RORs in Autoimmune Disease

Mi Ra Chang, Hugh Rosen and Patrick R. Griffin

Abstract The retinoic acid receptor-related orphan receptor (ROR) subfamily of nuclear receptors are transcription factors involved in the maintenance of circadian rhythm and are essential for proper immune function. The T cell-specific isoform, RORγt, is required for T helper 17 cells (T_H17) development and it has been implicated in the pathogenesis of autoimmune diseases including multiple sclerosis and rheumatoid arthritis. Thus, pharmacological repression of RORγt may provide a strategy for therapeutic intervention in autoimmune disorders. This chapter provides a summary of the current status for target validation and development of new chemical entities targeting RORγt.

Contents

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1 Nuclear Receptors

Nuclear receptors (NRs) are a highly conserved superfamily of ligand-dependent transcription factors that control a diverse set of biological activities by translating dietary and endocrine signals into changes in expression of gene networks. NRs have been implicated in a range of diseases and disorders including diabetes and obesity, cancer, inflammation, and atherosclerosis. The superfamily contains 48 members in the human genome and these receptors bind a range of ligands from retinoids, fatty acids, sterols, and vitamins. NRs are characterized by a multi-domain architecture comprised of an N-terminal ligand-independent Activating Function 1 (AF1) domain, DNA-binding domain (DBD), hinge, and ligand-binding domain (LBD) containing the ligand-dependent AF2 (Evans 1988). The canonical domain structure of the NR superfamily is shown in Fig. 8.1. The AF1 and hinge regions of NRs are the most divergent in sequence and length across the superfamily, are considered intrinsically disordered (Krasowski et al. 2008), and their function and significance have been reviewed (Moore et al. 2006; Warnmark et al. 2003; Tremblay et al. 1999; Clinckemalie et al. 2012; Zwart et al. 2010). The DBD is the most highly conserved sequence among NRs and contains two zinc finger motifs to bind distinct DNA response elements. NR response elements are commonly arranged as either direct or inverted repeats of a consensus half-site (RGGTCA; R = purine). NRs can bind DNA as monomers, homodimers, or heterodimers with the retinoid X receptor alpha (RXRα).

The activity and function of NRs can be modulated upon binding small lipophilic ligands. This feature makes the superfamily attractive as therapeutic drug targets. For a majority of the family members examples of controlling their activity by exogenous synthetic small molecules have been published. Interestingly, nuclear receptors are the molecular target of approximately 10–15 % of drugs currently approved by the FDA, highlighting their tractability for therapeutic intervention (Overington et al. 2006). The ligand binding domain has been the focus of drug discovery efforts as it is structurally conserved across the superfamily, containing an internal hydrophobic cavity to which small molecule ligands bind (Moore et al. 2006). The ligand-dependent AF2 structural element that is contained within the LBD is the surface of the receptor directly involved in interactions with coregulatory proteins that have either intrinsic chromatin remodeling activity or that tether in enzymes such as histone acetyltransferases (HATs) or histone deacetylases (HDACs). Coactivator proteins contain a highly conserved hydrophobic LXXLL motif known as a "NR box." This motif is involved in direct interactions with the AF2 surface of NRs when they are in an active conformation (e.g., when receptor is liganded to agonist) (Heery et al. 1997). Coactivators like steroid receptor coactivator 1 (SRC-1) facilitate acetylation of histones. This aids in relaxing chromatin to allow recruitment of the basal transcription complex to the initiation site of target genes of a particular NR (Spencer et al. 1997). In contrast, corepressors like the nuclear receptor co-repressor (NCoR) and silencing mediators of retinoid and thyroid (SMRT) contain a slightly different hydrophobic motif referred to as

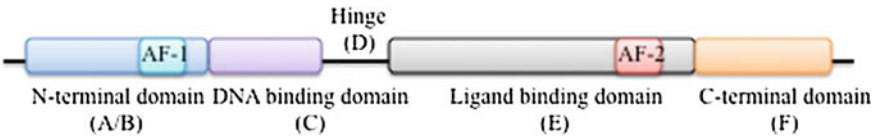

Fig. 8.1 Structural organization of nuclear receptors: *A/B* domain contains *AF-1* (activation function) whose action is independent of the presence of ligand; *C* domain contains zinc fingers that bind to specific sequences of DNA (HRE: hormone response elements); *D* region to be a flexible domain that connects the DBD with the LBD; *E* domain contains ligand binding cavity and *AF-2* whose action is dependent on the presence of bound ligand; *F* domain is highly variable in sequence between various nuclear receptors

"CoRNR boxes" that interact with high affinity at the AF2 when the receptor is in the inactive conformation (e.g., when receptor is liganded to antagonist or inverse agonist) (Hu and Lazar 1999). SMRT and NCoR tether HDAC3 to promoters keeping chromatin compact leading to repression of basal transcriptional activity (Privalsky 2004).

2 The NR1F Subfamily of NRs

The first member of the NR1F subfamily of nuclear receptors was identified in the early 1990s based on sequence similarities to the retinoic acid receptor (RAR) and the retinoid X receptor (RXR), hence the name "retinoic acid receptor-related orphan receptor alpha" or RORα (Giguere et al. 1994; Becker-Andre et al. 1993). Two additional members of this subfamily were subsequently identified, RORβ and RORγ, (Carlberg et al. 1994; Hirose et al. 1994). The three RORs display modest sequence homology and are conserved across species, with each ROR gene encoding multiple isoforms as a result of alternative promoter usage and splicing. The RORs display distinct patterns of tissue expression with RORα being widely expressed and is abundant in liver, skeletal muscle, skin, lungs, adipose tissue, kidney, thymus, and brain (Hamilton et al. 1996; Steinmayr et al. 1998). The expression of RORβ is extremely restricted and is limited to the central nervous system (Andre et al. 1998a, b). Two forms of RORγ are found in both humans and mice (RORγ1 and RORγ2) with RORγ2 commonly referred to as RORγt as it was originally identified in the thymus (Jetten et al. 2001). RORγt has been the focus of considerable attention due to its role in T helper 17 cells (T_H17) development and the pathology autoimmune disease. RORγ, specifically RORγ2 or RORγt, is highly expressed in immune tissues, including the thymus, but there is significant expression of RORγ in the liver, skeletal muscle, adipose tissue, and kidney and this receptor is also involved in metabolic pathways and adipogenesis (Jetten 2009). All RORs recognize and bind to specific sequences of DNA termed ROR response elements or ROREs and these ROREs typically consist of an AGGTCA "half site" with a 5′ AT-rich extension. Unlike most NRs that bind response

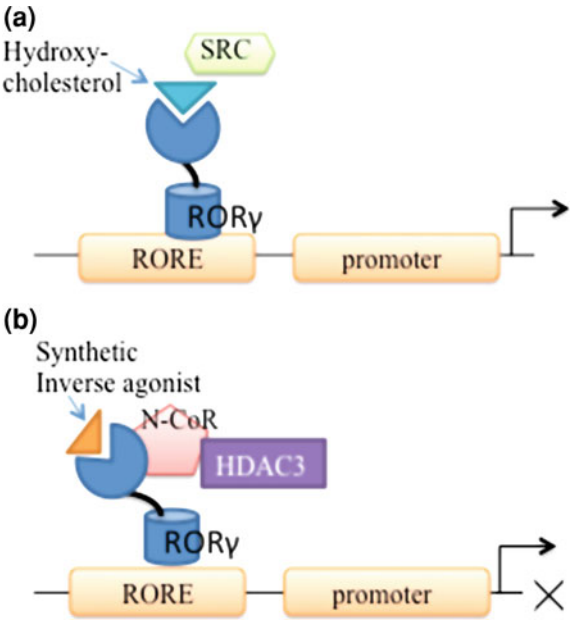

Fig. 8.2 Mechanism of repression of RORs by synthetic ligands. (**a**) ROR agonists drive recruitment of transcriptional coactivators such as SRC2 (**b**) Inverse agonists of ROR displace coactivator and drive recruitment of transcriptional repressors such as NCoR/SMRT

elements as homodimers or heterodimers, the RORs bind to DNA as monomers. As shown in Fig. 8.2a, when RORs are bound to ROREs within the promoter of a target gene, they recruit coactivators independent of ligand status resulting in constitutive transactivation of target gene expression (Jetten 2009; Wang et al. 2010). ROR binding to inverse agonists would repress target gene expression by driving binding to the corepressor NCoR and tethering HDAC3 as shown in Fig. 8.2b. It is interesting to note that another subfamily of orphan nuclear receptors, the Rev-erbs, bind to the same response elements as the RORs as constitutive repressors (constitutive interaction with NCoR) and they functionally antagonize the action of the RORs (Burris 2008; Raghuram et al. 2007).

3 RORγ and T_H17 Cells

Acquired immune responses orchestrated toward protection against various classes of pathogens are facilitated by differentiation of naïve CD4 T cells into cytokine-secreting effector T_H cells. Effector T_H cells historically are classified into T_H1 and T_H2 subsets. T_H1 cells produce interferon γ (IFNγ) and regulate antigen presentation and cellular immunity whereas T_H2 cells secrete IL-4, IL-5, and IL-13, which together regulate humoral and anti-parasite immunity. Recently, T_H17 cells have been identified as an inflammatory T_H subset. Several transcription factors including RORγ are required for the differentiation of T_H17 cells from naïve CD4 T cells (Yang et al. 2008). The innate immune response is an antigen-nonspecific

defense mechanism that a host uses immediately after exposure to microbe. Unlike adaptive immunity, innate immune cells present pattern recognition receptors (PRRs) that recognize molecules broadly shared by pathogens. Phagocytic cells including neutrophils, monocytes, and macrophages, basophils, mast cells, eosinophils and natural killer (NK) cells are part of the first line defense immune cells against pathogens. Interestingly, the expression of RORs is induced in these cells upon infection (Barish et al. 2005).

RORγ is essential for survival of intrathymic CD4 + CD8 + DP cells and for differentiation of T_H17 cells in periphery (Ivanov et al. 2006; Sun et al. 2000; Yu et al. 2004). While both T_H17 cells, and macrophages as well, play important roles in host defense against bacterial and fungal infections, they have been linked to several autoimmune diseases, including psoriasis, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease (Korn et al. 2009; Tesmer et al. 2008). Therefore, pharmacological repression of RORγ might be attractive starting point for the development of a novel therapeutic for the treatment of inflammatory diseases.

4 Ligand Modulation of the RORs

Given the specific tissue distribution of each ROR isoform, and their role in pathophysiological conditions, the utility of synthetic ligands that modulate the activity of these receptors is apparent. As expected, development of small molecule synthetic ligands, including agonists, antagonists, and inverse agonists as dual RORα/RORγ or as isoform selective modulators, is occurring at a rapid pace. These efforts are briefly summarized below. For a more detailed discussion on the state-of-the-art modulators please see a recent review by Kamenecka et al. (2013).

Recently, a well-characterized agonist of LXRα and LXRβ, T0901317, was shown to be a dual RORα/γ inverse agonist (Kumar et al. 2010, a). T0901317 repressed RORα/γ-dependent transactivation of an ROR promoter-reporter gene in HEK293 cells and in HepG2 cells reduced recruitment of the steroid receptor coactivator-2 (SRC2) by RORα at an endogenous ROR target gene (*G6Pase*). Thus, T0901317 represented a novel chemical starting point for the development of selective dual RORα/γ and isoform-specific modulators. More importantly, this finding suggested for the first time that small molecules could be used to target the RORs for potential therapeutic treatments in immune disorders.

A range of compounds with improved selectivity and improved potency emerged from the T0901317 scaffold. SR1001 was the first to be reported as a T0901317 analog devoid of LXR activity (Solt et al. 2011; Griffin et al. 2011). Removal of the sulfonamide alkyl group led to complete loss of LXR activity. In a competitive radioligand binding assay, SR1001 dose-dependently displaced [^{3}H]25-hydroxycholesterol (25-OHC) binding to RORα and RORγ with K_i's of 172 and 111 nM, respectively, and the compound inhibited the development of murine T_H17 cells, as demonstrated by inhibition of interleukin-17A (IL-17a) gene expression and protein production. More importantly, SR1001 was shown to

effectively delay the onset and clinical severity of autoimmune disease (EAE) in a MOG-induced mouse model of multiple sclerosis. This data demonstrates the feasibility of targeting the orphan receptors RORα and RORγt to inhibit specifically T_H17 cell differentiation and function, and indicate that this novel class of compound has potential utility in the treatment of autoimmune diseases.

Using a modular chemistry approach, modifications to the SR1001 scaffold were made to improve potency on RORγ, diminish RORα activity, and maintain selectivity over LXR. Two compounds that emerged from these efforts have been described in the literature (SR2211 and SR1555) (Kumar et al. 2012; Solt et al. 2012). SR2211 and SR1555 were screened in a radioligand binding assay in a scintillation proximity assay (SPA) format. The calculated Ki values for SR2211 and SR1555 were 105 nM and 1 μM on RORγ, respectively. Neither small molecule could displace the radioligand from RORα demonstrating its specificity for RORγ. Both compounds can repress RORγ target genes in cells and minimal activation of LXRα can be detected at the highest concentrations tested. These data demonstrate that SR2211 and SR1555 are selective for RORγ with SR2211 being significantly more potent. Both SR2211 and SR1555 were capable of repressing the expression of Il17a in stimulated EL-4 cells. Interestingly, SR1555 was also shown to induce regulatory T cell populations when cultured splenocytes were treated with T regulatory cell polarizing conditions (TGFβ and IL-2). This unique feature of SR1555 (this effect was not observed with SR2211) may offer additional benefits above and beyond RORγt mediated repression in the treatment of autoimmune disorders. Figure 8.3 summaries the evolution of these interesting ROR modulators from the LXR agonist T0901317.

5 RORs in Multiple Sclerosis

Multiple sclerosis (MS) is a neuroinflammatory disease in which the insulating covers of nerve cells in the brain ad spinal cord are damage by one's own immune system results in loss of muscle control, vision, balance, and sensation. Thus, the condition is called an autoimmune disease. In MS, the immune system attacks the brain and spinal cord. The blood–brain barrier (BBB) disruption is an early and central event in MS pathogenesis. Proinflammatory cytokines such as IL-17 and IL-22 are key factor in immunopathogenesis of MS. Auto-reactive T_H17 cells can migrate through the BBB by the production of proinflammatory cytokines, which disrupt tight junction proteins in the central nervous system (CNS) endothelial cells. T_H17-mediated inflammation is characterized by neutrophil recruitment into the CNS and neurons damage. EAE (experimental autoimmune encephalomyelitis) animal model has been used for the observation of the role of T_H17 cells in MS pathogenesis. As mentioned above, the dual RORα/RORγ inverse agonist SR1001 demonstrated the ability to delay the onset and clinical severity in the EAE model (Solt et al. 2011).

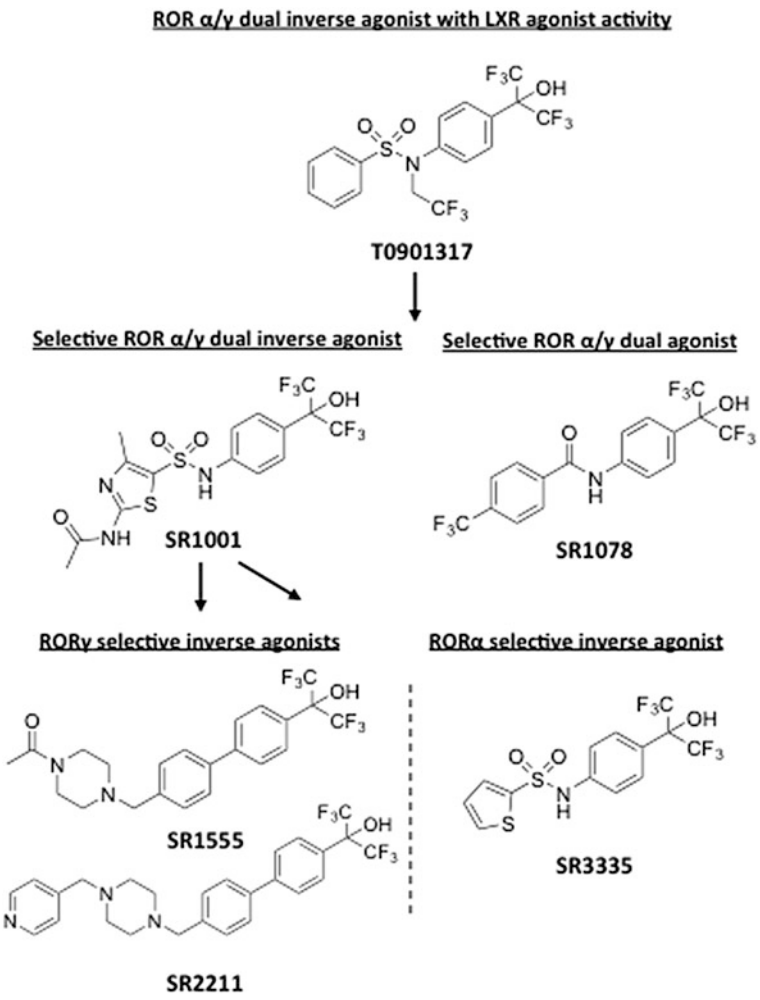

Fig. 8.3 The evolution of ROR modulators from the LXR agonist T0901317

6 RORs in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory disease that is characterized by extensive synovial hyperplasia, cartilage damage, bone erosion, and functional joint disability (Smolen et al. 1995). The inflammation in RA results from infiltration of inflammatory cells and the production of proinflammatory cytokines, prostaglandins, and nitric oxide (Park et al. 2010). The cytokine TNFα has been shown to play a major role in the pathophysiology of RA and increased exposure to TNFα leads to degradation of cartilage and bone (Dayer et al. 1985; Bertolini et al. 1986). The efficacy of anti-TNFα therapy in the treatment of RA is well

documented and exemplified by clinical use of infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). However, chronic administration of these anti-TNFα agents is directly associated with an increased risk of urinary tract and respiratory infections, and pneumonia. In addition to targeting TNFα, repression of other inflammatory cytokines such as IL1-β (Joosten et al. 1999) IL-6 (Kishimoto 2005; Alonzi et al. 1998), LTαlβ2 (Takemura et al. 2001), and IL-17A (van den Berg and Miossec 2009) have shown efficacy in various animal models of arthritis. Targeted sequestration of IL-17A, commonly referred to as IL-17, using antibodies has gained significant momentum recently. The receptor for IL-17 (IL-17RA) was found to be overexpressed in peripheral whole blood of RA patients and the receptor was detected locally in synovium of the same patients (Gaffen 2008; Toy et al. 2006). IL-17 is an inflammatory cytokine produced by T_H17 cells and it has been shown that IL-17 is present at sites of inflammatory arthritis and it synergizes the inflammatory response induced by other cytokines such as TNFα (Miossec 2007; Fossiez et al. 1996; Kolls and Linden 2004). T_H17 cells differ from T_H1 and T_H2 lineages in that they develop under the influence of TGFβ, IL6, and IL1. Further, these cells have IL23 as a maturation factor and exclusively express the T cell-specific isoform of RORγ, RORγt (Ivanov et al. 2006). T_H17 cell differentiation and function in humans is associated with susceptibility to inflammatory bowel disease, rheumatoid arthritis, and psoriasis (Duerr et al. 2006; Nair et al. 2009; Stahl et al. 2010). Recently, the therapeutic potential of anti-IL-17 therapy was evaluated in a phase I study as adjunct therapy to patients taking oral disease-modifying anti-rheumatic drugs (DMARDs). As compared to placebo, patients given LY2439821, a potent anti-IL-17 antibody, had reduced joint inflammation and erosion (Genovese et al. 2010).

In addition to T_H17 cells, other cell types play major roles in inflammation. Macrophages are specialized differentiated mononuclear phagocytic cells that perform key roles in antimicrobial defense, autoimmunity, and inflammatory disease (Fujiwara and Kobayashi 2005). It has been shown that macrophages can produce a wide range of inflammatory cytokines including TNFα and IL-17. Several studies have shown a role for RORs in regulating macrophage activation (Song et al. 2008; Gu et al. 2008). Of relevance to the pathogenesis of RA are the effects of IL-17 in driving osteoclastogenesis, leading to bone resorption (Kolls and Linden 2004; Kotake et al. 1999). Prior reports have shown that neutralization of IL-17 in mice decreases the severity of antigen-induced arthritis (Koenders et al. 2005). Further, the severity of collagen-induced arthritis was decreased in IL-17-deficient mice and mice administered IL-17 neutralizing antibodies (Lubberts et al. 2005). Despite the complex etiology of RA, IL-17 has been shown to be associated with the severity of RA (Hot and Miossec 2011; van de Veerdonk et al. 2011).

As discussed above, SR2211 was effective at suppressing IL-17 and IL-23R gene expression in EL4 cells (Lubberts et al. 2005). Based on this SR2211 was evaluated in the CIA mouse model. As shown in Chang et al. (2014) administration of SR2211 was efficient at pharmacological repression of RORγ activity affording a therapeutic effect in CIA mice. In the published studies, repression of T_H17 cell differentiation by SR2211 also resulted in induction of IFNγ production

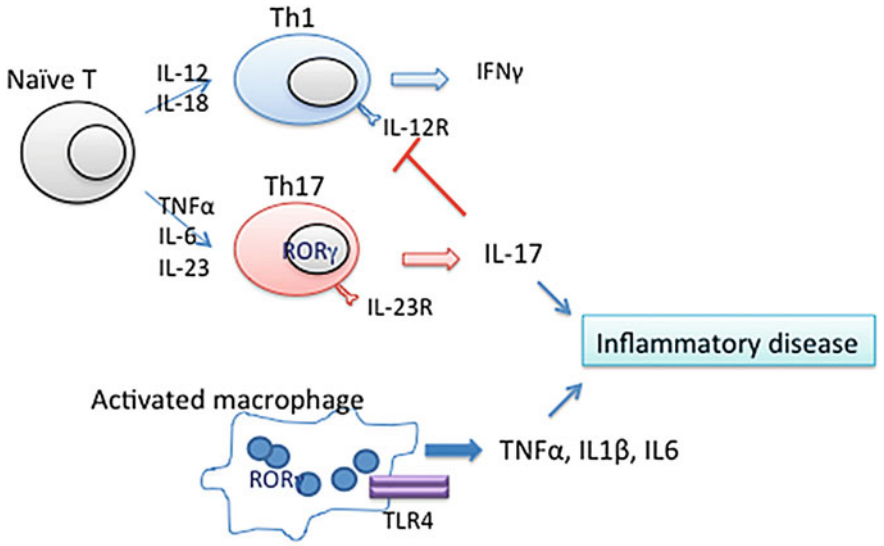

Fig. 8.4 A proposed model for targeting RORγ for autoimmune disease therapy

in murine draining lymph nodes an observation that is consistent with the relationship of T_H17 cells to T_H1 cells. It was also demonstrated that treatment of cells in culture or tissues ex vivo with SR2211 inhibits T_H17 cell differentiation, IL-17 and IL-23R expression, reduces inflammatory cytokines expression in activated macrophages, and systemic activation of T_H1 cells as shown by the induction of IFNγ. A proposed mechanism by which pharmacological repression of RORγ impacts the inflammatory process is shown in Fig. 8.4.

7 Summary and Perspective

While most NRs are considered druggable, selective modulation of target genes involved in disease has been difficult to achieve. For example, pharmacological activation (agonism) or repression (antagonism or inverse agonism) of a specific NR impacts directly the expression of target genes of interest but often alters many target genes not involved in disease leading to pleiotropic effects. There is a wealth of structural data on the LBD of the RORs that can aid the design and development of selective and potent binders, but this information does not provide insight into functional selectivity. Detailed analysis of the proteome and transcriptome upon pharmacological modulation of the RORs should provide detailed information on pathways critical to controlling genes of interest. Finally, while genetic and pharmacological repression of RORg has been shown powerful in reducing inflammation in rodents, there is still no clinical evidence that will translate to humans.

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