Retinoic Acid Receptors
1 Overview

Retinoic acid receptors (RAR) are nuclear receptors from ‘Thyroid hormone receptor-like family’ that mediate the effects of retinoids (compounds such as Vitamin A, its metabolites, and synthetic analogs). RARs play a role in various biological processes such as vertebrate embryonic morphogenesis, organogenesis, cell growth arrest, differentiation and apoptosis, homeostasis. On a structural level, RARs are similar to other nuclear receptors and have A to F domains (Figure 1). Domain A/B is termed as AF-1 and functions as a ligand-independent transcriptional activation domain. Domain C is highly conserved between different isoforms and corresponds to DNA-binding domain. Region E contains ligand-binding domain, dimerization domain and a silencing domain. Upon ligand binding, the receptor undergoes major structural changes exposing/creating new surfaces for coactivator binding. The function of domain F is not known (McKenna and O’Malley 2002).

There are three subtypes of RARs namely RARα (NR1B1, also known as RARA), RARβ (NR1B2, also known as RARB or HAP), and RARγ (NR1B3, also known as RARG). For each subtype several isoforms exist which differ from one another in their N-terminal region (A domain). Two major isoforms exist for RARα (α1 and α2), and RARγ (γ1 and γ2) whereas RARβ has four isoforms (β1, β2, β3, β4). These isoforms are formed due to differential usage of promoters and alternative splicing. RARα is present in most of the tissues. RARβ is found in brain, liver, kidney, heart, pituitary, colon, uterus, ovary, testis, prostate, adrenal, and eye. RARγ is highly expressed in epidermis. All three RARs play important roles, more specifically:

RARα
- is needed for parietal endodermal differentiation
- inhibits cell proliferation in breast cancer cell line
- induces maturation of acute myeloid leukemia cell line

RARβ
- Mutations in RARβ show growth retardation, behavioral defects, congenital defects etc. Additionally many cancers have RARβ promoter silenced and as result decreased expression of RARβ.

RARγ
- is essential for growth arrest, visceral endodermal differentiation
- Mutations lead to growth deficiency, male sterility, webbed digits, malformations of respiratory system etc.

2. Basic Mechanism of Action

RARs heterodimerize with retinoid X receptor (RXR) α (NR2B1), RXRβ (NR2B2) and RXRγ (NR2B3) (see Figure 2). In the absence of an agonist RARs bind to RXR and recruit the co-repressor proteins NCoR or SMRT along with factors such as histone deacetylase (HDACs) or DNA methyltransferases. Upon availability of an agonist or ligand, corepressors are released and coactivator complexes such as histone acetyltransferases or histone arginine methyltransferases are recruited (Tang & Gudas 2011, Glass & Rosenfeld 2011, le Maire, A. et al 2010). Upon activation RAR-RXR heterodimers bind to retinoic acid response element (RARE) DNA sequences found in responsive genes such as CD38, CEBP, Hoxa-1, HNF3α, HNF1β, Strm4 and Stra6 (Perissi and Rosenfeld 2005).

RARs also take part in various signaling pathways through posttranslational modifications including phosphorylation. Kinases (cdks, MAPKs) act on AF-1 domain and LBDs of RARs. It is also known that ligand-driven RARs lead to inhibition of AP-1 although the
mechanism of which remains unknown (Rochette-Egly and Chambon 2001, Chambon 2005)

3. RARs as a therapeutic target

Acute promyelocytic leukemia is a cancer of blood & bone marrow, in which promyelocytes accumulate in blood and result in anemia. The disease is characterized by chromosomal translocation between RAR alpha gene and promyelocyte leukemia protein resulting in formation of fusion protein. The fusion protein binds strongly to transcriptional corepressors resulting in RAR alpha gene silencing. This in-turn results in blockade of differentiation of cells. High doses of all-trans retinoic acid (ATRA) rescue RARα from the silencing complex resulting in activation of differentiation. Approximately 72% patients suffering from this disease can be cured upon ATRA treatment.

Dermatological indications—Clinically ATRA, 9-cis retinoic acid (9CRA), 13-cis-retinoic acid have been used for acne, psoriasis or photoaging. Additionally various synthetic retinoids are used for treatment of stable plaque psoriasis (eg. Tazarotene, adapalene).

Cancer—Retinoids can be used as chemopreventive agents for treatment of preneoplastic diseases such as oral leukoplakia, cervical dysplasia, and xerodermapigmentosum.

4. Natural RAR Modulators

Natural retinoids are produced in the body from oxidation of vitamin A by alcohol and aldehyde dehydrogenases. The resulting ATRA is a very potent ligand for RARα, β, and γ subtypes. ATRA can isomerize to form 9CRA which can bind to RARs as well as RXRs and peroxisome proliferator-activated receptors (PPARs). Many synthetic analogs were developed recently which have specific activities for one or more of RAR subtypes such as AM80 which is a selective RARα agonist (Allenby G. et al. 1993, Germain P. et al. 2006).

5. References