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SnapShot: Retinoic Acid Signaling

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Abstract

Retinoic acid (RA), a lipid soluble signaling molecule derived from vitamin A (retinol), regulates diverse biological processes, including cellular proliferation, differentiation, and apoptosis, throughout embryonic development. RA controls the expression of genes involved in patterning and morphogenesis during organogenesis. Disruptions in the regulation of RA signaling results in several developmental disorders, including limb and skeletal defects, abnormal patterning of the central nervous system, ocular and craniofacial defects, cardiac malformation, foregut endoderm defects, and renal agenesis. Identification of pleiotropic functions for RA during organogenesis has provided a better understanding of cellular and molecular events controlling embryonic development. Loss-of-function studies using mutants of RA-synthesizing enzymes and RA receptors (RARs) have been particularly helpful in unraveling the mechanism of RA signaling. Further studies using genetic models are required to fully understand the molecular logic of RA signaling from embryogenesis to adulthood.

RA Synthesis and Signaling

RA is synthesized by sequential oxidation steps: retinol is first converted to retinaldehyde, which is then converted to RA. The liver hydrolyzes retinyl esters to produce retinol. Retinol-binding protein (RBP4) binds retinol in the liver and then enters the bloodstream, delivering retinol to cells expressing the retinol receptor STRA6. Once inside the cell, retinol is bound by cytosolic retinol-binding proteins (CRBP), buffering the available free retinol that can be converted to retinaldehyde by retinol dehydrogenase (Rdh10). Another source of retinaldehyde comes from nutritional sources. For instance, β-carotene, commonly found in carrots, can be converted to retinaldehyde by β-carotene monooxygenase (BCMO1). Oxidation of retinaldehyde to RA is catalyzed by retinaldehyde dehydrogenases (Raldh1, Raldh2, and Raldh3, also known as Aldh1a1, Aldh1a2, and Aldh1a3, respectively). These enzymes exhibit nonoverlapping tissue-specific patterns of expression and are responsible for the majority of RA synthesis during embryogenesis. RA diffuses from its cell of origin, acting in a paracrine fashion to influence cell behaviors; cellular-RA-binding protein (CRABP) facilitates RA uptake in some cells. Cells with high levels of cytochrome P450 enzymes (e.g., Cyp26a1, Cyp26b1, and Cyp26c1), which rapidly degrade RA, do not respond to RA. In cells with low or no cytochrome P450s, RA receptors (RARs) bind RA in the nucleus to tune the transcriptional output of RA target genes. Unlike the specific and restricted patterns of enzymes that generate or degrade RA, RARs are widely expressed. The exact physiological functions of RA are mediated by multiple isotypes of RARs, which form heterodimers with RXRs. This complex binds RA response elements (RAREs) to regulate transcription of target genes. Various coactivator and corepressor proteins associate with RARs, influencing the activity of RAR-RXR-RA complexes at RA responsive genes. In the absence of RA, RAR/RXR heterodimers recruit a corepressor complex with histone deacetylase (HDAC) activity. When RA binds RAR/RXR heterodimers, corepressors are replaced with coactivator proteins containing histone acetyltransferase (HAT) activity. Epigenetic modifications such as DNA methylation and chromatin remodeling have also

been linked to induction and repression of RA-responsive genes during embryonic development.

Role of RA Signaling during Development

Intricate networks of signaling pathways and transcriptional responses, some regulated by RA, control developmental processes. RA regulates a variety of master transcription factors in a tissue-specific manner to pattern tissues and shape organs. In the forebrain basal ganglia, *Drd2* responds to RA signaling to activate dopamine responsiveness, and RA induces *Gad67* to stimulate GABAergic differentiation. In the hindbrain, RA is required for expression of *Hnf1b* and several members of the *Hox* gene family to define hindbrain patterning. RA contributes to optic cup and anterior eye formation, regulating genes that guide morphogenetic movements; RA, secreted by the retina, directly induces *Pitx2* in perioptic mesenchyme, which influences the proliferation and differentiation of perioptic mesenchyme and retinal neurons. In the spinal cord neuroectoderm, RA activity induces *Pax2* and *Olig2*, which specify motor neuron lineages.

RA signaling provides a permissive signal for organizing the body plan through repression of *Fgf8* in early cardiac and caudal domains, thus ensuring proper somitogenesis and forelimb initiation during the early stages of body axis extension. RA induction of *Cdx1* and *Hox* genes is required for vertebral identity, and RA is also required to maintain bilateral symmetry of the left and right columns of somites. RA plays an important role during early heart development, and loss of RA signaling leads to a severe heart phenotype characterized by looping defects, ventricular myocardial hypoplasia, and aortic arch defects.

In posterior foregut endoderm, RA acts as an inducer of *Hoxa5* and inhibitor of *TGF-β1* signaling during pulmonary organogenesis, an inducer of *Pdx1* for endocrine pancreas formation, and an inducer of *Epo* during liver development, which coordinates hepatic erythropoiesis with cardiomyocyte expansion. RA signaling plays an essential role in kidney development through induction of *Ret* expression required for ureteric bud formation and branching morphogenesis.

RA Signaling as a Target of Toxicity

Exposure to toxic chemical compounds leads to detrimental biological effects involving growth retardation, impaired immune function, and developmental disorders. The RA-signaling pathway is modulated by toxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and nitrofen that are used as herbicides. TCDD is known to alter RA levels through effects on the aryl hydrocarbon receptor, and exposure during organogenesis causes cleft palate. Nitrofen perturbs RA signaling by inhibition of the RA-synthesizing enzyme Raldh2, leading to congenital diaphragmatic hernia.

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