

# International Union of Pharmacology. LXIII. Retinoid X Receptors

PIERRE GERMAIN, PIERRE CHAMBON, GREGOR EICHELE, RONALD M. EVANS, MITCHELL A. LAZAR, MARK LEID, ANGEL R. DE LERA, REUBEN LOTAN, DAVID J. MANGELSDORF, AND HINRICH GRONEMEYER

*Institut de Génétique et de Biologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique/Institut National de la Santé et de la Recherche Médicale/Université Louis Pasteur, Illkirch, Communauté Urbaine de Strasbourg, France (P.G., P.C., H.G.); Max-Planck-Institute of Experimental Endocrinology, Hannover, Germany (G.E.); Howard Hughes Medical Institute, Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, California (R.M.E.); Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, and the Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania (M.A.L.); Program in Molecular and Cellular Biology, Oregon State University, Corvallis, Oregon (M.L.); Departamento de Química Orgánica, Facultad de Química, Universidade de Vigo, Lagoas Marcosende, Vigo, Galicia, Spain (A.R.d.L.); Department of Thoracic/Head and Neck Medical Oncology—Unit 432, The University of Texas MD Anderson Cancer Center, Houston, Texas (R.L.); and Howard Hughes Medical Institute, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas (D.J.M.)*

**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, *RXR $\alpha$* , *RXR $\beta$* , and *RXR $\gamma$* . 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<sup>1</sup>), referred to as RXR $\alpha$  (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 RXR $\alpha$ , 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 RXR $\alpha$ , as well as for the two additional related subtypes, RXR $\beta$  (NR2B2) and RXR $\gamma$  (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

Address correspondence to: Dr. Pierre Germain, Department of Cell Biology and Signal Transduction, Institut de Génétique et de Biologie Moléculaire et Cellulaire, 1 rue Laurent Fries, BP 10142, 67404 Illkirch Cedex, France. E-mail: germain@titus.u-strasbg.fr

<sup>1</sup> 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.

Article, publication date, and citation information can be found at <http://pharmrev.aspetjournals.org>.

doi:10.1124/pr.58.4.7.

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 RXR $\alpha$  ( $\alpha 1$  and  $\alpha 2$ ), RXR $\beta$  ( $\beta 1$  and  $\beta 2$ ), and RXR $\gamma$  ( $\gamma 1$  and  $\gamma 2$ ) (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. RXR $\alpha$  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 of 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 RXR $\alpha$  was established by knockout experiments (Mark and Chambon, 2003). Moreover, studies using reporter transgenic mice based on GAL4DBD-RXRLBD fusion constructs and a  $\beta$ -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 PPAR $\gamma$  (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 exhibit very different shapes

(Renaud et al., 1995; Bourguet et al., 2000; Egea et al., 2002; Germain et al., 2004). A comparison of RAR $\gamma$  and RXR $\alpha$  LBPs indicates that, in contrast to the linear I shape of RAR $\gamma$  LBP, RXR $\alpha$  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 used 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 RXR $\alpha$ -RAR $\alpha$  and RXR $\alpha$ -PPAR $\gamma$  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. RXR $\beta$  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). RXR $\alpha$  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). RXR $\gamma$  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 *RXR $\alpha$*  gene has more severe consequences than the ablation of *RXR $\beta$*  and *RXR $\gamma$* . The loss of *RXR $\alpha$*  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  $RXR\alpha$  have ocular malformations (Kastner et al., 1994). Importantly, both defects due to  $RXR\alpha$  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  $RXR\alpha$  is essential in the transduction of a retinoid signal required for myocardial development and ocular morphogenesis, supporting the idea that  $RXR\alpha$  is involved in retinoid signaling in vivo. This view is also supported by the fact that  $RXR\alpha$  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  $RXR\alpha$  mutants (Sucov et al., 1995).

The ablation of  $RXR\beta$  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  $RXR\beta$  mutation leads to abnormal lipid metabolism in Sertoli cells, suggesting functional interactions of  $RXR\beta$  with other nuclear receptors that control lipid metabolism (Mascrez et al., 2004).

$RXR\gamma$ -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  $RXR\gamma$  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  $RXR\alpha$  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  $RXR$ s. In addition, owing to the in utero lethality, observed, for in-

stance, in  $RXR\alpha$  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  $RXR\alpha$  from hepatocytes led to the conclusion that  $RXR\alpha$  is a crucial functional partner for many other nuclear receptors such as  $LXR\alpha$ ,  $PXR$ ,  $FXR$ ,  $CAR\beta$ , and  $PPAR\alpha$  (Wan et al., 2000). Without  $RXR\alpha$ , all these receptors cannot activate their target genes efficiently. Hence, the absence of  $RXR\alpha$  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  $RXR\alpha$  has been specifically performed in epidermal keratinocytes of the adult mouse (Li et al., 2005; Metzger et al., 2005). This selective ablation shows that  $RXR\alpha$  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  $RXR\alpha$  exerts its role in the skin through the  $VDR$ - $RXR\alpha$  heterodimer.

Lastly, to address the critical issue of whether the transcriptional activity of  $RXR\alpha$  is required for its function in vivo or whether its heterodimerization capacity is the principal role of  $RXR\alpha$ , 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  $RXR\alpha$  null mice, suggesting that the  $RXR\alpha$  transactivation function was required for the developmental functions of the  $RXR\alpha$ - $RAR$  heterodimers. Animals expressing truncated  $RXR\alpha$  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 retinoids in cancer therapy and chemoprevention are poorly understood, clinical examination of these compounds is in progress. Strikingly, the synthetic retinoid 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 retinoids (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 PPAR $\gamma$  activity including the expression of genes involved in the uptake of glucose in muscle, lipid metabolism, and energy expenditure (Tontonoz et al., 1994). PPAR $\gamma$  has been implicated in several important metabolic diseases. The antidiabetic agents, thiazolidinediones (TZDs) selectively bind to PPAR $\gamma$  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-PPAR $\gamma$  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-PPAR $\gamma$  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-PPAR $\gamma$  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-PPAR $\gamma$  heterodimer, but not other permissive heterodimers formed with LXR, FXR, or NGFIB (Lala et al., 1996; Schulman et al., 1997). With PPAR $\gamma$  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.

#### REFERENCES

- Allenby G, Bocquel MT, Saunders M, Kazmer S, Speck J, Rosenberger M, Lovey A, Kastner P, Grippo JF, Chambon P, and et al (1993) Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proc Natl Acad Sci USA* **90**:30–34.
- Altucci L and Gronemeyer H (2001) The promise of retinoids to fight against cancer. *Nat Rev Cancer* **1**:181–193.
- Altucci L, Rossin A, Hirsch O, Nebbioso A, Vitoux D, Wilhelm E, Guidez F, De Simone N, Schiavone EM, Grimwade D, et al. (2005) Retinoid-triggered differentiation and tumor-selective apoptosis of acute myeloid leukemia by protein kinase A-mediated desubordination of retinoid X receptor. *Cancer Res* **65**:8754–8765.
- Apfel CM, Kamber M, Klaus M, Mohr P, Keidel S, and LeMotte PK (1995) Enhancement of HL-60 differentiation by a new class of retinoids with selective activity on retinoid X receptor. *J Biol Chem* **270**:30765–30772.
- Benoit G, Altucci L, Flexor M, Ruchaud S, Lillehaug J, Raffelsberger W, Gronemeyer H, and Lanotte M (1999) RAR-independent RXR signaling induces t(15:17) leukemia cell maturation. *EMBO (Eur Mol Biol Organ) J* **18**:7011–7018.
- Berger J, Biswas C, Hayes N, Ventre J, Wu M, and Doebber TW (1996) An antidiabetic thiazolidinedione potentiates insulin stimulation of glycogen synthase in rat adipose tissues. *Endocrinology* **137**:1984–1990.
- Boehm MF, Zhang L, Badea BA, White SK, Mais DE, Berger E, Suto CM, Goldman ME, and Heyman RA (1994) Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. *J Med Chem* **37**:2930–2941.
- Boehm MF, Zhang L, Zhi L, McClurg MR, Berger E, Wagoner M, Mais DE, Suto CM, Davies JA, Heyman RA, et al. (1995) Design and synthesis of potent retinoid X receptor selective ligands that induce apoptosis in leukemia cells. *J Med Chem* **38**:3146–3155.
- Bourguet W, Vivat V, Wurtz JM, Chambon P, Gronemeyer H, and Moras D (2000) Crystal structure of a heterodimeric complex of RAR and RXR ligand-binding domains. *Mol Cell* **5**:289–298.
- Brocard J, Kastner P, and Chambon P (1996) Two novel RXR $\alpha$  isoforms from mouse testis. *Biochem Biophys Res Commun* **229**:211–218.
- Brown NS, Smart A, Sharma V, Brinkmeier ML, Greenlee L, Camper SA, Jensen DR, Eckel RH, Krezel W, Chambon P, et al. (2000) Thyroid hormone resistance and increased metabolic rate in the RXR- $\gamma$ -deficient mouse. *J Clin Invest* **106**:73–79.
- Cesario RM, Klausung K, Razzaghi H, Crombie D, Rungta D, Heyman RA, and Lala DS (2001) The rexinoid LG100754 is a novel RXR:PPAR $\gamma$  agonist and decreases glucose levels in vivo. *Mol Endocrinol* **15**:1360–1369.
- Cha BS, Ciaraldi TP, Carter L, Nikoulina SE, Mudaliar S, Mukherjee R, Paterniti JR Jr, and Henry RR (2001) Peroxisome proliferator-activated receptor (PPAR)  $\gamma$  and retinoid X receptor (RXR) agonists have complementary effects on glucose and lipid metabolism in human skeletal muscle. *Diabetologia* **44**:444–452.

- Chambon P (1996) A decade of molecular biology of retinoic acid receptors. *FASEB J* **10**:940–954.
- Chawla A, Repa JJ, Evans RM, and Mangelsdorf DJ (2001) Nuclear receptors and lipid physiology: opening the X-files. *Science (Wash DC)* **294**:1866–1870.
- Chen JY, Clifford J, Zusi C, Starrett J, Tortolani D, Ostrowski J, Reczek PR, Chambon P, and Gronemeyer H (1996) Two distinct actions of retinoid-receptor ligands. *Nature (Lond)* **382**:819–822.
- Cheski B and Freedman LP (1996) Modulation of nuclear receptor interactions by ligands: kinetic analysis using surface plasmon resonance. *Biochemistry* **35**:3309–3318.
- Chiang MY, Misner D, Kempermann G, Schikorski T, Giguere V, Sucov HM, Gage FH, Stevens CF, and Evans RM (1998) An essential role for retinoid receptors RAR $\beta$  and RXR $\gamma$  in long-term potentiation and depression. *Neuron* **21**:1353–1361.
- Chiba H, Clifford J, Metzger D, and Chambon P (1997) Distinct retinoid X receptor-retinoid acid receptor heterodimers are differentially involved in the control of expression of retinoid target genes in F9 embryonal carcinoma cells. *Mol Cell Biol* **17**:3013–3020.
- Clarke N, Germain P, Altucci L, and Gronemeyer H (2004) Retinoids: potential in cancer prevention and therapy. *Expert Rev Mol Med* **6**:1–23.
- Clifford J, Chiba H, Sobieszczuk D, Metzger D, and Chambon P (1996) RXR $\alpha$ -null F9 embryonal carcinoma cells are resistant to the differentiation, anti-proliferative and apoptotic effects of retinoids. *EMBO (Eur Mol Biol Organ) J* **15**:4142–4155.
- Crowe DL and Chandraratna RA (2004) A retinoid X receptor (RXR)-selective retinoid reveals that RXR- $\alpha$  is potentially a therapeutic target in breast cancer cell lines, and that it potentiates antiproliferative and apoptotic responses to peroxisome proliferator-activated receptor ligands. *Breast Cancer Res* **6**:R546–R555.
- Dawson MI (2004) Synthetic retinoids and their nuclear receptors. *Curr Med Chem Anticancer Agents* **4**:199–230.
- de Urquiza AM, Liu S, Sjöberg M, Zetterstrom RH, Griffiths W, Sjövall J, and Perlmann T (2000) Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science (Wash DC)* **290**:2140–2144.
- Dolle P, Frauloh V, Kastner P, and Chambon P (1994) Developmental expression of murine retinoid X receptor (RXR) genes. *Mech Dev* **45**:91–104.
- Dragnev KH, Petty WJ, Shah S, Biddle A, Desai NB, Memoli V, Rigas JR, and Dmitrovsky E (2005) Bexarotene and erlotinib for aerodigestive tract cancer. *J Clin Oncol* **23**:8757–8764.
- Egea PF, Mitschler A, and Moras D (2002) Molecular recognition of agonist ligands by RXRs. *Mol Endocrinol* **16**:987–997.
- Fleischhauer K, Park JH, DiSanto JP, Marks M, Ozato K, and Yang SY (1992) Isolation of a full-length cDNA clone encoding a N-terminally variant form of the human retinoid X receptor  $\beta$ . *Nucleic Acids Res* **20**:1801.
- Forman BM (2002) The anti-diabetic agent LG100754 sensitizes cells to low concentrations of peroxisome proliferator-activated receptor  $\gamma$  ligands. *J Biol Chem* **277**:12503–12506.
- Forman BM, Umesono K, Chen J, and Evans RM (1995) Unique response pathways are established by allosteric interactions among nuclear hormone receptors. *Cell* **81**:541–550.
- Germain P, Iyer J, Zechel C, and Gronemeyer H (2002) Coregulator recruitment and the mechanism of retinoic acid receptor synergy. *Nature (Lond)* **415**:187–192.
- Germain P, Kammerer S, Perez E, Peluso-Itlis C, Tortolani D, Zusi FC, Starrett J, Lapointe P, Daris JP, Marinier A, et al. (2004) Rational design of RAR-selective ligands revealed by RAR $\beta$  crystal structure. *EMBO Rep* **5**:877–882.
- Glass CK (1994) Differential recognition of target genes by nuclear receptor monomers, dimers, and heterodimers. *Endocr Rev* **15**:391–407.
- Gronemeyer H, Gustafsson JA, and Laudet V (2004) Principles for modulation of the nuclear receptor superfamily. *Nat Rev Drug Discov* **3**:950–964.
- Hamada K, Gleason SL, Levi BZ, Hirschfeld S, Appella E, and Ozato K (1989) H-2RIIBP, a member of the nuclear hormone receptor superfamily that binds to both the regulatory element of major histocompatibility class I genes and the estrogen response element. *Proc Natl Acad Sci USA* **86**:8289–8293.
- Haugen BR, Brown NS, Wood WM, Gordon DF, and Ridgway EC (1997) The thyrotrope-restricted isoform of the retinoid-X receptor- $\gamma$ 1 mediates 9-cis-retinoic acid suppression of thyrotropin- $\beta$  promoter activity. *Mol Endocrinol* **11**:481–489.
- Heald P (2000) The treatment of cutaneous T-cell lymphoma with a novel retinoid. *Clin Lymphoma* **1** (Suppl 1):S45–S49.
- Heyman RA, Mangelsdorf DJ, Dyck JA, Stein RB, Eichele G, Evans RM, and Thaller C (1992) 9-cis Retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell* **68**:397–406.
- Hurst RE (2000) Bexarotene ligand pharmaceuticals. *Curr Opin Investig Drugs* **1**:514–523.
- Ijpenberg A, Tan NS, Gelman L, Kersten S, Seydoux J, Xu J, Metzger D, Canaple L, Chambon P, Wahli W, et al. (2004) In vivo activation of PPAR target genes by RXR homodimers. *EMBO (Eur Mol Biol Organ) J* **23**:2083–2091.
- Kagechika H and Shudo K (2005) Synthetic retinoids: recent developments concerning structure and clinical utility. *J Med Chem* **48**:5875–5883.
- Kastner P, Grondona JM, Mark M, Gansmuller A, LeMeur M, Decimo D, Vonesch JL, Dolle P, and Chambon P (1994) Genetic analysis of RXR  $\alpha$  developmental function: convergence of RXR and RAR signaling pathways in heart and eye morphogenesis. *Cell* **78**:987–1003.
- Kastner P, Mark M, and Chambon P (1995) Nonsteroid nuclear receptors: what are genetic studies telling us about their role in real life? *Cell* **83**:859–869.
- Kastner P, Mark M, Leid M, Gansmuller A, Chin W, Grondona JM, Decimo D, Krezel W, Dierich A, and Chambon P (1996) Abnormal spermatogenesis in RXR $\beta$  mutant mice. *Genes Dev* **10**:80–92.
- Kastner P, Messaddeq N, Mark M, Wendling O, Grondona JM, Ward S, Ghyselinck N, and Chambon P (1997) Vitamin A deficiency and mutations of RXR $\alpha$ , RXR $\beta$  and RAR $\alpha$  lead to early differentiation of embryonic ventricular cardiomyocytes. *Development* **124**:4749–4758.
- Kempf W, Kettelhack N, Duvic M, and Burg G (2003) Topical and systemic retinoid therapy for cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am* **17**:1405–1419.
- Klaholz BP, Renaud JP, Mitschler A, Zusi C, Chambon P, Gronemeyer H, and Moras D (1998) Conformational adaptation of agonists to the human nuclear receptor RAR $\gamma$ . *Nat Struct Biol* **5**:199–202.
- Krezel W, Dupe V, Mark M, Dierich A, Kastner P, and Chambon P (1996) RXR $\gamma$  null mice are apparently normal and compound RXR $\alpha^{+/-}$ RXR $\beta^{-/-}$ /RXR $\gamma^{-/-}$  mutant mice are viable. *Proc Natl Acad Sci USA* **93**:9010–9014.
- Krezel W, Ghyselinck N, Samad TA, Dupe V, Kastner P, Borrelli E, and Chambon P (1998) Impaired locomotion and dopamine signaling in retinoid receptor mutant mice. *Science (Wash DC)* **279**:863–867.
- Lala DS, Mukherjee R, Schulman IG, Koch SS, Dardashti LJ, Nadzan AM, Croston GE, Evans RM, and Heyman RA (1996) Activation of specific RXR heterodimers by an antagonist of RXR homodimers. *Nature (Lond)* **383**:450–453.
- Lampen A, Meyer S, and Nau H (2001) Phytanic acid and docosahexaenoic acid increase the metabolism of all-trans-retinoic acid and CYP26 gene expression in intestinal cells. *Biochim Biophys Acta* **1521**:97–106.
- Laudet V and Gronemeyer H (2002) *The Nuclear Receptor Facts Book*, Academic Press, San Diego.
- Laudet V, Hanni C, Coll J, Catzeflis F, and Stehelin D (1992) Evolution of the nuclear receptor gene superfamily. *EMBO (Eur Mol Biol Organ) J* **11**:1003–1013.
- Leblanc BP and Stunnenberg HG (1995) 9-cis retinoic acid signaling: changing partners causes some excitement. *Genes Dev* **9**:1811–1816.
- Lehmann JM, Jong L, Fanjul A, Cameron JF, Lu XP, Haefner P, Dawson MI, and Pfahl M (1992) Retinoids selective for retinoid X receptor response pathways. *Science (Wash DC)* **258**:1944–1946.
- Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, and Kliewer SA (1995) An anti-diabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ). *J Biol Chem* **270**:12953–12956.
- Leibowitz MD, Ardecky RJ, Boehm MF, Broderick CL, Carfagna MA, Crombie DL, D'Arrigo J, Etgen GJ, Faul MM, Grese TA, et al. (2006) Biological characterization of a heterodimer selective RXR modulator: potential benefits for the treatment of type 2 diabetes. *Endocrinology* **147**:1044–1053.
- Leid M, Kastner P, Lyons R, Nakshatri H, Saunders M, Zacharewski T, Chen JY, Staub A, Garnier JM, Mader S, et al. (1992) Purification, cloning, and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. *Cell* **68**:377–395.
- Lemotte PK, Keidel S, and Apfel CM (1996) Phytanic acid is a retinoid X receptor ligand. *Eur J Biochem* **236**:328–333.
- Lenhard JM, Lancaster ME, Paulik MA, Weiel JE, Binz JG, Sundseth SS, Gaskill BA, Lightfoot RM, and Brown HR (1999) The RXR agonist LG100268 causes hepatomegaly, improves glycaemic control and decreases cardiovascular risk and cachexia in diabetic mice suffering from pancreatic  $\beta$ -cell dysfunction. *Diabetologia* **42**:545–554.
- Levin AA, Sturzenbecker LJ, Kazmer S, Bosakowski T, Huselton C, Allenby G, Speck J, Kratzseisen C, Rosenberger M, Lovey A, et al. (1992) 9-cis retinoic acid stereoisomer binds and activates the nuclear receptor RXR $\alpha$ . *Nature (Lond)* **355**:359–361.
- Li M, Chiba H, Warot X, Messaddeq N, Gerard C, Chambon P, and Metzger D (2001) RXR- $\alpha$  ablation in skin keratinocytes results in alopecia and epidermal alterations. *Development* **128**:675–688.
- Li M, Indra AK, Warot X, Brocard J, Messaddeq N, Kato S, Metzger D, and Chambon P (2000) Skin abnormalities generated by temporally controlled RXR $\alpha$  mutations in mouse epidermis. *Nature (Lond)* **407**:633–636.
- Li M, Messaddeq N, Teletin M, Pasquali JL, Metzger D, and Chambon P (2005) Retinoid X receptor ablation in adult mouse keratinocytes generates an atopic dermatitis triggered by thymic stromal lymphopoietin. *Proc Natl Acad Sci USA* **102**:14795–14800.
- Liu Q and Linney E (1993) The mouse retinoid-X receptor- $\gamma$  gene: genomic organization and evidence for functional isoforms. *Mol Endocrinol* **7**:651–658.
- Lowe MN and Plosker GL (2000) Bexarotene. *Am J Clin Dermatol* **1**:245–250; discussion 251–252.
- Luria A and Furlow JD (2004) Spatiotemporal retinoid-X receptor activation detected in live vertebrate embryos. *Proc Natl Acad Sci USA* **101**:8987–8992.
- Mader S, Chen JY, Chen Z, White J, Chambon P, and Gronemeyer H (1993) The patterns of binding of RAR, RXR and TR homo- and heterodimers to direct repeats are dictated by the binding specificities of the DNA binding domains. *EMBO (Eur Mol Biol Organ) J* **12**:5029–5041.
- Mangelsdorf DJ, Borgmeyer U, Heyman RA, Zhou JY, Ong ES, Oro AE, Kakizuka A, and Evans RM (1992) Characterization of three RXR genes that mediate the action of 9-cis retinoic acid. *Genes Dev* **6**:329–344.
- Mangelsdorf DJ, Ong ES, Dyck JA, and Evans RM (1990) Nuclear receptor that identifies a novel retinoic acid response pathway. *Nature (Lond)* **345**:224–229.
- Mangelsdorf DJ, Umesono K, Kliewer SA, Borgmeyer U, Ong ES, and Evans RM (1991) A direct repeat in the cellular retinoid-binding protein type II gene confers differential regulation by RXR and RAR. *Cell* **66**:555–561.
- Mark M and Chambon P (2003) Functions of RARs and RXRs in vivo: genetic dissection of the retinoid signaling pathway. *Pure Appl Chem* **75**:1709–1732.
- Mark M, Ghyselinck NB, and Chambon P (2006) Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signalling pathway during mouse embryogenesis. *Annu Rev Pharmacol Toxicol* **46**:451–480.
- Mascrez B, Ghyselinck NB, Watanabe M, Annicotte JS, Chambon P, Auwerx J, and Mark M (2004) Ligand-dependent contribution of RXR $\beta$  to cholesterol homeostasis in Sertoli cells. *EMBO Rep* **5**:285–290.
- Mascrez B, Mark M, Krezel W, Dupe V, LeMeur M, Ghyselinck NB, and Chambon P (2001) Differential contributions of AF-1 and AF-2 activities to the developmental functions of RXR $\alpha$ . *Development* **128**:2049–2062.
- Mertz JR, Shang E, Piantadosi R, Wei S, Wolgemuth DJ, and Blaner WS (1997) Identification and characterization of a stereospecific human enzyme that catalyzes 9-cis-retinol oxidation: a possible role in 9-cis-retinoic acid formation. *J Biol Chem* **272**:11744–11749.



- Metzger D, Li M, and Chambon P (2005) Targeted somatic mutagenesis in the mouse epidermis. *Methods Mol Biol* **289**:329–340.
- Michaelis S, Cozzio A, Kempf W, Graf P, Burg G, and Dummer R (2004) Combination of bexarotene and psoralen-UVA therapy in a patient with mycosis fungoides. *Dermatology* **209**:72–74.
- Michelllys PY, Ardecky RJ, Chen JH, Crombie DL, Etgen GJ, Faul MM, Faulkner AL, Grese TA, Heyman RA, Karanewsky DS, et al. (2003) Novel (2E,4E,6Z)-7-(2-alkoxy-3,5-dialkylbenzene)-3-methylocta-2,4,6-trienoic acid retinoid X receptor modulators are active in models of type 2 diabetes. *J Med Chem* **46**:2683–2696.
- Mukherjee R, Davies PJ, Crombie DL, Bischoff ED, Cesario RM, Jow L, Hamann LG, Boehm MF, Mondon CE, Nadzan AM, et al. (1997) Sensitization of diabetic and obese mice to insulin by retinoid X receptor agonists. *Nature (Lond)* **386**:407–410.
- Nagata T, Kanno Y, Ozato K, and Taketo M (1994) The mouse Rxb gene encoding RXR $\beta$ : genomic organization and two mRNA isoforms generated by alternative splicing of transcripts initiated from CpG island promoters. *Gene* **142**:183–189.
- Perlmann T and Jansson L (1995) A novel pathway for vitamin A signaling mediated by RXR heterodimerization with NGFI-B and NURR1. *Genes Dev* **9**:769–782.
- Picard F and Auwerx J (2002) PPAR $\gamma$  and glucose homeostasis. *Annu Rev Nutr* **22**:167–197.
- Reginato MJ and Lazar MA (1999) Mechanisms by which thiazolidinediones enhance insulin action. *Trends Endocrinol Metab* **10**:9–13.
- Renaud JP, Rochel N, Ruff M, Vivat V, Chambon P, Gronemeyer H, and Moras D (1995) Crystal structure of the RAR- $\gamma$  ligand-binding domain bound to all-*trans* retinoic acid. *Nature (Lond)* **378**:681–689.
- Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietsch JM, and Mangelsdorf DJ (2000) Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science (Wash DC)* **289**:1524–1529.
- Romert A, Tuvendal P, Simon A, Dencker L, and Eriksson U (1998) The identification of a 9-*cis* retinol dehydrogenase in the mouse embryo reveals a pathway for synthesis of 9-*cis* retinoic acid. *Proc Natl Acad Sci USA* **95**:4404–4409.
- Rowe A, Eager NS, and Brickell PM (1991) A member of the RXR nuclear receptor family is expressed in neural-crest-derived cells of the developing chick peripheral nervous system. *Development* **111**:771–778.
- Roy B, Taneja R, and Chambon P (1995) Synergistic activation of retinoic acid (RA)-responsive genes and induction of embryonal carcinoma cell differentiation by an RA receptor  $\alpha$  (RAR  $\alpha$ ), RAR  $\beta$ , or RAR  $\gamma$ -selective ligand in combination with a retinoid X receptor-specific ligand. *Mol Cell Biol* **15**:6481–6487.
- Schulman IG, Juguilon H, and Evans RM (1996) Activation and repression by nuclear hormone receptors: hormone modulates an equilibrium between active and repressive states. *Mol Cell Biol* **16**:3807–3813.
- Schulman IG, Li C, Schwabe JW, and Evans RM (1997) The phantom ligand effect: allosteric control of transcription by the retinoid X receptor. *Genes Dev* **11**:299–308.
- Shen Q, Cline GW, Shulman GI, Leibowitz MD, and Davies PJ (2004) Effects of retinoids on glucose transport and insulin-mediated signaling in skeletal muscles of diabetic (*db/db*) mice. *J Biol Chem* **279**:19721–19731.
- Shulman AI, Larson C, Mangelsdorf DJ, and Ranganathan R (2004) Structural determinants of allosteric ligand activation in RXR heterodimers. *Cell* **116**:417–429.
- Shulman AI and Mangelsdorf DJ (2005) Retinoid X receptor heterodimers in the metabolic syndrome. *N Engl J Med* **353**:604–615.
- Smit JV, Franssen ME, de Jong EM, Lambert J, Roseeuw DI, De Weert J, Yocum RC, Stevens VJ, and van De Kerkhof PC (2004) A phase II multicenter clinical trial of systemic bexarotene in psoriasis. *J Am Acad Dermatol* **51**:249–256.
- Solomin L, Johansson CB, Zetterstrom RH, Bissonnette RP, Heyman RA, Olson L, Lendahl U, Frisen J, and Perlmann T (1998) Retinoid-X receptor signalling in the developing spinal cord. *Nature (Lond)* **395**:398–402.
- Standeven AM, Beard RL, Johnson AT, Boehm MF, Escobar M, Heyman RA, and Chandraratna RA (1996) Retinoid-induced hypertriglyceridemia in rats is mediated by retinoic acid receptors. *Fundam Appl Toxicol* **33**:264–271.
- Sucov HM, Dyson E, Gumeringer CL, Price J, Chien KR, and Evans RM (1994) RXR $\alpha$  mutant mice establish a genetic basis for vitamin A signaling in heart morphogenesis. *Genes Dev* **8**:1007–1018.
- Sucov HM, Izpisua-Belmonte JC, Ganan Y, and Evans RM (1995) Mouse embryos lacking RXR $\alpha$  are resistant to retinoic-acid-induced limb defects. *Development* **121**:3997–4003.
- Szanto A, Narkar V, Shen Q, Uray IP, Davies PJ, and Nagy L (2004) Retinoid X receptors: X-ploring their (patho)physiological functions. *Cell Death Differ* **11** (Suppl 2):S126–S143.
- Thacher SM, Vasudevan J, and Chandraratna RA (2000) Therapeutic applications for ligands of retinoid receptors. *Curr Pharm Des* **6**:25–58.
- Thompson PD, Jurutka PW, Haussler CA, Whitfield GK, and Haussler MR (1998) Heterodimeric DNA binding by the vitamin D receptor and retinoid X receptors is enhanced by 1,25-dihydroxyvitamin D $_3$  and inhibited by 9-*cis*-retinoic acid: evidence for allosteric receptor interactions. *J Biol Chem* **273**:8483–8491.
- Tontozov P, Graves RA, Budavari AI, Erdjument-Bromage H, Lui M, Hu E, Tempst P, and Spiegelman BM (1994) Adipocyte-specific transcription factor ARF6 is a heterodimeric complex of two nuclear hormone receptors, PPAR $\gamma$  and RXR $\alpha$ . *Nucleic Acids Res* **22**:5628–5634.
- Vivat-Hannah V, Bourguet W, Gottardis M, and Gronemeyer H (2003) Separation of retinoid X receptor homo- and heterodimerization functions. *Mol Cell Biol* **23**:7678–7688.
- Vivat-Hannah V and Zusi FC (2005) Retinoids as therapeutic agents: today and tomorrow. *Mini Rev Med Chem* **5**:755–760.
- Wan YJ, An D, Cai Y, Repa JJ, Hung-Po Chen T, Flores M, Postic C, Magnuson MA, Chen J, Chien KR, et al. (2000) Hepatocyte-specific mutation establishes retinoid X receptor  $\alpha$  as a heterodimeric integrator of multiple physiological processes in the liver. *Mol Cell Biol* **20**:4436–4444.
- Westin S, Kurokawa R, Nolte RT, Wisely GB, McInerney EM, Rose DW, Milburn MV, Rosenfeld MG, and Glass CK (1998) Interactions controlling the assembly of nuclear-receptor heterodimers and co-activators. *Nature (Lond)* **395**:199–202.
- Yu VC, Delsert C, Andersen B, Holloway JM, Devary OV, Naar AM, Kim SY, Boutin JM, Glass CK, and Rosenfeld MG (1991) RXR $\beta$ : a coregulator that enhances binding of retinoic acid, thyroid hormone, and vitamin D receptors to their cognate response elements. *Cell* **67**:1251–1266.
- Zhang C and Duvic M (2003) Retinoids: therapeutic applications and mechanisms of action in cutaneous T-cell lymphoma. *Dermatol Ther* **16**:322–330.
- Zhang J, Hu X, and Lazar MA (1999) A novel role for helix 12 of retinoid X receptor in regulating repression. *Mol Cell Biol* **19**:6448–6457.
- Zhang J, Zamir I, and Lazar MA (1997) Differential recognition of liganded and unliganded thyroid hormone receptor by retinoid X receptor regulates transcriptional repression. *Mol Cell Biol* **17**:6887–6897.
- Zomer AW, van Der Burg B, Jansen GA, Wanders RJ, Poll-The BT, and van Der Saag PT (2000) Pristanic acid and phytanic acid: naturally occurring ligands for the nuclear receptor peroxisome proliferator-activated receptor  $\alpha$ . *J Lipid Res* **41**:1801–1807.

TABLE 1  
RXR $\alpha$ 

Receptor Nomenclature	NR2B1
Receptor code	4.1:RX:2:B1
Molecular information	Hs:462aa, P19793, chr. 9q34.3 <sup>1-3</sup> Rn:467aa, P28700 <sup>4</sup> Mm: 467aa, Q05343, chr. 2 <sup>5-8</sup>
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 <sup>7,9,10</sup> ; VDR (physical, functional): DNA binding <sup>9,10</sup> ; RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ (physical, functional): DNA binding <sup>7,9-14</sup> ; PPAR $\alpha$ , PPAR $\beta$ , and PPAR $\gamma$ (physical, functional): DNA binding <sup>15,16</sup> ; LXR $\alpha$ and LXR $\beta$ (physical, functional): DNA binding <sup>17-20</sup> ; FXR (physical, functional): DNA binding <sup>21</sup> ; PXR (physical, functional): DNA binding <sup>22-25</sup> ; CAR (physical, functional): DNA binding <sup>26,27</sup> ; NGFI-B (physical, functional): DNA binding <sup>28,29</sup> ; NURR1 (physical, functional): DNA binding <sup>29</sup>
Agonists	CD3254 (3 nM), LG100268 (3.2 nM), LGD1069 (36 nM),* 9- <i>cis</i> -retinoic acid (6.7–73 nM),* methoprenic acid (2 $\mu$ M) [IC <sub>50</sub> ] <sup>8,12,30-39</sup> ; AGN194204 (0.4 nM) [K <sub>d</sub> ] <sup>40</sup> ; SR11237, docosahexaenoic acid, phytanic acid <sup>41-44</sup>
Antagonists	LG100754 (3.4 nM) [IC <sub>50</sub> ] <sup>36,45,46</sup> ; PA451, UVI3003 <sup>47,48</sup>
Coactivators	NCOA1, NCOA2, NCOA3, PGC-1 $\alpha$ , PPARBP, TBP, TAFII110, TAFII28, CREBBP, p300 <sup>36,49-59</sup>
Biologically important isoforms	RXR $\alpha$ 1 [Mm]: differs from RXR $\alpha$ 2 in the A/B domain <sup>60</sup> ; RXR $\alpha$ 2 [Mm]: specifically expressed in testis <sup>60</sup>
Tissue distribution	Liver, lung, muscle, kidney, epidermis, and intestine; major isotype in the skin (Hs, Mm, Rn) [Northern blot, in situ hybridization, Western blot] <sup>3,8,61</sup>
Functional assays	Differentiation of 3T3-L1 cells to adipocytes measured by the accumulation of triglyceride produced within the cytoplasm of the adipocyte [Mm] <sup>33,62,63</sup> ; induction of apoptosis (associated with RAR $\alpha$ activation) in leukemia cell lines [Hs] <sup>38,64</sup> ; primitive endodermal differentiation and morphological differentiation in F9 murine embryonal carcinoma cell line [Mm] <sup>65,66</sup>
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] <sup>51,67-73</sup>

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

\* Radioligand.

- Almasan A, Mangelsdorf DJ, Ong ES, Wahl GM, and Evans RM (1994) Chromosomal localization of the human retinoid X receptors. *Genomics* **20**:397–403.
- Jones KA, Fitzgibbon J, Woodward KJ, Goudie D, Ferguson-Smith MA, Povey S, Wolfe J, and Solomon E (1993) Localization of the retinoid X receptor  $\alpha$  gene (RXRA) to chromosome 9q34. *Ann Hum Genet* **57**:195–201.
- Mangelsdorf DJ, Ong ES, Dyck JA, and Evans RM (1990) Nuclear receptor that identifies a novel retinoic acid response pathway. *Nature (Lond)* **345**:224–229.
- Gearing KL, Gottlicher M, Teboul M, Widmark E, and Gustafsson JA (1993) Interaction of the peroxisome-proliferator-activated receptor and retinoid X receptor. *Proc Natl Acad Sci USA* **90**:1440–1444.
- Hoopes CW, Taketo M, Ozato K, Liu Q, Howard TA, Linney E, and Seldin MF (1992) Mapping of the mouse Rrx loci encoding nuclear retinoid X receptors RXR $\alpha$ , RXR $\beta$ , and RXR $\gamma$ . *Genomics* **14**:611–617.
- Leid M, Kastner P, and Chambon P (1992) Multiplicity generates diversity in the retinoic acid signalling pathways. *Trends Biochem Sci* **17**:427–433.
- Leid M, Kastner P, Lyons R, Nakshatri H, Saunders M, Zacharewski T, Chen JY, Staub A, Garnier JM, Mader S, et al. (1992) Purification, cloning, and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. *Cell* **68**:377–395.
- Mangelsdorf DJ, Borgmeyer U, Heyman RA, Zhou JY, Ong ES, Oro AE, Kakizuka A, and Evans RM (1992) Characterization of three RXR genes that mediate the action of 9-*cis* retinoic acid. *Genes Dev* **6**:329–344.
- Bugge TH, Pohl J, Lonnoy O, and Stunnenberg HG (1992) RXR $\alpha$ , a promiscuous partner of retinoic acid and thyroid hormone receptors. *EMBO (Eur Mol Biol Organ) J* **11**:1409–1418.
- Glass CK (1994) Differential recognition of target genes by nuclear receptor monomers, dimers, and heterodimers. *Endocr Rev* **15**:391–407.
- Berrodin TJ, Marks MS, Ozato K, Linney E, and Lazar MA (1992) Heterodimerization among thyroid hormone receptor, retinoic acid receptor, retinoid X receptor, chicken ovalbumin upstream promoter transcription factor, and an endogenous liver protein. *Mol Endocrinol* **6**:1468–1478.
- Germain P, Iyer J, Zechel C, and Gronemeyer H (2002) Coregulator recruitment and the mechanism of retinoic acid receptor synergy. *Nature (Lond)* **415**:187–192.
- Kliwer SA, Umesono K, Mangelsdorf DJ, and Evans RM (1992) Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D<sub>3</sub> signalling. *Nature (Lond)* **355**:446–449.
- Zhang XK, Lehmann J, Hoffmann B, Dawson MI, Cameron J, Graupner G, Hermann T, Tran P, and Pfahl M (1992) Homodimer formation of retinoid X receptor induced by 9-*cis* retinoic acid. *Nature (Lond)* **358**:587–591.
- Kliwer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-*cis* retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
- Tontonoz P, Graves RA, Budavari AI, Erdjument-Bromage H, Lui M, Hu E, Tempst P, and Spiegelman BM (1994) Adipocyte-specific transcription factor ARF6 is a heterodimeric complex of two nuclear hormone receptors, PPAR $\gamma$  and RXR $\alpha$ . *Nucleic Acids Res* **22**:5628–5634.
- Feltkamp D, Wiebel FF, Alberti S, and Gustafsson JA (1999) Identification of a novel DNA binding site for nuclear orphan receptor OR1. *J Biol Chem* **274**:10421–10429.
- Teboul M, Enmark E, Li Q, Wikstrom AC, Pelto-Huikko M, and Gustafsson JA (1995) OR-1, a member of the nuclear receptor superfamily that interacts with the 9-*cis*-retinoic acid receptor. *Proc Natl Acad Sci USA* **92**:2096–2100.
- Wiebel FF and Gustafsson JA (1997) Heterodimeric interaction between retinoid X receptor  $\alpha$  and orphan nuclear receptor OR1 reveals dimerization-induced activation as a novel mechanism of nuclear receptor activation. *Mol Cell Biol* **17**:3977–3986.
- Willy PJ and Mangelsdorf DJ (1997) Unique requirements for retinoid-dependent transcriptional activation by the orphan receptor LXR. *Genes Dev* **11**:289–298.
- Seol W, Choi HS, and Moore DD (1995) Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol Endocrinol* **9**:72–85.
- Blumberg B, Kang H, Bolado J Jr, Chen H, Craig AG, Moreno TA, Umesono K, Perlmann T, De Robertis EM, and Evans RM (1998) BXR, an embryonic orphan nuclear receptor activated by a novel class of endogenous benzoate metabolites. *Genes Dev* **12**:1269–1277.
- Blumberg B, Sabbagh W Jr, Juguilon H, Bolado J Jr, van Meter CM, Ong ES, and Evans RM (1998) SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes Dev* **12**:3195–3205.
- Kliwer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterstrom RH, et al. (1998) An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* **92**:73–82.
- Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, and Kliwer SA (1998) The human orphan nuclear receptor PXR is activated by compounds that



- regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* **102**:1016–1023.
26. Baes M, Gulick T, Choi HS, Martinoli MG, Simha D, and Moore DD (1994) A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. *Mol Cell Biol* **14**:1544–1552.
27. Choi HS, Chung M, Tzamelis I, Simha D, Lee YK, Seol W, and Moore DD (1997) Differential transactivation by two isoforms of the orphan nuclear hormone receptor CAR. *J Biol Chem* **272**:23565–23571.
28. Forman BM, Umesono K, Chen J, and Evans RM (1995) Unique response pathways are established by allosteric interactions among nuclear hormone receptors. *Cell* **81**:541–550.
29. Perlmann T and Jansson L (1995) A novel pathway for vitamin A signaling mediated by RXR heterodimerization with NGFI-B and NURR1. *Genes Dev* **9**:769–782.
30. Allenby G, Bocquel MT, Saunders M, Kazmer S, Speck J, Rosenberger M, Lovey A, Kastner P, Grippo JF, Chambon P, et al. (1993) Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proc Natl Acad Sci USA* **90**:30–34.
31. Boehm MF, McClurg MR, Pathirana C, Mangelsdorf D, White SK, Hebert J, Winn D, Goldman ME, and Heyman RA (1994) Synthesis of high specific activity [<sup>3</sup>H]-9-*cis*-retinoic acid and its application for identifying retinoids with unusual binding properties. *J Med Chem* **37**:408–414.
32. Boehm MF, Zhang L, Badea BA, White SK, Mais DE, Berger E, Suto CM, Goldman ME, and Heyman RA (1994) Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. *J Med Chem* **37**:2930–2941.
33. Canan Koch SS, Dardashti LJ, Cesario RM, Croston GE, Boehm MF, Heyman RA, and Nadzan AM (1999) Synthesis of retinoid X receptor-specific ligands that are potent inducers of adipogenesis in 3T3-L1 cells. *J Med Chem* **42**:742–750.
34. Harmon MA, Boehm MF, Heyman RA, and Mangelsdorf DJ (1995) Activation of mammalian retinoid X receptors by the insect growth regulator methoprene. *Proc Natl Acad Sci USA* **92**:6157–6160.
35. Heyman RA, Mangelsdorf DJ, Dyck JA, Stein RB, Eichele G, Evans RM, and Thaller C (1992) 9-*cis* retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell* **68**:397–406.
36. Lala DS, Mukherjee R, Schulman IG, Koch SS, Dardashti LJ, Nadzan AM, Croston GE, Evans RM, and Heyman RA (1996) Activation of specific RXR heterodimers by an antagonist of RXR homodimers. *Nature (Lond)* **383**:450–453.
37. Levin AA, Sturzenbecker LJ, Kazmer S, Bosakowski T, Huselton C, Allenby G, Speck J, Kratzstein C, Rosenberger M, Lovey A, et al. (1992) 9-*cis* retinoic acid stereoisomer binds and activates the nuclear receptor RXR $\alpha$ . *Nature (Lond)* **355**:359–361.
38. Nagy L, Thomazy VA, Shipley GL, Fesus L, Lamph W, Heyman RA, Chandraratna RA, and Davies PJ (1995) Activation of retinoid X receptors induces apoptosis in HL-60 cell lines. *Mol Cell Biol* **15**:3540–3551.
39. Thacher SM, Vasudevan J, and Chandraratna RA (2000) Therapeutic applications for ligands of retinoid receptors. *Curr Pharm Des* **6**:25–58.
40. Vuligonda V, Thacher SM, and Chandraratna RA (2001) Enantioselective syntheses of potent retinoid X receptor ligands: differential biological activities of individual antipodes. *J Med Chem* **44**:2298–2303.
41. de Urquiza AM, Liu S, Sjoberg M, Zetterstrom RH, Griffiths W, Sjoval J, and Perlmann T (2000) Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science* **290**:2140–2144.
42. Lampen A, Meyer S, and Nau H (2001) Phytanic acid and docosahexaenoic acid increase the metabolism of all-*trans*-retinoic acid and CYP26 gene expression in intestinal cells. *Biochim Biophys Acta* **1521**:97–106.
43. Lehmann JM, Jong L, Fanjul A, Cameron JF, Lu XP, Haefner P, Dawson MI, and Pfahl M (1992) Retinoids selective for retinoid X receptor response pathways. *Science* **258**:1944–1946.
44. Lemotte PK, Keidel S, and Apfel CM (1996) Phytanic acid is a retinoid X receptor ligand. *Eur J Biochem* **236**:328–333.
45. Cesario RM, Klausung K, Razzaghi H, Crombie D, Rungta D, Heyman RA, and Lala DS (2001) The retinoid LG100754 is a novel RXR:PPAR $\gamma$  agonist and decreases glucose levels in vivo. *Mol Endocrinol* **15**:1360–1369.
46. Forman BM (2002) The antiadipic agent LG100754 sensitizes cells to low concentrations of peroxisome proliferator-activated receptor  $\gamma$  ligands. *J Biol Chem* **277**:12503–12506.
47. Pogenberg V, Guichou JF, Vivat-Hannah V, Kammerer S, Perez E, Germain P, de Lera AR, Gronemeyer H, Royer CA, and Bourguet W (2005) Characterization of the interaction between retinoic acid receptor/retinoid X receptor (RAR/RXR) heterodimers and transcriptional coactivators through structural and fluorescence anisotropy studies. *J Biol Chem* **280**:1625–1633.
48. Takahashi B, Ohta K, Kawachi E, Fukasawa H, Hashimoto Y, and Kagechika H (2002) Novel retinoid X receptor antagonists: specific inhibition of retinoid synergism in RXR-RAR heterodimer actions. *J Med Chem* **45**:3327–3330.
49. Chakravarti D, LaMorte VJ, Nelson MC, Nakajima T, Schulman IG, Juguilon H, Montminy M, and Evans RM (1996) Role of CBP/p300 in nuclear receptor signalling. *Nature (Lond)* **383**:99–103.
50. Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, and Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multiprotein activation complex with P/CAF and CBP/p300. *Cell* **90**:569–580.
51. Delerive P, Wu Y, Burris TP, Chin WW, and Suen CS (2002) PGC-1 functions as a transcriptional coactivator for the retinoid X receptors. *J Biol Chem* **277**:3913–3917.
52. Kamei Y, Xu L, Heinzel T, Torchia J, Kurokawa R, Glass B, Lin SC, Heyman RA, Rose DW, Glass CK, et al. (1996) A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. *Cell* **85**:403–414.
53. May M, Mengus G, Lavigne AC, Chambon P, and Davidson I (1996) Human TAF(II28) promotes transcriptional stimulation by activation function 2 of the retinoid X receptors. *EMBO (Eur Mol Biol Organ) J* **15**:3093–3104.
54. McKenna NJ, Lanz RB, and O'Malley BW (1999) Nuclear receptor coregulators: cellular and molecular biology. *Endocr Rev* **20**:321–344.
55. Onate SA, Tsai SY, Tsai MJ, and O'Malley BW (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* **270**:1354–1357.
56. Schulman IG, Chakravarti D, Juguilon H, Romo A, and Evans RM (1995) Interactions between the retinoid X receptor and a conserved region of the TATA-binding protein mediate hormone-dependent transactivation. *Proc Natl Acad Sci USA* **92**:8288–8292.
57. Voegel JJ, Heine MJ, Tini M, Vivat V, Chambon P, and Gronemeyer H (1998) The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and -independent pathways. *EMBO (Eur Mol Biol Organ) J* **17**:507–519.
58. Voegel JJ, Heine MJ, Zechel C, Chambon P, and Gronemeyer H (1996) TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *EMBO (Eur Mol Biol Organ) J* **15**:3667–3675.
59. Yuan CX, Ito M, Fondell JD, Fu ZY, and Roeder RG (1998) The TRAP220 component of a thyroid hormone receptor-associated protein (TRAP) coactivator complex interacts directly with nuclear receptors in a ligand-dependent fashion. *Proc Natl Acad Sci USA* **95**:7939–7944.
60. Brocard J, Kastner P, and Chambon P (1996) Two novel RXR $\alpha$  isoforms from mouse testis. *Biochem Biophys Res Commun* **229**:211–218.
61. Dolle P, Fraulob V, Kastner P, and Chambon P (1994) Developmental expression of murine retinoid X receptor (RXR) genes. *Mech Dev* **45**:91–104.
62. Chawla A and Lazar MA (1993) Induction of Rev-ErbA $\alpha$ , an orphan receptor encoded on the opposite strand of the  $\alpha$ -thyroid hormone receptor gene, during adipocyte differentiation. *J Biol Chem* **268**:16265–16269.
63. Chawla A and Lazar MA (1994) Peroxisome proliferator and retinoid signaling pathways co-regulate preadipocyte phenotype and survival. *Proc Natl Acad Sci USA* **91**:1786–1790.
64. Monczak Y, Trudel M, Lamph WW, and Miller WH Jr (1997) Induction of apoptosis without differentiation by retinoic acid in PLB-985 cells requires the activation of both RAR and RXR. *Blood* **90**:3345–3355.
65. Chiba H, Clifford J, Metzger D, and Chambon P (1997) Distinct retinoid X receptor-retinoic acid receptor heterodimers are differentially involved in the control of expression of retinoid target genes in F9 embryonal carcinoma cells. *Mol Cell Biol* **17**:3013–3020.
66. Clifford J, Chiba H, Sobieszczyk D, Metzger D, and Chambon P (1996) RXR $\alpha$ -null F9 embryonal carcinoma cells are resistant to the differentiation, anti-proliferative and apoptotic effects of retinoids. *EMBO (Eur Mol Biol Organ) J* **15**:4142–4155.
67. Kastner P, Grondona JM, Mark M, Gansmuller A, LeMeur M, Decimo D, Vonesch JL, Dolle P, and Chambon P (1994) Genetic analysis of RXR $\alpha$  developmental function: convergence of RXR and RAR signaling pathways in heart and eye morphogenesis. *Cell* **78**:987–1003.
68. Kastner P, Mark M, and Chambon P (1995) Nonsteroid nuclear receptors: what are genetic studies telling us about their role in real life? *Cell* **83**:859–869.
69. Kastner P, Messaddeq N, Mark M, Wendling O, Grondona JM, Ward S, Ghyselinck N, and Chambon P (1997) Vitamin A deficiency and mutations of RXR $\alpha$ , RXR $\beta$  and RAR $\alpha$  lead to early differentiation of embryonic ventricular cardiomyocytes. *Development* **124**:4749–4758.
70. Mark M and Chambon P (2003) Functions of RARs and RXRs in vivo: genetic dissection of the retinoid signaling pathway. *Pure Appl Chem* **75**:1709–1732.
71. Mark M, Ghyselinck NB, and Chambon P (2006) Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signalling pathway during mouse embryogenesis. *Annu Rev Pharmacol Toxicol* **46**:451–480.
72. Sucov HM, Dyson E, Gumeringer CL, Price J, Chien KR, and Evans RM (1994) RXR $\alpha$  mutant mice establish a genetic basis for vitamin A signaling in heart morphogenesis. *Genes Dev* **8**:1007–1018.
73. Sucov HM, Izpissua-Belmonte JC, Ganan Y, and Evans RM (1995) Mouse embryos lacking RXR $\alpha$  are resistant to retinoic-acid-induced limb defects. *Development* **121**:3997–4003.

TABLE 2  
RXR $\beta$ 

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 <sup>1,2</sup> Rn: 458aa, P49743 <sup>3</sup> Mm: 520aa, P28704, chr. 17 <sup>2,4-7</sup>
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 <sup>2,8-10</sup> ; VDR (physical, functional): DNA binding <sup>8-10</sup> ; RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ (physical, functional): DNA binding <sup>2,8-14</sup> ; PPAR $\alpha$ , PPAR $\beta$ , and PPAR $\gamma$ (physical, functional): DNA binding <sup>10,15,16</sup> ; LXR $\alpha$ and LXR $\beta$ (physical, functional): DNA binding <sup>10,17-21</sup> ; FXR (physical, functional): DNA binding <sup>10,22</sup> ; PXR (physical, functional): DNA binding <sup>10,23-26</sup> ; CAR (physical, functional): DNA binding <sup>10,27,28</sup> ; NGFI-B (physical, functional): DNA binding <sup>10,29,30</sup> ; NURR1 (physical, functional): DNA binding <sup>10,30</sup>
Agonists	LG100268 (3–6.8 nM), LGD1069 (21 nM),* 9- <i>cis</i> -retinoic acid (6.2–117 nM),* [IC <sub>50</sub> ] <sup>7,31-39</sup> ; AGN194204 (3.6 nM) [K <sub>d</sub> ] <sup>40</sup>
Antagonists	LG100754 (10 nM) [IC <sub>50</sub> ] <sup>36,41,42</sup>
Coactivators	NCOA1, NCOA2, NCOA3 <sup>10,43-47</sup>
Biologically important isoforms	RXR $\beta$ 1 (Hs, Mm): differs from RXR $\beta$ 2 in the A/B domain <sup>48,49</sup> ; RXR $\beta$ 2 (Hs, Mm) <sup>49,50</sup>
Tissue distribution	Ubiquitous (Hs, Mm, Rn) [Northern blot, in situ hybridization, Western blot] <sup>3,4,7,51</sup>
Functional assays	Differentiation of 3T3-L1 cells to adipocytes measured by the accumulation of triglyceride produced within the cytoplasm of the adipocyte [Mm] <sup>34,52,53</sup> ; induction of apoptosis (associated with RAR $\alpha$ activation) in leukemia cell lines [Hs] <sup>38,54</sup>
Mutant phenotype	Male sterility due to defective spermatogenesis, abnormal lipid metabolism in Sertoli cells and behavioral defects [Mm] [knockout] <sup>18,55-57</sup>

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

\* Radioligand.

- Almasan A, Mangelsdorf DJ, Ong ES, Wahl GM, and Evans RM (1994) Chromosomal localization of the human retinoid X receptors. *Genomics* **20**:397–403.
- Leid M, Kastner P, Lyons R, Nakshatri H, Saunders M, Zacharewski T, Chen JY, Staub A, Garnier JM, Mader S, et al. (1992) Purification, cloning, and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. *Cell* **68**:377–395.
- Yu VC, Delsert C, Andersen B, Holloway JM, Devary OV, Naar AM, Kim SY, Boutin JM, Glass CK, and Rosenfeld MG (1991) RXR $\beta$ : a coregulator that enhances binding of retinoic acid, thyroid hormone, and vitamin D receptors to their cognate response elements. *Cell* **67**:1251–1266.
- Hamada K, Gleason SL, Levi BZ, Hirschfeld S, Appella E, and Ozato K (1989) H-2RIIBP, a member of the nuclear hormone receptor superfamily that binds to both the regulatory element of major histocompatibility class I genes and the estrogen response element. *Proc Natl Acad Sci USA* **86**:8289–8293.
- Hoopes CW, Taketo M, Ozato K, Liu Q, Howard TA, Linney E, and Seldin MF (1992) Mapping of the mouse Rrx loci encoding nuclear retinoid X receptors RXR $\alpha$ , RXR $\beta$ , and RXR $\gamma$ . *Genomics* **14**:611–617.
- Leid M, Kastner P, and Chambon P (1992) Multiplicity generates diversity in the retinoic acid signalling pathways. *Trends Biochem Sci* **17**:427–433.
- Mangelsdorf DJ, Borgmeyer U, Heyman RA, Zhou JY, Ong ES, Oro AE, Kakizuka A, and Evans RM (1992) Characterization of three RXR genes that mediate the action of 9-*cis* retinoic acid. *Genes Dev* **6**:329–344.
- Bugge TH, Pohl J, Lonnoy O, and Stunnenberg HG (1992) RXR $\alpha$ , a promiscuous partner of retinoic acid and thyroid hormone receptors. *EMBO (Eur Mol Biol Organ) J* **11**:1409–1418.
- Glass CK (1994) Differential recognition of target genes by nuclear receptor monomers, dimers, and heterodimers. *Endocr Rev* **15**:391–407.
- Laudet V and Gronemeyer H (2002) *The Nuclear Receptor Facts Book*. Academic Press, San Diego.
- Berrodin TJ, Marks MS, Ozato K, Linney E, and Lazar MA (1992) Heterodimerization among thyroid hormone receptor, retinoic acid receptor, retinoid X receptor, chicken ovalbumin upstream promoter transcription factor, and an endogenous liver protein. *Mol Endocrinol* **6**:1468–1478.
- Germain P, Iyer J, Zechel C, and Gronemeyer H (2002) Coregulator recruitment and the mechanism of retinoic acid receptor synergy. *Nature (Lond)* **415**:187–192.
- Kliwer SA, Umesono K, Mangelsdorf DJ, and Evans RM (1992) Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D3 signalling. *Nature (Lond)* **355**:446–449.
- Zhang XK, Lehmann J, Hoffmann B, Dawson MI, Cameron J, Graupner G, Hermann T, Tran P, and Pfahl M (1992) Homodimer formation of retinoid X receptor induced by 9-*cis* retinoic acid. *Nature (Lond)* **358**:587–591.
- Kliwer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-*cis* retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
- Tontonoz P, Graves RA, Budavari AI, Erdjument-Bromage H, Lui M, Hu E, Tempst P, and Spiegelman BM (1994) Adipocyte-specific transcription factor ARF6 is a heterodimeric complex of two nuclear hormone receptors, PPAR $\gamma$  and RXR $\alpha$ . *Nucleic Acids Res* **22**:5628–5634.
- Feltkamp D, Wiebel FF, Alberti S, and Gustafsson JA (1999) Identification of a novel DNA binding site for nuclear orphan receptor OR1. *J Biol Chem* **274**:10421–10429.
- Mascrez B, Ghyselinck NB, Watanabe M, Annicotte JS, Chambon P, Auwerx J, and Mark M (2004) Ligand-dependent contribution of RXR $\beta$  to cholesterol homeostasis in Sertoli cells. *EMBO Rep* **5**:285–290.
- Teboul M, Enmark E, Li Q, Wikstrom AC, Pelto-Huikko M and Gustafsson JA (1995) OR-1, a member of the nuclear receptor superfamily that interacts with the 9-*cis*-retinoic acid receptor. *Proc Natl Acad Sci USA* **92**:2096–2100.
- Wiebel FF and Gustafsson JA (1997) Heterodimeric interaction between retinoid X receptor  $\alpha$  and orphan nuclear receptor OR1 reveals dimerization-induced activation as a novel mechanism of nuclear receptor activation. *Mol Cell Biol* **17**:3977–3986.
- Willy PJ and Mangelsdorf DJ (1997) Unique requirements for retinoid-dependent transcriptional activation by the orphan receptor LXR. *Genes Dev* **11**:289–298.
- Seol W, Choi HS, and Moore DD (1995) Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol Endocrinol* **9**:72–85.
- Blumberg B, Kang H, Bolado J Jr, Chen H, Craig AG, Moreno TA, Umesono K, Perlmann T, De Robertis EM, and Evans RM (1998) BXR, an embryonic orphan nuclear receptor activated by a novel class of endogenous benzoate metabolites. *Genes Dev* **12**:1269–1277.
- Blumberg B, Sabbagh W Jr, Juguilon H, Bolado J Jr, van Meter CM, Ong ES and Evans RM (1998) SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes Dev* **12**:3195–3205.
- Kliwer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterstrom RH, et al. (1998) An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* **92**:73–82.
- Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, and Kliwer SA (1998) The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* **102**:1016–1023.

27. Baes M, Gulick T, Choi HS, Martinoli MG, Simha D, and Moore DD (1994) A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. *Mol Cell Biol* **14**:1544–1552.
28. Choi HS, Chung M, Tzamelis I, Simha D, Lee YK, Seol W, and Moore DD (1997) Differential transactivation by two isoforms of the orphan nuclear hormone receptor CAR. *J Biol Chem* **272**:23565–23571.
29. Forman BM, Umesono K, Chen J, and Evans RM (1995) Unique response pathways are established by allosteric interactions among nuclear hormone receptors. *Cell* **81**:541–550.
30. Perlmann T and Jansson L (1995) A novel pathway for vitamin A signaling mediated by RXR heterodimerization with NGFI-B and NURR1. *Genes Dev* **9**:769–782.
31. Allenby G, Bocquel MT, Saunders M, Kazmer S, Speck J, Rosenberger M, Lovey A, Kastner P, Grippo JF, Chambon P, et al. (1993) Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proc Natl Acad Sci USA* **90**:30–34.
32. Boehm MF, McClurg MR, Pathirana C, Mangelsdorf D, White SK, Hebert J, Winn D, Goldman ME, and Heyman RA (1994) Synthesis of high specific activity [<sup>3</sup>H]-9-*cis*-retinoic acid and its application for identifying retinoids with unusual binding properties. *J Med Chem* **37**:408–414.
33. Boehm MF, Zhang L, Badea BA, White SK, Mais DE, Berger E, Suto CM, Goldman ME, and Heyman RA (1994) Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. *J Med Chem* **37**:2930–2941.
34. Canan Koch SS, Dardashti LJ, Cesario RM, Croston GE, Boehm MF, Heyman RA, and Nadzan AM (1999) Synthesis of retinoid X receptor-specific ligands that are potent inducers of adipogenesis in 3T3-L1 cells. *J Med Chem* **42**:742–750.
35. Heyman RA, Mangelsdorf DJ, Dyck JA, Stein RB, Eichele G, Evans RM, and Thaller C (1992) 9-*cis* retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell* **68**:397–406.
36. Lala DS, Mukherjee R, Schulman IG, Koch SS, Dardashti LJ, Nadzan AM, Croston GE, Evans RM, and Heyman RA (1996) Activation of specific RXR heterodimers by an antagonist of RXR homodimers. *Nature (Lond)* **383**:450–453.
37. Levin AA, Sturzenbecker LJ, Kazmer S, Bosakowski T, Huselton C, Allenby G, Speck J, Kratzstein C, Rosenberger M, Lovey A, et al. (1992) 9-*cis* retinoic acid stereoisomer binds and activates the nuclear receptor RXR $\alpha$ . *Nature (Lond)* **355**:359–361.
38. Nagy L, Thomazy VA, Shipley GL, Fesus L, Lamph W, Heyman RA, Chandraratna RA, and Davies PJ (1995) Activation of retinoid X receptors induces apoptosis in HL-60 cell lines. *Mol Cell Biol* **15**:3540–3551.
39. Thacher SM, Vasudevan J, and Chandraratna RA (2000) Therapeutic applications for ligands of retinoid receptors. *Curr Pharm Des* **6**:25–58.
40. Vuligonda V, Thacher SM, and Chandraratna RA (2001) Enantioselective syntheses of potent retinoid X receptor ligands: differential biological activities of individual antipodes. *J Med Chem* **44**:2298–2303.
41. Cesario RM, Klausung K, Razzaghi H, Crombie D, Rungta D, Heyman RA, and Lala DS (2001) The retinoid LG100754 is a novel RXR:PPAR $\gamma$  agonist and decreases glucose levels in vivo. *Mol Endocrinol* **15**:1360–1369.
42. Forman BM (2002) The antidiabetic agent LG100754 sensitizes cells to low concentrations of peroxisome proliferator-activated receptor  $\gamma$  ligands. *J Biol Chem* **277**:12503–12506.
43. Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, and Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* **90**:569–580.
44. McKenna NJ, Lanz RB, and O'Malley BW (1999) Nuclear receptor coregulators: cellular and molecular biology. *Endocr Rev* **20**:321–344.
45. Onate SA, Tsai SY, Tsai MJ, and O'Malley BW (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* **270**:1354–1357.
46. Voegel JJ, Heine MJ, Tini M, Vivat V, Chambon P, and Gronemeyer H (1998) The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and -independent pathways. *EMBO (Eur Mol Biol Organ) J* **17**:507–519.
47. Voegel JJ, Heine MJ, Zechel C, Chambon P, and Gronemeyer H (1996) TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *EMBO (Eur Mol Biol Organ) J* **15**:3667–3675.
48. Fleischhauer K, Park JH, DiSanto JP, Marks M, Ozato K, and Yang SY (1992) Isolation of a full-length cDNA clone encoding a N-terminally variant form of the human retinoid X receptor  $\beta$ . *Nucleic Acids Res* **20**:1801.
49. Nagata T, Kanno Y, Ozato K, and Taketo M (1994) The mouse Rxb gene encoding RXR $\beta$ : genomic organization and two mRNA isoforms generated by alternative splicing of transcripts initiated from CpG island promoters. *Gene* **142**:183–189.
50. Numasawa T, Koga H, Ueyama K, Maeda S, Sakou T, Harata S, Leppert M, and Inoue I (1999) Human retinoic X receptor  $\beta$ : complete genomic sequence and mutation search for ossification of posterior longitudinal ligament of the spine. *J Bone Miner Res* **14**:500–508.
51. Dolle P, Fraulob V, Kastner P, and Chambon P (1994) Developmental expression of murine retinoid X receptor (RXR) genes. *Mech Dev* **45**:91–104.
52. Chawla A and Lazar MA (1993) Induction of Rev-ErbA $\alpha$ , an orphan receptor encoded on the opposite strand of the  $\alpha$ -thyroid hormone receptor gene, during adipocyte differentiation. *J Biol Chem* **268**:16265–16269.
53. Chawla A and Lazar MA (1994) Peroxisome proliferator and retinoid signaling pathways co-regulate preadipocyte phenotype and survival. *Proc Natl Acad Sci USA* **91**:1786–1790.
54. Monczak Y, Trudel M, Lamph WW, and Miller WH Jr (1997) Induction of apoptosis without differentiation by retinoic acid in PLB-985 cells requires the activation of both RAR and RXR. *Blood* **90**:3345–3355.
55. Kastner P, Mark M, Leid M, Gansmuller A, Chin W, Grondona JM, Decimo D, Krezel W, Dierich A, and Chambon P (1996) Abnormal spermatogenesis in RXR $\beta$  mutant mice. *Genes Dev* **10**:80–92.
56. Mark M and Chambon P (2003) Functions of RARs and RXRs in vivo: genetic dissection of the retinoid signaling pathway. *Pure Appl Chem* **75**:1709–1732.
57. Mark M, Ghyselinck NB, and Chambon P (2006) Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signalling pathway during mouse embryogenesis. *Annu Rev Pharmacol Toxicol* **46**:451–480.



TABLE 3  
RXR $\gamma$ 

Receptor Nomenclature	NR2B1
Receptor code	4.10.1:RX:2:B3
Molecular information	Hs: 463aa, P48443, chr. 1q22-q23 <sup>1,2</sup> Mm: 463aa, P28705, chr. 1 <sup>2-5</sup>
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 <sup>5-8</sup> ; VDR (physical, functional): DNA binding <sup>6-8</sup> ; RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ (physical, functional): DNA binding <sup>5-12</sup> ; PPAR $\alpha$ , PPAR $\beta$ , and PPAR $\gamma$ (physical, functional): DNA binding <sup>8,13,14</sup> ; LXR $\alpha$ and LXR $\beta$ (physical, functional): DNA binding <sup>8,15-18</sup> ; FXR (physical, functional): DNA binding <sup>8,19</sup> ; PXR (physical, functional): DNA binding <sup>8,20-23</sup> ; CAR (physical, functional): DNA binding <sup>8,24,25</sup> ; NGFI-B (physical, functional): DNA binding <sup>8,26,27</sup> ; NURR1 (physical, functional): DNA binding <sup>8,27</sup>
Agonists	LG100268 (3–9.7 nM), LGD1069 (29 nM),* 9- <i>cis</i> -retinoic acid (9.7–85 nM)* [IC <sub>50</sub> ] <sup>128-36</sup> ; AGN194204 (3.8 nM) [K <sub>d</sub> ] <sup>37</sup>
Antagonists	LG100754 (12.2 nM) [IC <sub>50</sub> ] <sup>33,38,39</sup>
Coactivators	NCOA1, NCOA2, NCOA3 <sup>8,40-44</sup>
Biologically important isoforms	RXR $\gamma$ 1 {Mm}: differs from RXR $\gamma$ 2 in the A/B domain <sup>45,46</sup> ; RXR $\gamma$ 2 {Mm} <sup>45,46</sup> .
Tissue distribution	RXR $\gamma$ 1 is expressed in the brain and muscle, whereas RXR $\gamma$ 2 is highly expressed in both cardiac and skeletal muscles [Mm, Rn] [Northern blot, in situ hybridization, Western blot] <sup>45,47-49</sup>
Mutant phenotype	Knockout mice have metabolic and behavioral defects {Mm} [knockout] <sup>50-54</sup>

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

- Almasan A, Mangelsdorf DJ, Ong ES, Wahl GM, and Evans RM (1994) Chromosomal localization of the human retinoid X receptors. *Genomics* **20**:397–403.
- Mangelsdorf DJ, Borgmeyer U, Heyman RA, Zhou JY, Ong ES, Oro AE, Kakizuka A, and Evans RM (1992) Characterization of three RXR genes that mediate the action of 9-*cis* retinoic acid. *Genes Dev* **6**:329–344.
- Hoopes CW, Taketo M, Ozato K, Liu Q, Howard TA, Linney E, and Seldin MF (1992) Mapping of the mouse Rxr loci encoding nuclear retinoid X receptors RXR $\alpha$ , RXR $\beta$ , and RXR $\gamma$ . *Genomics* **14**:611–617.
- Leid M, Kastner P, and Chambon P (1992) Multiplicity generates diversity in the retinoic acid signalling pathways. *Trends Biochem Sci* **17**:427–433.
- Leid M, Kastner P, Lyons R, Nakshatri H, Saunders M, Zacharewski T, Chen JY, Staub A, Garnier JM, Mader S, et al. (1992) Purification, cloning, and RXR identity of the HeLa cell factor with which RAR or TR heterodimerizes to bind target sequences efficiently. *Cell* **68**:377–395.
- Bugge TH, Pohl J, Lonnoy O, and Stunnenberg HG (1992) RXR $\alpha$ , a promiscuous partner of retinoic acid and thyroid hormone receptors. *EMBO (Eur Mol Biol Organ) J* **11**:1409–1418.
- Glass CK (1994) Differential recognition of target genes by nuclear receptor monomers, dimers, and heterodimers. *Endocr Rev* **15**:391–407.
- Laudet V and Gronemeyer H (2002) *The Nuclear Receptor Facts Book*, Academic Press, San Diego.
- Berrodin TJ, Marks MS, Ozato K, Linney E, and Lazar MA (1992) Heterodimerization among thyroid hormone receptor, retinoic acid receptor, retinoid X receptor, chicken ovalbumin upstream promoter transcription factor, and an endogenous liver protein. *Mol Endocrinol* **6**:1468–1478.
- Germain P, Iyer J, Zechel C, and Gronemeyer H (2002) Coregulator recruitment and the mechanism of retinoic acid receptor synergy. *Nature (Lond)* **415**:187–192.
- Kliwer SA, Umesono K, Mangelsdorf DJ, and Evans RM (1992) Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D<sub>3</sub> signalling. *Nature (Lond)* **355**:446–449.
- Zhang XK, Lehmann J, Hoffmann B, Dawson MI, Cameron J, Graupner G, Hermann T, Tran P, and Pfahl M (1992) Homodimer formation of retinoid X receptor induced by 9-*cis* retinoic acid. *Nature (Lond)* **358**:587–591.
- Kliwer SA, Umesono K, Noonan DJ, Heyman RA, and Evans RM (1992) Convergence of 9-*cis* retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature (Lond)* **358**:771–774.
- Tontonoz P, Graves RA, Budavari AI, Erdjument-Bromage H, Lui M, Hu E, Tempst P, and Spiegelman BM (1994) Adipocyte-specific transcription factor ARF6 is a heterodimeric complex of two nuclear hormone receptors, PPAR $\gamma$  and RXR $\alpha$ . *Nucleic Acids Res* **22**:5628–5634.
- Feltkamp D, Wiebel FF, Alberti S, and Gustafsson JA (1999) Identification of a novel DNA binding site for nuclear orphan receptor OR1. *J Biol Chem* **274**:10421–10429.
- Teboul M, Enmark E, Li Q, Wikstrom AC, Pelto-Huikko M, and Gustafsson JA (1995) OR-1, a member of the nuclear receptor superfamily that interacts with the 9-*cis*-retinoic acid receptor. *Proc Natl Acad Sci USA* **92**:2096–2100.
- Wiebel FF and Gustafsson JA (1997) Heterodimeric interaction between retinoid X receptor  $\alpha$  and orphan nuclear receptor OR1 reveals dimerization-induced activation as a novel mechanism of nuclear receptor activation. *Mol Cell Biol* **17**:3977–3998.
- Willy PJ and Mangelsdorf DJ (1997) Unique requirements for retinoid-dependent transcriptional activation by the orphan receptor LXR. *Genes Dev* **11**:289–298.
- Seol W, Choi HS, and Moore DD (1995) Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol Endocrinol* **9**:72–85.
- Blumberg B, Kang H, Bolado J Jr, Chen H, Craig AG, Moreno TA, Umesono K, Perlmann T, De Robertis EM, and Evans RM (1998) BXR, an embryonic orphan nuclear receptor activated by a novel class of endogenous benzoate metabolites. *Genes Dev* **12**:1269–1277.
- Blumberg B, Sabbagh W Jr, Juguilon H, Bolado J Jr, van Meter CM, Ong ES, and Evans RM (1998) SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes Dev* **12**:3195–3205.
- Kliwer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterstrom RH, et al. (1998) An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* **92**:73–82.
- Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, and Kliwer SA (1998) The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* **102**:1016–1023.
- Baes M, Gulick T, Choi HS, Martinoli MG, Simha D, and Moore DD (1994) A new orphan member of the nuclear hormone receptor superfamily that interacts with a subset of retinoic acid response elements. *Mol Cell Biol* **14**:1544–1552.
- Choi HS, Chung M, Tzamei I, Simha D, Lee YK, Seol W, and Moore DD (1997) Differential transactivation by two isoforms of the orphan nuclear hormone receptor CAR. *J Biol Chem* **272**:23565–23571.
- Forman BM, Umesono K, Chen J, and Evans RM (1995) Unique response pathways are established by allosteric interactions among nuclear hormone receptors. *Cell* **81**:541–550.
- Perlmann T and Jansson L (1995) A novel pathway for vitamin A signaling mediated by RXR heterodimerization with NGFI-B and NURR1. *Genes Dev* **9**:769–782.
- Allenby G, Bocquel MT, Saunders M, Kazmer S, Speck J, Rosenberger M, Lovey A, Kastner P, Grippo JF, Chambon P, et al. (1993) Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proc Natl Acad Sci USA* **90**:30–34.
- Boehm MF, McClurg MR, Pathirana C, Mangelsdorf D, White SK, Hebert J, Winn D, Goldman ME, and Heyman RA (1994) Synthesis of high specific activity [<sup>3</sup>H]-9-*cis*-retinoic acid and its application for identifying retinoids with unusual binding properties. *J Med Chem* **37**:408–414.

20. Boehm MF, Zhang L, Badea BA, White SK, Mais DE, Berger E, Suto CM, Goldman ME, and Heyman RA (1994) Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. *J Med Chem* **37**:2930–2941.
31. Canan Koch SS, Dardashti LJ, Cesario RM, Croston GE, Boehm MF, Heyman RA, and Nadzan AM (1999) Synthesis of retinoid X receptor-specific ligands that are potent inducers of adipogenesis in 3T3-L1 cells. *J Med Chem* **42**:742–750.
32. Heyman RA, Mangelsdorf DJ, Dyck JA, Stein RB, Eichele G, Evans RM, and Thaller C (1992) 9-*cis* retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell* **68**:397–406.
33. Lala DS, Mukherjee R, Schulman IG, Koch SS, Dardashti LJ, Nadzan AM, Croston GE, Evans RM, and Heyman RA (1996) Activation of specific RXR heterodimers by an antagonist of RXR homodimers. *Nature (Lond)* **383**:450–453.
34. Levin AA, Sturzenbecker LJ, Kazmer S, Bosakowski T, Huselton C, Allenby G, Speck J, Kratzeisen C, Rosenberger M, Lovey A, et al. (1992) 9-*cis* retinoic acid stereoisomer binds and activates the nuclear receptor RXR $\alpha$ . *Nature (Lond)* **355**:359–361.
35. Nagy L, Thomazy VA, Shipley GL, Fesus L, Lamph W, Heyman RA, Chandraratna RA, and Davies PJ (1995) Activation of retinoid X receptors induces apoptosis in HL-60 cell lines. *Mol Cell Biol* **15**:3540–3551.
36. Thacher SM, Vasudevan J, and Chandraratna RA (2000) Therapeutic applications for ligands of retinoid receptors. *Curr Pharm Des* **6**:25–58.
37. Vuligonda V, Thacher SM, and Chandraratna RA (2001) Enantioselective syntheses of potent retinoid X receptor ligands: differential biological activities of individual antipodes. *J Med Chem* **44**:2298–2303.
38. Cesario RM, Klausning K, Razzaghi H, Crombie D, Rungta D, Heyman RA, and Lala DS (2001) The retinoid LG100754 is a novel RXR:PPAR $\gamma$  agonist and decreases glucose levels in vivo. *Mol Endocrinol* **15**:1360–1369.
39. Forman BM (2002) The antidiabetic agent LG100754 sensitizes cells to low concentrations of peroxisome proliferator-activated receptor  $\gamma$  ligands. *J Biol Chem* **277**:12503–12506.
40. Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, and Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell* **90**:569–580.
41. McKenna NJ, Lanz RB, and O'Malley BW (1999) Nuclear receptor coregulators: cellular and molecular biology. *Endocr Rev* **20**:321–344.
42. Onate SA, Tsai SY, Tsai MJ, and O'Malley BW (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* **270**:1354–1357.
43. Voegel JJ, Heine MJ, Tini M, Vivat V, Chambon P, and Gronemeyer H (1998) The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and -independent pathways. *EMBO (Eur Mol Biol Organ) J* **17**:507–519.
44. Voegel JJ, Heine MJ, Zechel C, Chambon P, and Gronemeyer H (1996) TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *EMBO (Eur Mol Biol Organ) J* **15**:3667–3675.
45. Liu Q and Linney E (1993) The mouse retinoid-X receptor- $\gamma$  gene: genomic organization and evidence for functional isoforms. *Mol Endocrinol* **7**:651–658.
46. Nagata T, Kanno Y, Ozato K, and Taketo M (1994) The mouse Rxrb gene encoding RXR $\beta$ : genomic organization and two mRNA isoforms generated by alternative splicing of transcripts initiated from CpG island promoters. *Gene* **142**:183–189.
47. Chiang MY, Misner D, Kempermann G, Schikorski T, Giguere V, Sucov HM, Gage FH, Stevens CF, and Evans RM (1998) An essential role for retinoid receptors RAR $\beta$  and RXR $\gamma$  in long-term potentiation and depression. *Neuron* **21**:1353–1361.
48. Dolle P, Fraulob V, Kastner P, and Chambon P (1994) Developmental expression of murine retinoid X receptor (RXR) genes. *Mech Dev* **45**:91–104.
49. Haugen BR, Brown NS, Wood WM, Gordon DF, and Ridgway EC (1997) The thyrotrope-restricted isoform of the retinoid-X receptor- $\gamma$  1 mediates 9-*cis*-retinoic acid suppression of thyrotropin- $\beta$  promoter activity. *Mol Endocrinol* **11**:481–489.
50. Brown NS, Smart A, Sharma V, Brinkmeier ML, Greenlee L, Camper SA, Jensen DR, Eckel RH, Krezel W, Chambon P, et al. (2000) Thyroid hormone resistance and increased metabolic rate in the RXR- $\gamma$ -deficient mouse. *J Clin Invest* **106**:73–79.
51. Krezel W, Dupe V, Mark M, Dierich A, Kastner P, and Chambon P (1996) RXR  $\gamma$  null mice are apparently normal and compound RXR $\alpha$ <sup>+/-</sup>/RXR $\beta$ <sup>-/-</sup>/RXR $\gamma$ <sup>-/-</sup> mutant mice are viable. *Proc Natl Acad Sci USA* **93**:9010–9014.
52. Krezel W, Ghyselinck N, Samad TA, Dupe V, Kastner P, Borrelli E, and Chambon P. (1998) Impaired locomotion and dopamine signaling in retinoid receptor mutant mice. *Science* **279**:863–867.
53. Mark M and Chambon P (2003) Functions of RARs and RXRs in vivo: genetic dissection of the retinoid signaling pathway. *Pure Appl Chem* **75**:1709–1732.
54. Mark M, Ghyselinck NB, and Chambon P (2006) Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signalling pathway during mouse embryogenesis. *Annu Rev Pharmacol Toxicol* **46**:451–480.