr. 15[26] Mm: 482aa, P22605, chr. 14 A[26,28,45,46]
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	PuG(G/T)TCA (DR5)
Partners	AP-1 (functional): RARβ inhibits AP-1-driven transactivation[4,30]
Agonists	9-*cis*-Retinoic acid (0.2 nM),* all-*trans*-retinoic acid (0.4 nM)* [K_d][14,15,29,37]; BMS641 (2.5 nM), TTNPB (5–22 nM) [IC_{50}][10,14,15,29,37]
Antagonists	BMS493 (2.9 nM), AGN193109 (2–7 nM) [IC_{50}][9,16,17,37]
Coactivators	NCOA1, NCOA2, NCOA3, PPARBP[3,8,9,20–23,27,31,33,38,44]
Biologically important isoforms	RARβ 1 {Hs, Mm}: differs from RARβ 2 in the A domain[46]; RARβ 2 {Hs, Mm}: in contrast to the RARβ 1 isoform, RARβ 2 is transcribed from promoter (the downstream one, P2) that contains a DR5 and is inducible by retinoid[46]; RARβ 3 {Mm}: the RARβ 3 isoform is generated from the promoter P1 and differs from RARβ 1 by its N-terminal part—not detected in human[46]; RARβ 4 {Hs, Mm}: RARβ 4 is generated from the promoter P2 and differs from RARβ 2 by its N terminus that initiates a non-AUG codon, CUG[28]
Tissue distribution	Brain, liver, kidney, heart, pituitary, colon, uterus, ovary, testis, prostate, adrenal, eye {Hs, Mm, Rn} [Northern blot, in situ hybridization, Western blot][5–7,13,19,35,36]
Mutant phenotype	Abnormalities observed: growth retardation, behavioral defects, altered alveolar formation; congenital defects observed: homeotic transformations and malformations of cervical vertebrae, persistence and hyperplasia of the primary vitreous body; note that specific RARβ 1/β 3-null mutants are apparently normal, and specific RARβ 2/β 4-null mutants exhibited persistence and hyperplasia of the primary vitreous body {Mm} [knockout][11,12,18,24,25]
Human disease	Human nonsmall cell lung cancer: associated with loss of RARβ expression[2,32,43]; human esophageal cancer: associated with loss of RARβ expression[34]; human breast cancer: associated with loss of RARβ expression[39–42]

aa, amino acids; chr., chromosome; HRE, hormone response element; TTNPB, 4-[(*E*)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid; PPARBP, peroxisome proliferator-activated receptor binding protein.

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TABLE 3
RARγ

Receptor Nomenclature	NR1B3
Receptor code	4.10.1:RA:1:B3
Molecular information	Hs: 454aa, P13631, chr. 12q13[1–3] Rn: chr. 7[3–5] Mm: 458aa, P18911, chr. 15 F[3,6]
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	PuG(G/T)TCA (DR2, DR5)
Partners	AP-1 (functional): RARγ inhibits AP-1-driven transactivation[7–11]; cdk7/TFIIH (physical, functional): TFIIH phosphorylates RARγ 2 in its A/B region (Ser^{68}) by cdk7 subunit[12,13]; p38 MAPK (functional): required for RA-induced RARγ degradation and transactivation[13–15]; SUG1 (physical, functional): required for RA-induced RARγ degradation and transactivation[13–15]; vinexin β (physical, functional): interacts with AF-1 domain of RARγ and represses RAR-mediated transcription[16]
Agonists	All-*trans*-retinoic acid (0.2 nM),* 9-*cis*-retinoic acid (0.8 nM)* [K_d][17–21]; TTNPB (15–26 nM), CD666 (68 nM), BMS270394 (528 nM), BMS961 (500 nM) [IC_{50}][18–23]
Antagonists	AGN193109 (3–7 nM), BMS493 (98 nM), CD2665 (81 nM) [IC_{50}][21,24–27]
Coactivators	NCOA1, NCOA2, NCOA3[4,28–34]
Corepressors	NCOR1, NCOR2[29,31,35–38]
Biologically important isoforms	RARγ 1 {Hs, Mm}: differs from RARγ 2 in its N-terminal domain[6,39]; RARγ 2 {Hs, Mm}: the expression of RARγ 2 is regulated through a specific RARE element; RARγ 2 is phosphorylated by p38 MAPK (Ser^{66}) and by cdk7/TFIIH (Ser^{68}) {Hs, Mm}[6,12,14,15,40–43]
Tissue distribution	Highly expressed in the epidermis {Hs, Mm} [Northern blot, in situ hybridization, Western blot][2,6,41,44–47]
Functional assays	Primitive endodermal differentiation and morphological differentiation of the F9 murine embryonal carcinoma cell line {Mm}[48–50]
Main target genes	Activated: laminin B1 {Mm}[50], RARβ 2 {Hs, Mm, Rn}[48,51,52], Hoxa-1 {Mm}[4,48,53], CRBP1 {Mm}[48,54], CRABPII {Mm}[48,55]; repressed:
Mutant phenotype	Abnormalities observed: growth deficiency, male sterility, squamous epithelia of various epithelia, impaired alveolar formation; congenital defects observed: webbed digits, homeotic transformations and malformations of cervical vertebrae, malformed laryngeal cartilages and tracheal rings, agenesis of the Harderian glands, agenesis of the metopic pillar of the skull, abnormal differentiation of granular keratinocytes; note that specific RARγ 2-null mutants are apparently normal, and specific RARγ 1-null mutants exhibited a growth deficiency, malformations of cervical vertebrae, and abnormal differentiation of granular keratinocytes {Mm} [knockout][56–60]
Human disease	Photoaging: level of RARγ is reduced after UV treatment of human skin[61–63]

aa, amino acids; chr., chromosome; HRE, hormone response element; TFIIH, transcription factor IIH; TTNPB, 4-[(*E*)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid.

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