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***Abstract*——The physiological effects of retinoic acids (RAs) are mediated by members of two families of nuclear receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), which are encoded by three distinct human genes, *RXRα*, *RXRβ*, and *RXRγ*. RARs bind both all-*trans*- and 9-*cis*-RA, whereas only the 9-*cis*-RA stereoisomer binds to RXRs. As RXR/RAR heterodimers, these receptors control the transcription of RA target genes through binding to RA-response elements. This review is focused on the structure, mode of action, ligands, expression, and pharmacology of RXRs. Given their role as common partners to many other members of the nuclear receptor superfamily, these receptors have been the subject of intense scrutiny. Moreover, and despite numerous studies since their initial discovery, RXRs remain enigmatic nuclear receptors, and there is still no consensus regarding their role. Indeed, multiple questions about the actual biological role of RXRs and the existence of an endogenous ligand have still to be answered.**

Introduction

The first identified retinoid X receptor (RXR[1]), referred to as RXRα (NR2B1), was initially described as an orphan receptor (Mangelsdorf et al., 1990). However, it specifically responded to retinoids because high concentrations of all-*trans*-retinoic acid (ATRA) could activate RXRα, leading to the term RXR. Further it was found that 9-*cis*-retinoic acid (9CRA), an isomer of ATRA, is a high-affinity ligand for RXRα, as well as for the two additional related subtypes, RXRβ (NR2B2) and RXRγ (NR2B3), that were later discovered (Rowe et al., 1991; Yu et al., 1991; Heyman et al., 1992; Leid et al., 1992; Levin et al., 1992; Mangelsdorf et al., 1992). Despite the fact that 9CRA also displays a high affinity for all three retinoic acid receptors (RARs), RARs exhibit less homology with RXRs than with the thyroid hormone receptor (TR). Indeed, both RARs and RXRs belong to two different groups of the nuclear receptor superfamily, suggesting very different functions (Laudet and Gronemeyer, 2002). The actual significance of the 9CRA-binding capacity for both RXRs and RARs remains to be established. Importantly, RXRs were also independently identified as factors necessary for efficient binding to DNA of several members of the nuclear receptor superfamily and were shown to form heterodimers with these other nuclear receptors (Laudet et al., 1992; Leid et al., 1992; Glass, 1994). Furthermore, in vitro studies have shown that the RXRs can also form RXR-RXR homodimers, raising the question of the existence of an independent RXR signaling pathway (Mangelsdorf et al., 1991; Mader et al., 1993). Because of these features, RXRs seem unique among the members of the nuclear receptor superfamily. Moreover, and despite numerous studies since their initial discovery, RXRs remain enigmatic nuclear receptors, and there is still no consensus regarding their role. Indeed, multiple questions about the actual biological role of RXRs and the existence of an endogenous ligand have still to be answered.

Although all these basic questions still remain unanswered or are controversial, it is clear that RXRs are

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[1] Abbreviations: RXR, retinoid X receptor; NR, nuclear receptor; ATRA, all-*trans*-retinoic acid; 9CRA, 9-*cis*-retinoic acid; RAR, retinoic acid receptor; TR, thyroid hormone receptor; VDR, vitamin D receptor; PPAR, peroxisome proliferator-activated receptor; LXR, liver X receptor; FXR, farnesoid X receptor; PXR, pregnane X receptor; CAR, constitutively activated receptor; NGFIB, nerve growth factor-induced clone B; DR, direct repeat; AF, activation function; LBD, ligand-binding domain; LBP, ligand-binding pocket; TZD, thiazolidinedione.

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essential players in several pathways because they form many heterodimers and can act as ligand-activated transcription factors. Ligand activation of RXRs has potentially pleiotropic effects on numerous biological pathways and hence therapeutic opportunities, as demonstrated by the clinical use of RXR-selective ligands, referred to as rexinoids, for the treatment of cancer and metabolic diseases (Thacher et al., 2000; Altucci and Gronemeyer, 2001; Chawla et al., 2001; Clarke et al., 2004; Dawson, 2004; Gronemeyer et al., 2004; Szanto et al., 2004; Dragnev et al., 2005; Shulman and Mangelsdorf, 2005).

The RXRs

The three RXR subtypes originate from three distinct genes. For each subtype, several isoforms exist that differ from one another in their N-terminal A/B domain (Chambon, 1996). There are two major isoforms each for RXRα (α1 and α2), RXRβ (β1 and β2), and RXRγ (γ1 and γ2) (Fleischhauer et al., 1992; Liu and Linney, 1993; Nagata et al., 1994; Brocard et al., 1996). So far no functional characterization of these isoforms has been performed.

All three RXR subtypes are common heterodimerization partners for members of the so-called subfamily 1 nuclear receptors (for a review, see Laudet and Gronemeyer, 2002). The first identified heterodimeric partners were the TRs, RARs, and vitamin D receptor (VDR). The peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), farnesoid X receptor (FXR), pregnane X receptor (PXR), and constitutively activated receptors (CARs) are also included in this group. In vitro studies demonstrated that these heterodimers act as ligand-dependent transcriptional regulators by binding to specific DNA-response elements found into the promoter region of target genes and the interaction of RXR increases the DNA-binding efficiency of its partner. Moreover, both in vitro and in vivo approaches have revealed that all these nuclear receptors require RXR as a heterodimerization partner for their function (Laudet and Gronemeyer, 2002). In addition, RXRs form heterodimers with two members of the small nerve growth factor-induced clone B (NGFIB) subfamily, namely NGFIB and NURR1, which can also interact with DNA as monomers and homodimers (Forman et al., 1995; Perlmann and Jansson, 1995). In most cases, the RXR partner does not exhibit a marked preference for one of the three RXR subtypes.

Importantly, numerous heterodimers that contain RXRs can recognize distinct types of response elements. For instance, RXR-RAR heterodimers bind to a direct repeat of the AGGTCA core motif with a 5-base pair spacing (DR-5) and DR-2, whereas RXR-TR and RXR-LXR bind to DR-4, RXR-VDR and RXR-PXR to DR-3, and RXR-PPAR to DR-1 (for a review, see Glass, 1994). Then, the spacing is determinant for the specificity of the binding. Nevertheless, the sequence of the core motif itself, the sequence of the spacer, or that of the flanking nucleotides can also play a role in this interaction. Because RXRs are obligate heterodimerization partners for these nuclear receptors, the number of their potential target genes is tremendous.

RXRs can also form homodimers in vitro that can bind to DNA through DR-1 elements, suggesting the existence of a RXR-specific signaling (Mangelsdorf et al., 1991; Mader et al., 1993). Interestingly, it has been recently demonstrated that in vivo RXR homodimers could activate PPAR target genes containing a DR-1 (Ijpenberg et al., 2004). Nevertheless, the question of the existence and the functional role of RXR-RXR homodimers remains open. RXRα mutants that exhibit increased homodimerization over heterodimerization capacity could help to address this question in an in vivo setting (Vivat-Hannah et al., 2003).

No interaction was found between RXRs and the corepressors nuclear receptor corepressor and silencing mediator for retinoid and thyroid hormone receptors, suggesting that in absence of ligand RXR-RXR homodimers have a weak repressive activity (Schulman et al., 1996; Zhang et al., 1997). It is thought that helix 12 of RXRs masks the corepressor binding site of RXRs (Zhang et al., 1999). Several studies have clearly shown that coactivators can be recruited in presence of an RXR agonist as confirmed by crystal structural investigations (Egea et al., 2002).

In the context of RXR heterodimers, nuclear receptor partners can be classified into functionally distinct permissive and nonpermissive groups (Leblanc and Stunnenberg, 1995; Shulman et al., 2004). RXR heterodimers that contain permissive partners can be activated by agonists of both RXR and the partner receptor independently or together to induce a synergistic activation. PPARs, LXRs, FXR, and PXR belong to this permissive NR class. In contrast, heterodimers formed by RXR and a nonpermissive partner (RARs, TRs, and VDR) cannot be activated by an RXR agonist but only by the agonist of the partner receptor (Westin et al., 1998). This phenomenon, referred to as "subordination" or "silencing," is not due to an inability of RXR for binding a ligand when the partner is unliganded because several reports have shown that in the context of heterodimers RXR retains the ability to bind a ligand (Cheskis and Freedman, 1996; Thompson et al., 1998; Germain et al., 2002). Rather, nonpermissive partners inhibit RXR activation. However, when the partner is liganded by an agonist or certain antagonists, an RXR agonist can trigger an activation, leading to a synergistic activation through a mechanism that engages a distinct receptor to receptor allosteric signaling pathway (Apfel et al., 1995; Roy et al., 1995; Chen et al., 1996; Germain et al., 2002; Shulman et al., 2004). Interestingly, permissive RXR heterodimer partners are receptors for dietary lipids that

bind with low affinity, whereas nonpermissive partners correspond to high-affinity hormone receptors.

Ligands

One the most controversial and unsolved questions regarding RXR research is whether or not endogenous ligands exist and, if so, whether they are able to activate RXRs in vivo. Nevertheless, the role of RXRs in development and the importance of the AF-2 function of RXRα was established by knockout experiments (Mark and Chambon, 2003). Moreover, studies using reporter transgenic mice based on GAL4DBD-RXRLBD fusion constructs and a β-galactosidase reporter gene under the control of Gal binding sites, which allow detection of activated RXR in vivo, revealed the important role played by ligand activation in RXR function. Indeed, RXR was found to be active in specific regions of the spinal cord, suggesting the presence of endogenous ligands (Solomin et al., 1998). All of these results have been confirmed by the use of a comparable system with green fluorescent proteins as reporter (Luria and Furlow, 2004). The search for a natural RXR ligand led to the discovery of 9CRA as a high-affinity ligand for all three RXRs, which also activates the RXR-RXR homodimers (Heyman et al., 1992). Even though the existence of a 9CRA signaling pathway is supported by the reported presence of this compound in the developing embryo and by the identification of enzymes that may contribute to its biosynthesis, 9CRA has not been clearly detected in mammalian cells (Mertz et al., 1997; Romert et al., 1998). Hence, it cannot definitively be concluded that this compound is the actual natural ligand for RXRs. Phytanic acid, a branched-chain fatty acid, and the *n*-3 polyunsaturated fatty acid (docosahexaenoic acid), have subsequently been proposed as natural ligands for RXRs (de Urquiza et al., 2000; Lampen et al., 2001; Lemotte et al., 1996). Phytanic acid is present in plasma at micromolar concentrations, which are required for RXR activation. Interestingly, phytanic acid can also activate PPARγ (Zomer et al., 2000). Docosahexaenoic acid originates from fish oil and is highly enriched in mammalian brain. Nevertheless, none of these molecules has proven to be the bona fide endogenous ligand so far, and further investigations are required to definitively solve this critical issue.

Initially, 9CRA was identified as an agonist for RXRs, but it is not an RXR-selective compound because it displays a high affinity for all three RARs (Allenby et al., 1993). Synthetic compounds (rexinoids) that only recognize RXRs became very valuable to decipher the role played by these receptors and their ligand-dependent activities and to better understand the relationship between the partners in the RXR heterodimers. Crystal structures of both RXR and RAR LBDs bound to various ligands have revealed that the ligand-binding pockets (LBPs) of RXRs and RARs exhibits very different shapes (Renaud et al., 1995; Bourguet et al., 2000; Egea et al., 2002; Germain et al., 2004). A comparison of RARγ and RXRα LBPs indicates that, in contrast to the linear I shape of RARγ LBP, RXRα LBP shows a more restrictive and shorter L shape. Because of its flexibility, 9CRA can adapt to both LBPs, according to its binding capacity (Klaholz et al., 1998). Importantly, the distinctive RXR LBP structural feature allows the generation of ligands that discriminate between RARs and RXRs. After the first published series of synthetic compounds that activate the RXR-RXR homodimer appeared, numerous additional selective RXR ligands have been reported (Lehmann et al., 1992; Dawson, 2004). The most widely use rexinoids are SR11237, LG100268, and LGD1069, which is currently used in therapy (see below) (Boehm et al., 1994, 1995). Nevertheless, no rexinoid with apparent subtype selectivity has been identified so far. This issue seems very challenging because all residues that constitute the LBP of the three RXRs are highly conserved. RXR-selective antagonists have also been identified (for reviews, see Thacher et al., 2000; Dawson, 2004; Kagechika and Shudo, 2005; Vivat-Hannah and Zusi, 2005). Interestingly, among the reported RXR antagonists, LG100754 has been described as an RXR antagonist that can transcriptionally activate on its own both RXRα-RARα and RXRα-PPARγ heterodimers, suggesting a particular conformation of RXR LBD induced by this compound (Lala et al., 1996).

Expression and Function of RXRs

Disparities are observed in the expression pattern of the RXRs. RXRβ is widely distributed and can be detected in almost every tissue (Hamada et al., 1989; Yu et al., 1991; Mangelsdorf et al., 1992; Dolle et al., 1994). RXRα is predominantly expressed in liver, kidney, epidermis, and intestine and is the major RXR in skin (Mangelsdorf et al., 1990, 1992; Dolle et al., 1994). RXRγ is mostly restricted to the muscle and certain parts of the brain as well as to the pituitary (Mangelsdorf et al., 1992; Dolle et al., 1994; Haugen et al., 1997; Chiang et al., 1998).

In addition to the fact that RXRs are heterodimeric partners of multiple nuclear receptors regulating various developmental and metabolic processes, this RXR distribution suggests that RXRs play critical roles in a wide range of these processes. To address the issue of the RXR functional role in vivo, knockout of all three RXRs has been performed in the mouse (for comprehensive reviews, see Kastner et al., 1995; Mark and Chambon, 2003; Szanto et al., 2004; Mark et al., 2006). This informative genetic approach showed that the inactivation of the *RXRα* gene has more severe consequences than the ablation of *RXRβ* and *RXRγ*. The loss of *RXRα* is lethal during fetal life (Kastner et al., 1994; Sucov et al., 1994). The major observed defect is a hypoplasia of the myocardium that seems to be the principal cause of

animal death that occurs by cardiac failure at approximately embryonic day 14.5. Furthermore, fetuses lacking RXRα have ocular malformations (Kastner et al., 1994). Importantly, both defects due to RXRα inactivation are similar to those observed in vitamin A-deficient fetuses and in RAR$\beta^{-/-}\gamma^{-/-}$ double mutants (Kastner et al., 1997). This suggests that RXRα is essential in the transduction of a retinoid signal required for myocardial development and ocular morphogenesis, supporting the idea that RXRα is involved in retinoid signaling in vivo. This view is also supported by the fact that RXRα is involved in the mediation of a teratogenic effect due to administration of exogenous retinoids. Indeed, treatment of embryos with vitamin A induces limb truncations that do not occur in *RXR*α mutants (Sucov et al., 1995).

The ablation of *RXR*β led to ~50% in utero lethality (Kastner et al., 1996). Those mice that survive seem normal except that the males are sterile and exhibit testicular defects and abnormal spermatid maturation, leading to defects of spermatozoa. Also *RXR*β mutation leads to abnormal lipid metabolism in Sertoli cells, suggesting functional interactions of *RXR*β with other nuclear receptors that control lipid metabolism (Mascrez et al., 2004).

RXRγ-null mutants seem normal and are fertile (Krezel et al., 1996). Nevertheless, these mice have higher serum levels both of thyroxine and thyroid-stimulating hormone and an increased metabolic rate compared with wild-type animals (Brown et al., 2000). This is in agreement with the expression of *RXR*γ in the thyrotrope cells of the anterior pituitary gland.

In addition to the above single-null mutant mice, mutants lacking a pair or more of RXR subtypes or RXR/RAR double-null mutants were generated. For instance RXR$\beta\gamma$ double mutants exhibit locomotor deficiencies due to a dysfunction in the dopamine signaling pathway (Krezel et al., 1998). Given the number of combinations, a complete description of the results, mainly found by Pierre Chambon's group, is not possible here (for recent reviews, see Mark and Chambon, 2003; Mark et al., 2006). Together these results demonstrate that the RXR-RAR heterodimers transduce in vivo the retinoid signal and that specific heterodimers are involved in given developmental processes. On the other hand, the differentiation of the F9 murine embryonal carcinoma cells by retinoic acid has been investigated in the context of various such combinations of mutants (Chiba et al., 1997). These cellular studies led to the conclusion that distinct RXR-RAR heterodimers have different roles in the control of target genes in F9 cells. Moreover, it has been shown that RXRα is specifically required for the correct differentiation of retinoid-treated F9 cells (Clifford et al., 1996).

Nevertheless, all these studies have shown that some functional redundancy exists between RXRs. In addition, owing to the in utero lethality, observed, for instance, in RXRα inactivation, analyses of the specific RXR functions at postnatal stages and in adult animals are not possible using classic knockout experiments. To elude these limitations, conditional knockouts were generated. The selective disruption of RXRα from hepatocytes led to the conclusion that RXRα is a crucial functional partner for many other nuclear receptors such as LXRα, PXR, FXR, CARβ, and PPARα (Wan et al., 2000). Without RXRα, all these receptors cannot activate their target genes efficiently. Hence, the absence of RXRα from the liver affects many metabolic processes. Furthermore, using an elegant method based on a cell type-specific expression of an inducible Cre recombinase that is only active in the presence of tamoxifen, somatic null mutation of RXRα has been specifically performed in epidermal keratinocytes of the adult mouse (Li et al., 2005; Metzger et al., 2005). This selective ablation shows that RXRα plays a critical role during skin development, notably in hair cycling (Li et al., 2000, 2001). Because VDR-null mutant mice display a similar phenotype, it is likely that RXRα exerts its role in the skin through the VDR-RXRα heterodimer.

Lastly, to address the critical issue of whether the transcriptional activity of RXRα is required for its function in vivo or whether its heterodimerization capacity is the principal role of RXRα, mice were generated in which either most of the terminal A/B domain or helix 12 of the LBD, that harbors AF-1 and AF-2 function, respectively, was lacking (Mascrez et al., 2001; Mark and Chambon, 2003). Eliminating AF-2 function resulted in a number of (but not all) abnormalities similar to those exhibited by RXRα null mice, suggesting that the RXRα transactivation function was required for the developmental functions of the RXRα-RAR heterodimers. Animals expressing truncated RXRα lacking AF-1 function also displayed some similar or less severe abnormalities, showing that AF-2 seems to be more important than AF-1 for the function of RXR during embryonic development.

Therapy and Diseases

Although the mechanisms of action of rexinoids in cancer therapy and chemoprevention are poorly understood, clinical examination of these compounds is in progress. Strikingly, the synthetic rexinoid LGD1069 (bexarotene, Targretin) was recently approved for treating refractory advanced-stage cutaneous T-cell lymphoma (Heald, 2000; Hurst, 2000; Kempf et al., 2003; Zhang and Duvic, 2003). However, adverse effects are observed, such as the induction of hyperglyceridemia (Lowe and Plosker, 2000). Nevertheless, several clinical trials are ongoing to assess the potential of LGD1069 for other disease indications (Smit et al., 2004; Dragnev et al., 2005). The combination with other therapeutic agents may likewise enhance the clinical value of rexinoids (Crowe and Chandraratna, 2004; Dawson, 2004;

Michaelis et al., 2004). On the other hand, the existence of a RAR-independent RXR signaling pathway that allows the differentiation of cells may also be a potential target in cancer research (Benoit et al., 1999; Altucci et al., 2005). Indeed, a cross-talk between rexinoids and protein kinase A signaling pathways has been demonstrated that can induce differentiation of retinoic acid-resistant t(15:17) leukemic promyeloblasts. This example highlights the anticancer potential of the combination of rexinoids with other signaling drugs.

Drugs that target heterodimerization partners of RXRs are already in clinical use for the treatment of cancer, endocrine disorders, dermatological diseases, and the metabolic syndrome (see the relevant articles) (Shulman and Mangelsdorf, 2005). Whereas the actual functional role of RXRs in vivo needs to be further clarified, through its heterodimeric interaction with a large number of other nuclear receptors that are involved in many processes, RXRs may play a role in a wide variety of diseases (Chawla et al., 2001). Notably, RXRs are obligate heterodimer partners for nuclear receptors related to lipid physiology, namely PPARS, LXRs, and FXRs. Furthermore, the observation that liver-specific inactivation of RXR in mice results in abnormalities in all metabolic pathways substantiates the pleiotropic role of this receptor (Wan et al., 2000). Because such permissive heterodimers can be activated by rexinoids, RXR-selective ligands have promising potential as clinical agents in the field of metabolic syndrome. For example, heterodimerization with RXR is required for PPARγ activity including the expression of genes involved in the uptake of glucose in muscle, lipid metabolism, and energy expenditure (Tontonoz et al., 1994). PPARγ has been implicated in several important metabolic diseases. The antidiabetic agents, thiazolidinediones (TZDs) selectively bind to PPARγ and are widely used as drugs that improved insulin sensitivity in patients with insulin resistance syndrome despite some associated adverse effects (Lehmann et al., 1995; Berger et al., 1996; Reginato and Lazar, 1999; Picard and Auwerx, 2002). Given the implication of the RXR-PPARγ heterodimers in this pathological condition, the hypothesis that rexinoids would have properties similar to those of the TZDs in type 2 diabetes was established (Mukherjee et al., 1997). Accordingly, the synthetic rexinoid LG100268, which has been widely investigated, can activate RXR-PPARγ heterodimers and shows several beneficial effects in rodent models of insulin resistance and type 2 diabetes, as do TZDs (Mukherjee et al., 1997; Lenhard et al., 1999). However, whereas both rexinoids and TZDs can activate RXR-PPARγ heterodimers, these compounds show pharmacological and mechanistic differences in their in vivo activity (Cha et al., 2001; Shen et al., 2004). On the other hand, LG100268 causes marked changes in cholesterol balance in mice, demonstrating the potential of rexinoids for the treatment of metabolic diseases. This effect is due to the inhibition of cholesterol absorption through the RXR-LXR heterodimer that increases cholesterol efflux and through the RXR-FXR heterodimer that reduces the bile acid pool (Repa et al., 2000). Interestingly, in contrast with the other rexinoid LGD1069 that is currently used in therapy, LG100268 did not seem to cause hypertriglyceridemia, whereas both ligands are full RXR agonists in in vitro assays (Standeven et al., 1996). This observation suggests that different RXR agonists do not necessarily display the same biological effects. Consistent with this assumption, novel rexinoids that retain the insulin-sensitizing activity but exhibit substantially reduced side effects have recently been described previously (Michellys et al., 2003; Leibowitz et al., 2006). Furthermore, additional differences between rexinoids can be found in their ability to target specific heterodimers (selective RXR modulators) (Leibowitz et al., 2006). For instance, rexinoid LG100754, described initially as a RXR-RXR homodimer antagonist, also functions as an agonist of the RXR-PPARγ heterodimer, but not other permissive heterodimers formed with LXR, FXR, or NGFIB (Lala et al., 1996; Schulman et al., 1997). With PPARγ playing a major role in the regulation of both glucose and lipid metabolism, rexinoid LG100754 efficiently induces lower glucose levels in type 2 diabetic mice (Cesario et al., 2001; Forman, 2002).

Tables 1 through 3 summarize the major molecular, physiological, and pharmacological properties for all three RXR subtypes.

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TABLE 1
RXRα

Receptor Nomenclature	NR2B1
Receptor code	4.1:RX:2:B1
Molecular information	Hs:462aa, P19793, chr. 9q34.3[1–3] Rn:467aa, P28700[4] Mm: 467aa, Q05343, chr. 2[5–8]
DNA binding	
Structure	Homodimer, heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-1, DR-2, DR-3, DR-4, DR-5)
Partners	TR2 and TR4 (physical, functional): DNA binding[7,9,10]; VDR (physical, functional): DNA binding[9,10]; RARα, RARβ, and RARγ (physical, functional): DNA binding[7,9–14]; PPARα, PPARβ, and PPARγ (physical, functional): DNA binding[15,16]; LXRα and LXRβ (physical, functional): DNA binding[17–20]; FXR (physical, functional): DNA binding[21]; PXR (physical, functional): DNA binding[22–25]; CAR (physical, functional): DNA binding[26,27]; NGFI-B (physical, functional): DNA binding[28,29]; NURR1 (physical, functional): DNA binding[29]
Agonists	CD3254 (3 nM), LG100268 (3.2 nM), LGD1069 (36 nM),* 9-*cis*-retinoic acid (6.7–73 nM),* methoprenic acid (2 μM) [IC_{50}][8,12,30–39]; AGN194204 (0.4 nM) [K_d][40]; SR11237, docosahexaenoic acid, phytanic acid[41–44]
Antagonists	LG100754 (3.4 nM) [IC_{50}][36,45,46]; PA451, UVI3003[47,48]
Coactivators	NCOA1, NCOA2, NCOA3, PGC-1α, PPARBP, TBP, TAFII110, TAFII28, CREBBP, p300[36,49–59]
Biologically important isoforms	RXRα1 {Mm}: differs from RXRα2 in the A/B domain[60]; RXRα2 {Mm}: specifically expressed in testis[60]
Tissue distribution	Liver, lung, muscle, kidney, epidermis, and intestine; major isotype in the skin {Hs, Mm, Rn} [Northern blot, in situ hybridization, Western blot][3,8,61]
Functional assays	Differentiation of 3T3-L1 cells to adipocytes measured by the accumulation of triglyceride produced within the cytoplasm of the adipocyte {Mm}[33,62,63]; induction of apoptosis (associated with RARα activation) in leukemia cell lines {Hs}[38,64]; primitive endodermal differentiation and morphological differentiation in F9 murine embryonal carcinoma cell line {Mm}[65,66]
Mutant phenotype	Knockout mice have hypoplasia of the myocardium, which leads to animal death due to cardiac failure at around embryonic day 14.5; animals also have ocular malformation {Mm} [knockout][51,67–73]

aa, amino acid; chr, chromosome; HRE, hormone response element; NGFI-B, nerve growth factor-induced clone B; PGC-1α, PPAR coactivator-1α; PPARBP, PPAR-binding protein; TBP, TATA-box binding protein; CREBBP, cAMP response element-binding protein-binding protein.

* Radioligand.

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TABLE 2
RXRβ

Receptor Nomenclature	NR2B2
Receptor code	4.10.1:RX:2:B2
Other names	H-2RIIBP, RCoR-1,
Molecular information	Hs: 533aa, P28702, chr. 6p21.3[1,2] Rn: 458aa, P49743[3] Mm: 520aa, P28704, chr. 17[2,4–7]
DNA binding	
Structure	Homodimer, heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-1, DR-2, DR-3, DR-4, DR-5)
Partners	TR2 and TR4 (physical, functional): DNA binding[2,8–10]; VDR (physical, functional): DNA binding[8–10]; RARα, RARβ, and RARγ (physical, functional): DNA binding[2,8–14]; PPARα, PPARβ, and PPARγ (physical, functional): DNA binding[10,15,16]; LXRα and LXRβ (physical, functional): DNA binding[10,17–21]; FXR (physical, functional): DNA binding[10,22]; PXR (physical, functional): DNA binding[10,23–26]; CAR (physical, functional): DNA binding[10,27,28]; NGFI-B (physical, functional): DNA binding[10,29,30]; NURR1 (physical, functional): DNA binding[10,30]
Agonists	LG100268 (3–6.8 nM), LGD1069 (21 nM),* 9-*cis*-retinoic acid (6.2–117 nM),* [IC_{50}][7,31–39]; AGN194204 (3.6 nM) [K_d][40]
Antagonists	LG100754 (10 nM) [IC_{50}][36,41,42]
Coactivators	NCOA1, NCOA2, NCOA3[10,43–47]
Biologically important isoforms	RXRβ 1 {Hs, Mm}: differs from RXRβ 2 in the A/B domain[48,49]; RXRβ 2 {Hs, Mm}[49,50]
Tissue distribution	Ubiquitous {Hs, Mm, Rn} [Northern blot, in situ hybridization, Western blot][3,4,7,51]
Functional assays	Differentiation of 3T3-L1 cells to adipocytes measured by the accumulation of triglyceride produced within the cytoplasm of the adipocyte {Mm}[34,52,53]; induction of apoptosis (associated with RARα activation) in leukemia cell lines {Hs}[38,54]
Mutant phenotype	Male sterility due to defective spermatogenesis, abnormal lipid metabolism in Sertoli cells and behavioral defects {Mm} [knockout][18,55–57]

aa, amino acid; chr, chromosome; HRE, hormone response element; NGFI-B, nerve growth factor-induced clone B.
* Radioligand.

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TABLE 3
RXRγ

Receptor Nomenclature	NR2B1
Receptor code	4.10.1:RX:2:B3
Molecular information	Hs: 463aa, P48443, chr. 1q22-q23[1,2] Mm: 463aa, P28705, chr. 1[2–5]
DNA binding	
Structure	Homodimer, heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-1, DR-2, DR-3, DR-4, DR-5)
Partners	TR2 and TR4 (physical, functional): DNA binding[5–8]; VDR (physical, functional): DNA binding[6–8]; RARα, RARβ, and RARγ (physical, functional): DNA binding[5–12]; PPARα, PPARβ, and PPARγ (physical, functional): DNA binding[8,13,14]; LXRα and LXRβ (physical, functional): DNA binding[8,15–18]; FXR (physical, functional): DNA binding[8,19]; PXR (physical, functional): DNA binding[8,20–23]; CAR (physical, functional): DNA binding[8,24,25]; NGFI-B (physical, functional): DNA binding[8,26,27]; NURR1 (physical, functional): DNA binding[8,27]
Agonists	LG100268 (3–9.7 nM), LGD1069 (29 nM),* 9-*cis*-retinoic acid (9.7–85 nM)* [IC_{50}][28–36]; AGN194204 (3.8 nM) [K_d][37]
Antagonists	LG100754 (12.2 nM) [IC_{50}][33,38,39]
Coactivators	NCOA1, NCOA2, NCOA3[8,40–44]
Biologically important isoforms	RXRγ1 {Mm}: differs from RXRγ 2 in the A/B domain[45,46]; RXRγ2 {Mm}[45,46].
Tissue distribution	RXRγ1 is expressed in the brain and muscle, whereas RXRγ 2 is highly expressed in both cardiac and skeletal muscles {Mm, Rn} [Northern blot, in situ hybridization, Western blot][45,47–49]
Mutant phenotype	Knockout mice have metabolic and behavioral defects {Mm} [knockout][50–54]

aa, amino acid; chr, chromosome; HRE, hormone response element; NGFI-B, nerve growth factor-induced clone B.

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