Nuclear Receptor Resource
Research Article
The Retinoid-Related Orphan Receptors
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Retinoid-Related Orphan Receptors (RORs)

1. Overview

Retinoid-related orphan receptors (RORs) are nuclear receptors (NR) which belong to the family of Thyroid hormone receptors. RORs play a role in various biological processes such as circadian rhythm, immune response, regulation of metabolic pathways, energy homeostasis, and thymopoiesis. They are also known to play a role in several pathologies such as cancer, osteoporosis, hypoxia, autoimmune diseases, asthma etc (Jetten A.M. 2009).

ROR genes encode proteins of 459 to 556 amino acids. Similar to other nuclear receptors, they have four major functional domains (Figure 1). Domain A/B, also referred to as AF-1 domain is the N-terminal domain. It is followed by DNA-binding domain (DBD) which is highly conserved in different RORs. Other two domains include a hinge domain and a ligand-binding domain which is also the C-terminal domain. (Jetten A.M. 2009).

There are three subtypes of RORs namely RORα (NR1F1, RORA or RZRα), RORβ (NR1F2, RORB or RZRβ), and RORγ (NR1F3, RORC, TOR). RORα is present in several organs such as brain, heart, liver, testis, and skin. RORβ is found in sensory processing areas of central nervous system such as pineal gland and retina. RORγ is highly expressed in thymus and other tissues such as liver (hepatocytes), kidney, heart, lung etc (Jetten A.M. & Ueda E. 2002, Kallen J.A. et al 2002).

ROR gene generates several isoforms of each subtype depending upon alternative promoter usage and exon splicing. All these isoforms differ in mainly their amino terminus. Four isoforms have been identified for RORα (α1-4). RORβ gene is expressed in only one isoform in humans whereas for RORγ- two isoforms have been identified (γ1 and γ2 also known as γt). Most isoforms present a distinct tissue-specific expression which results in involvement of regulation of different physiological processes and target genes. For example, human RORα3 is only found in human testis (Steinmayr M. et al 1998).

All three RORs play important roles, more specifically:

RORα

- Plays a critical role in the development of the cerebellum
- Required for maturation of photoreceptors in the retina
- May play a role in thymopoiesis and lymphocyte development
- Plays a role in Th17 cell differentiation and IL-17 expression

RORβ

- Required for maturation of photoreceptors in the retina
- May play a role in control of circadian rhythm

RORγ

- Is essential for the development of secondary lymphoid tissues including lymph nodes
- Plays a critical role in thymopoiesis
- Plays a role in Th17 cell differentiation and IL-17 expression

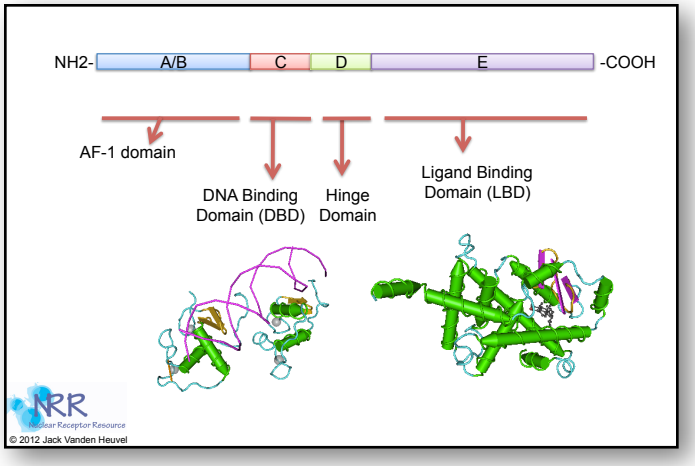

Figure 1. Basic Structure of the retinoid-related orphan receptors (RORs). Shown is the crystal structure of RARα bound to DNA or its natural ligand cholesterol sulfate

2. Basic Mechanism of Action

RORs bind to ROR-specific DNA response elements (ROREs) as monomers. They do not form heterodimers with retinoid-X-receptors (RXRs) like RARs. The ROREs consist of the consensus RGGTCA core motif preceded by a 6-bp A/T-rich sequence, in the regulatory region of target genes (Jetten A.M. 2009). Different subtypes of RORs recognize and show different affinities to different ROREs as a result of the role of A/B domain and due to different promoters.

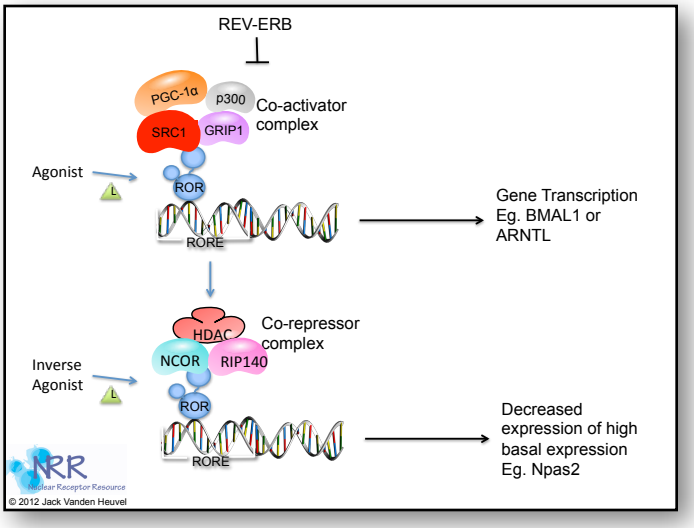

Figure 2. Regulation of gene expression by RORs.

It is also known that REV-ERB nuclear receptors are able to inhibit ROR-mediated transcriptional activation by competing for binding with ROREs.

Many co-regulators are found among protein complexes which affect the gene transcription of RORs. For example, coactivators such as NCOA1 (SRC1), NCOA2 (TIF2 or GRIP1), PGC-1α, p300, and CBP or corepressors such as NCOR1, NCOR2, RIP140, NIX1, and FOXP3.

3. RORs as a Possible Therapeutic Target

Spinocerebellar ataxia type 1 (SCA1) - is an autosomal dominant inherited neurodegenerative disorder characterized by progressive loss of motor coordination, speech impairement, and problems swallowing. It was concluded that decreased levels of RORα protein in SCA1 Purkinje cells affects development and function of Purkinje cells which results in neurodegeneration (Serra H.G. et al 2006, Steinmayr M. et al 1998).

Autoimmune and inflammatory diseases such as lupus, arthritis, multiple sclerosis, atopic dermatitis, psoriasis, asthma, inflammatory bowel disease – Th17 cells have been implicated in all of the above pathologies. Additionally IL-17 induces secretion of various proinflammatory cytokines. It was shown in studies with mice with loss of RORα and γ function greatly reduces susceptibility to autoimmune diseases or inflammatory conditions such as lung inflammation induced by ovalbumin.

RORα is known to impede NF-κB activity resulting in reduced secretion of interleukins and cox-2 (Duez H. & Staels B. 2008). Additionally RORα has been shown to play a role in ischemia-induced angiogenesis and to regulate expression of endothelial NO synthase (Duez H. & Staels B. 2008).

Lipid and steroid metabolism – Many recent studies suggest that RORs play an important role in regulation of lipid and steroid metabolism. RORα activates transcription of apolipoproteins. Additionally RORα in skeletal muscle may regulate muscle lipid metabolism (Duez H. & Staels B. 2008).

Cancer – Many studies indicate that RORs may play a role in cancer. Mice deficient in the expression of RORγ exhibit high incidence of thymic lymphomas that metastasize (Jetten & Ueda, 2002). Gastric tumors and ovarian cancers show an increase in the population of Th17 cells (Miyahara Y. et al 2008, Zhang et al 2008). Studies also indicate that RORα gene is down-regulated in several tumor-types such as breast and lung cancer (Lu et al 2007)

4. Natural ROR Modulators

In vitro studies indicate that cholesterol, 7-dehydrocholesterol and cholesterol sulfate can act as RORα agonists (Kallen JA et al 2002). In vitro studies also indicate ATRA can bind to RORβ and RORγ to inhibit the receptor-mediated transcription (Stehlin-Gaon et al 2003) thus acting as antagonists. It is still not known whether in vivo ROR activity is regulated by endogenous ligands.

5. References

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