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Review

Retinoic acid signaling in mammalian eye development

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ABSTRACT

Retinoic acid (RA) is a biologically active metabolite of vitamin A (retinol) that serves as a signaling molecule during a number of developmental and physiological processes. RA signaling plays multiple roles during embryonic eye development. RA signaling is initially required for reciprocal interactions between the optic vesicle and invaginating lens placode. RA signaling promotes normal development of the ventral retina and optic nerve through its activities in the neural crest cell-derived periocular mesenchyme. RA coordinates these processes by regulating biological activities of a family of non-steroid hormone receptors, RARα/β/γ, and RXRα/β/γ. These DNA-binding transcription factors recognize DNA as RAR/RXR heterodimers and recruit multiprotein transcriptional co-repressor complexes. RA-binding to RAR receptors induces a conformational change in the receptor, followed by the replacement of co-repressor with co-activator complexes. Inactivation of RARα/β/γ receptors in the periocular mesenchyme abrogates anterior eye segment formation. This review summarizes recent genetic studies of RA signaling and progress in understanding the molecular mechanism of transcriptional co-activators that function with RAR/RXR.

1. Introduction

Following the formation of individual retinal and lens lineage-specific progenitor cells in late gastrulation and neurulation, the subsequent stages of eye development depend on a precise coordination of cell-to-cell interactions governing the formation of the individual tissue primordia, their morphogenetic movements, and terminal differentiation. The size of the eye depends on the precise control of cell number. These processes are needed to ensure that the eye can function as a neurosensory organ with its anterior section serving as an optical instrument, and its posterior section functioning in light detection, transformation and transmission of visual signals to the brain. Embryonic development is regulated through seven major signaling pathways – receptor tyrosine kinase (e.g. FGF–MAPK and Ras), TGF-β/BMP, hedgehog, Notch, Wnt, nuclear receptors, and Jak/STAT (Barolo and Posakony, 2002). Mutual cell-to-cell interactions in the developing embryo establish expression patterns of lineage-specific DNA-binding transcription factors in individual embryonic germ layers, and, as development proceeds towards the organogenesis, in the individual cell type progenitors and committed precursors. These factors, in concert with chromatin remodeling complexes, control expression of genetic information stored as a DNA-nucleosome polymer, the chromatin, in the nucleus (Allis et al., 2007). Through the process of chromatin remodeling, individual epigenomes, representing the organized genomic DNA in nuclei of different cell types, originate from a single fertilized egg. This enables individual cell types to generate their unique molecular "signatures" of expressed mRNAs and ncRNAs that determine their distinct phenotypes.

The major signaling pathways are repeatedly used at multiple stages of vertebrate eye formation as well as in the formation of other organs. Controlling a variety of processes, these signals operate in the embryonic and extra embryonic space, activating different components of these pathways to perform individual regulatory steps. This review describes the RA signaling pathway and its critical molecular components at specific stages of eye development. In addition, this review provides background information on the biochemistry of RA-activated nuclear receptors, the potential use of RA signaling in eye regeneration, and the recruitment of RA pathway proteins as structural components of the cornea and lens.

2. The retinoic acid signaling pathway

Vitamin A (Fig. 1) is an essential dietary nutrient and precursor of retinoic acid. Carotenoids (from plants) and retinyl esters (from animal oils) are stored in the liver and other tissues as esters (retinoids, e.g. retinyl palmitate and retinyl stearate) produced by

Abbreviations: CBP, CREB-binding protein; HAT, histone acetyltransferase; POM, periocular mesenchyme; PPR, pre-placodal region; RA, retinoic acid; PE, retinal pigmented epithelium; RARE, retinoic acid responsive element.

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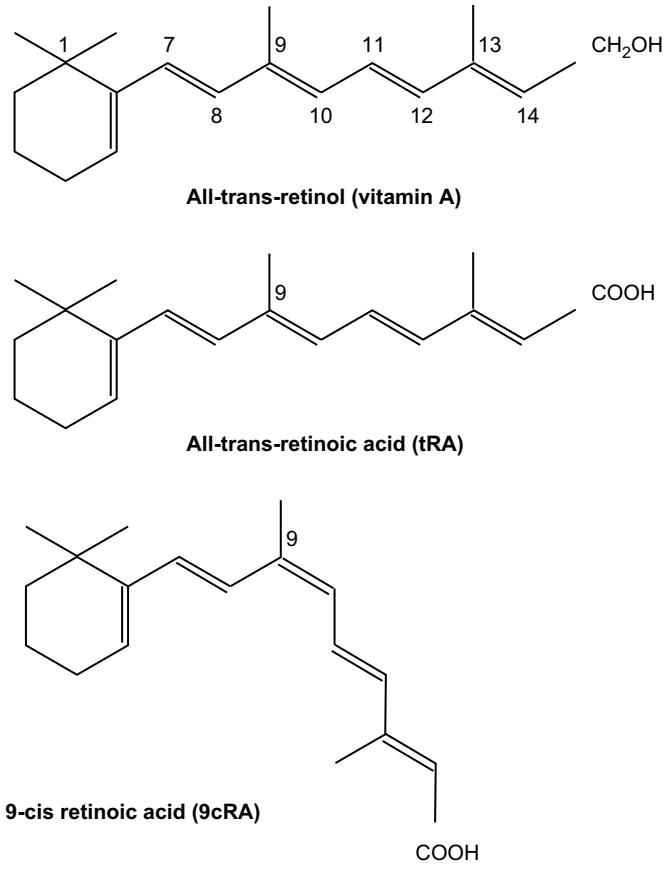

Fig. 1. Chemical structures of retinol, all-trans RA, and 9-cis RA.

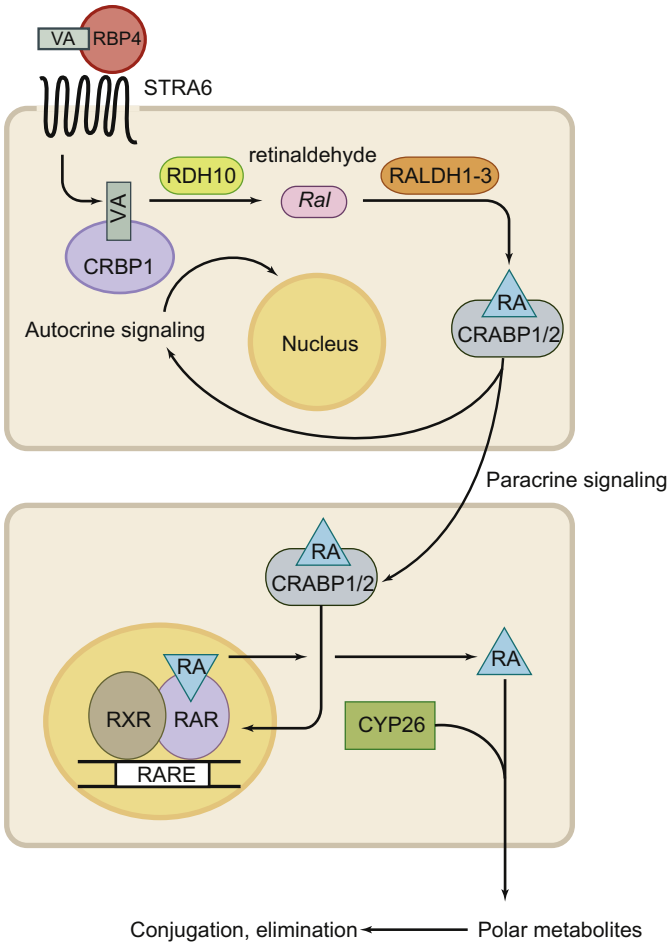

Fig. 2. Schematic diagram of pathways involved in the retention, metabolism and function of retinoic acid (RA). RA signaling can function as an autocrine and paracrine process.

lecithin-retinol acyltransferase (LRAT) and acyl-CoA:retinol acyltransferase (ARAT). Hydrolysis of these esters by microsomal carboxylesterases and other lipases produces retinol, which is released into the bloodstream and forms a complex with retinol-binding protein 4 (RBP4). Retinol/RBP4 complex targets cells through its interaction with nine-transmembrane receptor, STRA6 (stimulated by retinoic acid gene 6) (Kawaguchi et al., 2007), see Fig. 2. In the cytoplasm, retinol associates with retinol-binding protein 1 (CRBP1). Retinol is oxidized to retinaldehyde via the action of a family of retinol dehydrogenases such as RDH10 (Sandell et al., 2007), Adh1/3/4 and Rdh1 (Molotkov et al., 2002a,b) followed by its conversion to all-trans RA catalyzed by tissue-restricted and temporally regulated retinaldehyde dehydrogenases (in human, RALDH1/2/3/4; and in mouse Aldh1a1/2/3 and Aldh8a1). Recently, RALDH-independent generation of RA by CYP1B1, a member of the cytochrome p450 family of mono-oxygenases, has been shown in chicken (Chambers et al., 2007), but its role in RA synthesis in mammals requires further experimentation. The newly synthesized RA binds to the cellular RA-binding proteins, CRABP1/2. Upon ligand binding, a conformational change exposes a nuclear localization motif in CRABP2 and the apo-protein is transported into the nucleus. When the RA/CRABP2 complex enters the nucleus, the free RA ligand interacts with the receptors (see below), followed by a transcriptional activation of the target genes. Alternatively, the cytoplasm can release RA, which other cells can acquire through unknown mechanisms. Thus, RA can signal in an autocrine or a paracrine fashion (see Fig. 2). As RA enters the nucleus, it can bind to the nuclear RA receptors (RARα/β/γ) and retinoid X receptors (RXRα/β/γ) (see Table 1), assembled as specific heterodimers (RARα/RXRα, RARβ/RXRα and RARγ/RXRα) at the retinoic acid-response elements (RAREs) in regulatory regions of RA-direct target genes. Genetic evidence suggests that RA is bound by the RAR and not by the RXR receptors *in vivo* (Kastner et al., 1997).

Cellular concentration of RA is also regulated by RA-degrading enzymes from the CYP26 class of p450 enzymes, CYP26A1 and CYP26C1, localized in the cytoplasm (see Fig. 2). Temporally and spatially regulated expression of individual components of the RA signaling pathway and their antagonists generate concentration gradients of RA including zones free of RA along the anterior–posterior, dorso-ventral, and medio-lateral axes of the developing embryo. The localization of cells with active RA signaling and the identification of genes important for this pathway in individual ocular tissues are presented in Sections 3.2 and 3.3, respectively.

3. Retinoic acid signaling in mouse eye development

3.1. Vertebrate eye development

The vertebrate eye is formed from cells of neural ectoderm origin, surface ectoderm, and neural crest derived periocular mesenchyme (POM). The earliest stages of eye development can be traced to the neural plate stage, where a single bilateral region, the *eye field*, is established as a result of subdivisions of the anterior neural plate directed by specific patterns of expression of BMP antagonists in concert with FGF and Wnt signaling pathways that pattern the neural plate (Fuhrmann, 2008; Yamamoto et al., 2005; Zuber et al., 2003; Zuber and Harris, 2006). The sonic hedgehog