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# Role of Carotenoids and Retinoids During Heart Development

**Ovidiu Sirbu**[1,3,*], **Aimée Rodica Chiş**[1], **Alexander Radu Moise**[2,*]

[1]Biochemistry Department, Victor Babes University of Medicine and Pharmacy, Eftimie Murgu Nr. 2, 300041 Timisoara, Romania; Timisoara Institute of Complex Systems, V. Lucaciu 18, 300044 Timisoara, Romania.

[2]Biochemistry Department, Victor Babes University of Medicine and Pharmacy, Eftimie Murgu Nr. 2, 300041 Timisoara, Romania.

[3]Medical Sciences Division, Northern Ontario School of Medicine, Sudbury, ON P3E 2C6, Canada; Department of Chemistry and Biochemistry, Biology and Biomolecular Sciences Program, Laurentian University, Sudbury, ON P3E 2C6, Canada.

## Abstract

The nutritional requirements of the developing embryo are complex. In the case of dietary vitamin A (retinol, retinyl esters and provitamin A carotenoids), maternal derived nutrients serve as precursors to signaling molecules such as retinoic acid, which is required for embryonic patterning and organogenesis. Despite variations in the composition and levels of maternal vitamin A, embryonic tissues need to generate a precise amount of retinoic acid to avoid congenital malformations. Here, we summarize recent findings regarding the role and metabolism of vitamin A during heart development and we survey the association of genes known to affect retinoid metabolism or signaling with various inherited disorders. A better understanding of the roles of vitamin A in the heart and of the factors that affect retinoid metabolism and signaling can help design strategies to meet nutritional needs and to prevent birth defects and disorders associated with altered retinoid metabolism.

### Keywords

embryonic development; cardiogenesis; retinoic acid; vitamin A

[*]Correspondence to Alexander R. Moise, Ph.D.; Medical Sciences Division, Northern Ontario School of Medicine, 935 Ramsey Lake Rd., Sudbury, ON, P3E 2C6, Canada. amoise@nosm.ca; or Ioan Ovidiu Sirbu MD PhD.; Biochemistry Department, Victor Babes University of Medicine and Pharmacy, Eftimie Murgu Nr. 2, Timisoara 300041, Romania; ovidiu.sirbu@umft.ro.

Declaration of interests

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## INTRODUCTION

Vitamin A is an essential nutrient required in a multitude of biological processes to support embryonic development and postnatal life. The non-visual functions of vitamin A are mediated by its metabolite, all-*trans*-retinoic acid (RA), which activates nuclear hormone receptors (NR) consisting of heterodimers of retinoic acid receptors (RARα, β, and γ, or NR1B1, B2 and B3) and retinoid x receptors (RXRα, β, and γ, or NR2B1, B2 and B3) [1–4]. RA-signaling results in transcriptional regulation of genes that control embryonic development, immunity, reproduction, tissue differentiation and repair. In the classical model of RAR signaling, in the absence of RA, unliganded RAR/RXR associates with RA response elements (RARE) to repress transcription of RA-regulated genes. Unliganded RAR/RXR interact with corepressor proteins of the nuclear receptor corepressor (NCOR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) families which recruit histone deacetylases [5]. Upon binding of RA to the RAR partner, RAR/RXR heterodimers undergo a conformational change to allow corepressors to be replaced by coactivators and recruit histone acetyltransferases and methyltransferases which induce transcriptional activation (reviewed in [6]). There are also other less conventional models of RA-signaling. For some RA-regulated genes, ligand-bound RAR/RXR can causes active repression upon RA binding [7]. There are also examples of RA-mediated transrepression and transactivation mechanisms whereby RAR interferes with the activity of other NRs and transcription factors [8–10]. RXR is capable of signaling as a homodimer/homotetramer in response to various ligands, including 9-*cis*-retinoic acid and 9ffffff-*cis*-13,14-dihydroretinoic as well as other non-retinoid lipids such as docosahexaenoic acid [11–18]. This mode of signaling does not seem to be required during development, including the developing heart, since 9-*cis*-retinoic acid does not support heart development in vitamin A-deprived quail embryos [19]. Moreover, RAR-specific agonists can rescue development in mice deficient in enzymes required for RA production [20]. While, RXRα-ablation results in highly penetrant cardiac defects, a transcriptionally silent form of RXR allows for normal heart development, which suggests RXR operates as a passive heterodimeric partner during cardiogenesis [21, 22]. Some reports suggested that oxidised metabolites such as 4-oxo-RA can also activate RAR/RXR [23], however, it is not clear if this mode of signaling is operational during development. For example, developmental defects induced by ablation of the enzyme CYP26A1, which converts RA to 4-oxo-RA, can largely be rescued by a compound mutation in the enzyme RALDH2, which converts retinaldehyde to RA [24]. This suggests that the deleterious effects observed following CYP26A1 ablation are primarily a result of excess RA and not due to the absence of 4-oxo-RA. In conclusion, evidence suggests that the primary vitamin A signaling pathways that operate during heart development involve all-*trans*-RA binding to RAR to activate its cognate heterodimeric receptor RAR/RXR.

## REGULATION OF VITAMIN A METABOLISM IN TARGET TISSUES

Dietary sources of vitamin A include preformed vitamin A, such as all-*trans*-retinol, and retinyl esters, as well as plant-derived provitamin A carotenoids, such as β-carotene and β-cryptoxanthin. Though preformed vitamin A forms are more commonly employed in developmental studies, provitamin A carotenoids represent a very important source of vitamin A for the world's population [25, 26]. The conversion of these precursors to active

metabolites involves a tightly regulated biochemical pathway consisting of enzymes, transporters and binding proteins (reviewed in [27, 28]). These pathways allow embryonic issues to generate RA the ligand for RAR/RXR-signaling in a spatiotemporal regulated manner (depicted in Fig. 1).

Since RA-signaling is critical for the formation of the heart, we will briefly review retinoid metabolism by discussing enzymes and factors whose contribution to RA metabolism has been confirmed through genetic approaches in clinical studies or animal models [29]. Following intestinal absorption of all-*trans*-retinol from the maternal diet, all-*trans*-retinol and retinyl esters are delivered to the fetus and other tissues via serum retinol binding protein, RBP4, or via lipoprotein particles [30–32]. Being lipophilic, all-*trans*-retinol can be taken up by cells through passive diffusion [33]. However, tissues with high retinoid demand such as the retina or blood-organ barriers such as the choroid plexus and placenta also express a receptor for RBP4, namely, stimulated by retinoic acid 6 (STRA6), which facilitates both the cellular uptake as well as export of all-*trans*-retinol from cells to serum RBP4 [34–39]. Mutations affecting only fetal or maternal RBP4 production usually do not result in congenital defects, however, the combination of both maternal and fetal RBP4 loss-of-function, or mutations that cause RBP4 to interfere with STRA6 binding can cause more severe congenital defects [40–43]. Similarly, mutations in STRA6 have more severe manifestation than isolated mutations in RBP4, but also present a variable degree of penetrance [44–50]. The expression of STRA6 at the maternal-fetal interface, hints at a plausible mechanism in the transplacental transfer of retinoids, however, more studies are needed to demonstrate the contribution of STRA6 to transplacental retinol transfer [34, 51]. In addition, lipoproteins also play a significant role in delivery of retinoids to and within the fetus [32, 52].

Provitamin A carotenoids consist of carotenoids which retain at least one unmodified β-ionone ring. Carotenoids are absorbed through the activity of the scavenger receptors SCARB1 and CD36 [53–56]. Though a major fraction of provitamin A carotenoids are cleaved to all-*trans*-retinaldehyde by intestinal beta-carotene dioxygenase (BCO1) before being delivered to the fetus, a small percentage remains uncleaved and is converted by fetal BCO1 to all-*trans*-retinaldehyde and then further processed to RA to support its developmental functions [57–59]. Eccentric cleavage of carotenoids via BCO2 allows for the conversion of provitamin A carotenoids that contain one modified ionone ring, such as cryptoxanthin and α-carotene to β-apo-10'-carotenal, which can be further processed by BCO1 to all-*trans*-retinaldehyde [60, 61]. In fact, β-apo-10′-carotenal not only supports embryonic development in vitamin A deficient states, but was also reported to promote lipoprotein secretion by the placenta to enhance vitamin A delivery to the fetus [62–64].

Conversion of all-*trans*-retinol to RA occurs through two oxidation steps, the first of which is reversible. The interconversion of all-*trans*-retinol and all-*trans*-retinaldehyde by embryonic tissues is carried out primarily by microsomal short-chain dehydrogenases (SDR) enzymes, retinol dehydrogenase 10 (RDH10) and dehydrogenase reductase 3 (DHRS3), which form a complex [65–69]. Both all-*trans*-retinol and all-*trans*-retinal bind cellular retinol binding proteins 1, 2 and 3 (CRBP1–3) which control their distribution and metabolic fate. Being expressed in the intestine, CRBP2 is responsible for retinoid uptake and

metabolism while CRBP1 plays a widespread role in vitamin A homeostasis ([70–72] reviewed in [73, 74]).

The second oxidation step is catalyzed by cytosolic retinaldehyde dehydrogenases RALDH1–3 (ALDH1A1-A3) which irreversibly oxidize all-*trans*-retinaldehyde to RA and, thus, govern the time and place of RA formation. Of the three different RA-synthetic enzymes, RALDH2 is the most important in relation to heart development, since only *Raldh2*-deficient embryos manifest severe cardiac malformations, and the domain of expression of RALDH2 closely matches the domain of activity of a RA-reporter gene in the mouse heart [75–78].

Cytochrome P450 enzymes CYP26A1-C1 catabolize RA to polar metabolites to control the extent and timing of RA-signaling in adult and embryonic tissues including cardiogenic regions ([24, 79, 80] reviewed in [81–83]. The activity of CYP26 enzymes can serve to create “RA-free” zones to restrict RA-signaling within specific boundaries, free from interference from other RA-signaling fields. CYP26 enzymes can also act as a “sink” by clearing RA, and, in conjunction with a RALDH enzyme acting as a “source” of RA, will contribute to the creation of a morphogen gradient ([84–86] reviewed in [87, 88]). The levels of RA available for binding RAR are also influenced by the cellular, high affinity RA binding proteins 1–2 (CRABP1 and 2) which deliver it to CYP26 enzymes for degradation [89, 90]. Based on the substrate preference, CYP26A1 and B1 are most likely responsible for oxidizing RA to 4-hydroxy and 4-oxo-all*trans*-retinoic acid, while CYP26C1 further catalyzes the oxidation of 4-oxo-all-*trans*-retinoic acid to more polar metabolites (however, its expression pattern is much less widespread than those of CYP26A1 or B1) [89, 91–93].

RA controls its own metabolism via negative feedback regulation, a mechanism which serves to maintain RA homeostasis by buffering external influences (fluctuations in dietary vitamin A intake, alterations in metabolic rates, etc.). This feedback regulation is observed in the case of RA-induced upregulation of the intestinal homeobox transcription factor ISX which controls carotenoid uptake and conversion to all-*trans*-retinaldehyde [56, 94]. Similarly, storage of all-*trans*-retinol via lecithin:retinol acyl transferase (LRAT) as well as the enzymes and binding protein involved in the conversion of all-*trans*-retinol to RA and degradation of RA are subject to negative feedback regulation by RA [66, 83, 85, 88, 95–97]. The negative feedback regulatory mechanism is extremely sensitive to exogenous RA, such that a pharmacological dose of RA can result in a prolonged state of RA deficiency following the initial burst of excess RA, moreover, some defects caused by a teratogenic dose of RA can be reversed by subsequent supplementation of RA, which suggests that exogenous RA can cause a functional state of RA deficiency by inducing overcompensation [98].

In Table I, we surveyed molecular genetic evidence that links variations in the sequence of genes involved in carotenoid/retinoid metabolism or signaling with inherited disorders and diseases. We have not included mutations in retinoid genes that affect primarily vision or the phototransduction process, as these have been reviewed elsewhere [99, 100]. For most but not all listed genes, the effect of the potential pathogenic mutations has also been confirmed via knockout or knock-in animal models. However, this survey has at least two important

limitations. One is that due to the potential for highly deleterious developmental manifestations for loss-of-function mutations in ALDH1A2, RXRA, RDH10 or DHRS3, for example, these genes do not appear or are very briefly featured in this survey. Mutations affecting ALDH1A2, RDH10 or DHRS3 which lead to viable fetus are most likely not the result of a homozygous null-state, and could be the result of a hypomorphic allele or of an epistatic mutation which allows for survival to term. Another limitation is that some genes involved in RA metabolism or signaling, such as cytochrome P450 reductase (POR) or scavenger receptor B1, are also involved in other pathways that may impact development. In these cases, it is difficult to attribute the defects observed to an alteration in RA-signaling alone without knowing if the phenotype can be rescued via a change in RA-signaling or vitamin A status.

## CONGENITAL HEART DEFECTS AND VITAMIN A

The normal development and health of the fetus requires a sufficient, yet not excessive amount of vitamin A precursors in the maternal diet. Congenital malformations can result from either improper diet (deficiency or excess of vitamin A), or from changes in the activity of retinoid enzymes, transporters or receptors due to genetic mutations of interfering substances. A mere four-fold increase in the intake of preformed vitamin A during gestation over the recommended daily allowance (2,500IU preformed vitamin A, or 770μg retinol/day during gestation) can cause a significant increase in birth defects associated with impaired neural crest development [101, 102]. It should be noted, however, that teratogenic effects of dietary vitamin A are associated with intake of preformed vitamin A such as retinol or retinyl esters, and that there are no reports of teratogenic effects caused by provitamin A carotenoids in man.

Congenital heart defects (CHDs) account for nearly one third of all major birth defects having an incidence of 9/1,000 births and affecting over 1.3 million newborn each year [103]. Not included in these statistics are a significant percentage of stillbirths (10%) and spontaneous abortions (20%) resulting from earlier and/or more severe defects [104, 105]. The therapeutic options and survival rates for many types of CHDs have improved, but for patients living with a repaired CHD, residual damage and complications continue to pose challenges [106, 107]. A better understanding of the pathology and developmental processes that result in CHDs could shed light on their potential causes and help in the design of better therapies.

Seminal studies by Josef Warkany and colleagues have first described the effect of vitamin A deficiency on the incidence of heart defects in a rat model [108–110]. These observations have been expanded to include the effects of excess RA in rats, mice, zebrafish, frog, and avian models [111–116]; and have led to a comprehensive picture of the role of RA in cardiogenesis (reviewed in [117–120]). Given the multitude of cardiogenic events that rely on RA-signaling, it is not surprising that fetal exposure to RAR agonists can result in various, dose and stage of development dependent cardiac defects, including anomalies in heart looping, aortic arch malformations, transposition of the great arteries (TGA), coronary defects, double-outlet right ventricle (DORV), myocardial hypoplasia, tetralogy of Fallot (TOF), outflow tract defects and septal defects [121–126]. CHDs are also seen in cases of

human fetal exposure to retinoid-based therapies, such as 13-*cis*-retinoic acid (isotretinoin, Accutane) [127–129]. Moreover, drugs (valproate), toxins (nitrofen, tobacco, alcohol), infections (rubella), or comorbidities, (gestational diabetes) can influence fetal retinoid metabolism to cause birth defects or developmental disorders [130–135].

## ROLES OF RA IN THE DEVELOPMENT OF THE HEART.

The first functional organ during embryogenesis, the heart is critical for the post-implantation survival of the vertebrate embryo; changes in the fragile balance of cardiac specification, differentiation and maturation, and cell migration leads to CHDs. In humans, the global prevalence of congenital heart defects has been constantly rising in the last 50 years, mainly due improved detection of mild and minor CHDs [136]. Over fifty years of clinical and experimental research have shown that formation of the vertebrate heart is strongly dependent on (vitamin A and) retinoic acid signaling throughout embryonic and fetal development [118].

In mouse embryos, heart specification starts at early/mid-gastrulation stages and gives rise to a population of approximatively 250 *Mesp1*+ cardiac progenitors in the anterior primitive streak which subsequently migrate antero-laterally to generate a horseshoe-like structure beneath the head folds, the cardiac crescent (CC)[137] (shown in Fig. 2). Comparative fate mapping of gastrulating vertebrate embryos suggest that the cells in the anterior and posterior halves of the primitive streak represent distinct myocardial cell lineages and contribute to distinct anatomical locations in the CC and, later on, in the tetracameral heart [138, 139]. It is nevertheless becoming increasingly obvious that different cardiac progenitor populations are being specified throughout mid/late-gastrulation; the vast majority of the myocardial cells originate in temporally distinct cardiac pools of *Mesp1*+ cells whose destiny within the architecture of the heart are further defined/shaped by transitional/combinatorial expression of transcription factors like *Foxa2, Smarcd3, Mef2c and Hopx* [140–143].

Cardiogenic specification is governed by a complex ensemble of regulatory factors assembled into a conserved cardiogenic gene regulatory network (CGRN), at the top of which lie the HLH transcriptional regulator Id and the Tbox factor Eomesodermin (EOMES), the first specific cardiogenic marker and direct activator of *Mesp1*, and the actual inductor of CGRN [144]. Single cell transcriptome analysis of *Mesp1*+ cells shows a surprising diversity, pointing towards a MESP1 coordinated differentiation continuum in which regionalization (and segregation into first and second heart fields) is already present/happening between E6.5 and E7.5 [144–148]. Interestingly, MESP1 is not required for cardiogenic transdifferentiation, the core of transdifferentiating CGRN being formed of GATA4, TBX5, MEF2C and HAND2 [149, 150].

The cardiac crescent consists of two distinctively located populations of cells: First Heart Field (FHF), located anteriorly and laterally in the lateral plate mesoderm, and Second Heart Field (SHF), located posterior and medially in the pharyngeal mesoderm. The FHF dynamically expresses *Nkx2.5/Tbx5/Hand1/Gata4/Hcn4/Sfrp5* and will develop mainly into the left ventricle, part of the atria and the atrioventricular (AV) canal [151–156]. Initially

restricted to the medial splanchnic mesoderm adjacent to ventral pharyngeal endoderm, the SHF preserves its posterior and medial position (dorsal mesocardium/pericardial wall and pharyngeal mesoderm) throughout primary heart tube formation/early cardiac morphogenesis, and contributes to the right ventricle, part of the atria and the outflow tract. The SHF cells represent a pool of undifferentiated, highly proliferating cardiac progenitors characterized by the expression of a dynamic, combinatorial network of genes including *Isl1*, *Fgf8*, *Fgf10*, *Tbx1*, *Prdm1* and *Six1*, the transcription of which is downregulated upon cardiac differentiation and activation of *Nkx2.5/Gata4/Mef2c* [157–162]. Of note, none of these genes can be considered *bona fide* markers for either FHF or SHF. Later on during development, RA-dependent *Hoxa1/Hoxb1/Hoxa3* expression further refines the SHF into distinct posterior domains contributing to distal and proximal outflow tract [163, 164]. Altogether, alteration of SHF cells differentiation and migration impacts heart elongation and looping, and leads to conotruncal and atrioventricular septal defects [165].

The primitive heart tube (PHT) is formed around E8.0 in the pericardial coelom through movement (accompanying the body closure) towards midline and fusion at the ventral midline of the left and the right sides of the FHFs [166] (depicted in Fig. 2 left). The PHT is initially suspended in the pericardial coelom by the dorsal mesocardium (DM)/dorsal pericardial wall which connects it to the SHF in the pharyngeal visceral mesoderm [167]. The proliferating index of the CC decreases as the PHT is being formed, and the PHT growth is driven mainly by addition of cells from the SHF through DM [168]. As the heart tube elongates and begins looping, the DM breaks apart and the heart tube grows through addition of cardiac cells to the anterior pole from the anterior SHF (right ventricle and OFT) and to the posterior pole from the posterior SHF (atria and venous pole) (Fig. 2 right). The primitive cardiac tube consists of two layers (endocardium and myocardium) separated by an extracellular matrix known as cardiac jelly; the third layer, epicardium appears much later (E9.0/E9.5) from the proepicardium [169]. Of note, RA is required for the proper trabecular development distribution of extracellular matrix molecules (fibronectin, collagen I, hyaluronic acid) in the cardiac jelly [170–172]. The early, unconvoluted heart tube is already AP patterned, with the prospective atrial and ventricular segments defined at the posterior and the anterior poles, respectively. Looping starts shortly after E8.0 (around E8.25) and is accompanied by the first contractions, thus initiating circulation [173].

## Critical Roles of RA in Early Cardiogenesis

RA exerts its activity by binding to heterodimers of RARα, -β or γ and RXRα, -β and γ, of which RARα, RXRα and RXRβ are expressed ubiquitously at early and mid-gastrulation stages [174, 175]. Combinatorial analysis of RAR and RXR knockouts identified RARα and RXRα as the major players in cardiac development, although the role of RXR as heterodimer partner seems to be more promiscuous [22, 176, 177]. However, with the exception of CYP26A1 (present in the anterior epiblast), none of the RA-synthesizing or degrading enzymes are expressed in the early and mid-gastrulation stage embryo, indicating that cardiac specification events occur, physiologically, in an RA-free environment [178, 179]. Mid-gastrulating mouse embryos exposed to RA and *Cyp26a1*$^{-/-}$ embryos exhibit phenotypes surprisingly similar to deficiency of RA-signaling (looping defects, small atria, conotruncal defects), suggestive for the existence of early A-P cardiac patterning events

[180–182]. The consistent effect on atrial size also reinforces the concept of RA-dependent identity of atria, as it results from both *ex vivo* (pluripotent cells differentiation) and *in vivo* experiments[78, 114, 140, 183, 184]. Of note, similar RA-driven cardiac patterning defects can be observed in other vertebrates suggesting an evolutionary conserved role of RA in early cardiogenetic events [185–187].

RA synthesis starts at mid gastrulation (E7.5) after *Rdh10* and *Raldh2* (*Aldh1a2*) expression is initiated in the presomitic mesoderm, indicating that mid- and late-gastrulating cardiac progenitors, initially bathed in RA, escape RA signaling as they migrate anteriorly[84, 92, 188, 189]. Of note, neither RALDH1 nor RALDH3 play any role in heart development, while RDH10-dependent RA contribution to early heart morphogenetic events is restricted to later events, like heart looping, chambers development and myocardial trabeculation [190–193]. Several lines of evidence indicate that RA is not required for the cardiac crescent formation *per se*, but for its **shaping** through alteration of the ratio between FHF and SHF: the expression of SHF genes is expanded posteriorly (*Fgf8*, *Tbx1*, *Isl1*, *Fgf10* reporter transgene), and ventrally (*Hand1* and *Irx4*), while the expression of AHF genes (*Tbx5*, *AMHC1*) is downregulated [78, 189, 194, 195]. At this stage, the role of RA in the SHF is to control (through FGF8) *Isl1* expression and to promote (through GATA4) *Isl1*+ cells differentiation to *Mef2c*+ progenitors that are subsequently added to and elongate the OFT[196]. *Tbx1* expression further segregates the SHF into an anterior (aSH) and a posterior (pSH) domain, which contributes cells to the arterial and venous pole, respectively. In the aSH (depicted in Fig 2). RA modulates the TBX1FGF8-ISL1 signaling axis at the level of Fgf8, thus altering the expression of the final targets of this signaling cascade (*Hoxa1*, *Hoxb1*) [189, 197]. In the pSH, RA is required for shutting off the aSH program and initiation of a venous pole differentiation program through TBX5 activation in *Tbx1*-positive cells and consecutive modulation of hedgehog signaling and downregulation of *Mef2c* and *Fgf10*[198–200].

During post-gastrulation stages, RA is synthesized in the presomitic mesoderm, somites, and posterior region of the lateral plate mesoderm, which means the posterior primitive heart tube and the pSH are exposed to RA, thus creating a gradient of RA signaling across the A-P axis of the primitive heart [76, 78]. This is consistent with the results of *in vivo* experimental modulation of RA-signaling in vertebrate embryos, showing that RA is involved in the growth and looping of the primitive heart through cell addition to (mainly the) posterior pole, leading to expansion of the ventricles at the expense of atria, sinus venosus and (at least in zebrafish and mice) forelimb field [75, 78, 83, 184, 186, 201, 202]. **Primitive heart looping** is severely affected in *Raldh2*$^{-/-}$ mouse embryos and zebrafish morphants, a phenomenon associated with alteration in left-right gene networks; however, in vitamin A deficient chicken and quail embryos, the looping defect is not associated with left-right asymmetry defects [203–205].

## RA and Outflow Tract Formation and the AV Septum

There is a consensus that post-gastrulation, RA is required for the correct **morphogenesis and septation of the outflow tract** (OFT). OFT develops through addition of Fgf10+ cells to the anterior pole from two distinct domains of the pharyngeal arches mesoderm: anterior,

RA negative (the first two pharyngeal arches express Tbx1 which in turn promotes *Cyp26a1* expression) and posterior, RA positive (expressing *Raldh2*), with a boundary between pharyngeal arches 2 and 3[206, 207]. The anterior, RA-free domain contributes cells to the proximal OFT (sub-aortic/pulmonary OFT), while caudal OFT (base of ascending aorta) receives cells from the posterior pharyngeal arches (which express *Raldh2*)[159, 165, 206, 208–210]. Recent data suggest that the level of RAR signaling in the posterior pharyngeal arches, directly modulated by HECTD1 ubiquitin ligase through RARα ubiquitination, strongly impacts the development of the aortic arch in mice [126, 211]. OFT septation occurs through the fusion of the aorticopulmonary septum (cardiac neural crest cells) with the outflow cushion ridges, and the AV cushion tissue [212, 213]. Post-gastrulation changes in RA-signaling lead to aortic arch defects and conotruncal heart defects: transposition of the great arteries (TGA), double outlet right ventricle (DORV), tetralogy of Fallot (TOF), and persistent truncus arteriosus (PTA). RAR, RXR and RAR/RXR double mutants as well as vitamin A deficiency mouse embryos show hypoplastic posterior pharyngeal arches with OFT septation defect[176, 177, 214–217]. However, RA-signaling appears to play no role in in cardiac neural crest cell migration and differentiation, since neural crest specific deletion of RXRα/RARα1 has no distinguishable effect on heart morphology/OFT septation[218].

The role of RA-signaling in the formation of the AV septum is still elusive; a common AV canal associated with severe OFT defects has been reported in several vitamin A-deficient animal models and RXRα$^{-/-}$ embryos, most probably through the inability of the dorsal mesenchymal protrusion (DMP) derived from the posterior SHF, to contribute to the AV cushion tissues fusion, This phenomenon is mediated by an RA-dependent GATA4/hedgehog signaling event. [75, 177, 219, 220]. The DMP also contributes to the dorsal atrial septum that separates the pulmonary circulation from the systemic circulation, a morphogenetic event orchestrated by an evolutionary conserved RA-Shh-*Tbx5*-Wnt signaling axis [221, 222].

## Roles of RA in Epicardial Development

RA plays important roles in the development of the heart during late gestation, chiefly of which is its influence on the developmental processes that involve the embryonic epicardium (reviewed [223]). The epicardium is a mesothelial layer which envelops the myocardium and plays important role in promoting the formation of coronary vasculature and the growth of the myocardium, and by providing progenitor cells for various cardiac populations. The epicardium develops from the proepicardium, a transient outgrowth of the septum transversum which invests the myocardium starting at about E9.5 in mouse. From their location proximal to the inflow tract, proepicardial cells transition via various mechanisms to reach the myocardium where they establish a single layered epithelial epicardium and also contribute to cells found in the subepicardial space (Fig. 3). A second less well described source of epicardial progenitors is located near the arterial pole [224, 225]. Proepicardial induction, extrusion and attachment to the looping heart requires BMP-signaling and the T-box transcription factor TBX5 [226–228]. Of note, *Raldh2*-deficiency does not impair proepicardial organ formation, transfer and investment of the myocardium [229]. However, RXR-deficiency leads to defects in epicardial development including detachment and

increased apoptosis, but it is not clear if RAR or other NR partners of RXR contribute to this effect [230, 231].

The development of the epicardium evokes patterns seen in other mesothelia that cover coelomic organs such as lung, liver, pancreas and the gut tube [232–234]. Both the proepicardium and (by extension) its derivatives consist of a highly heterogenous population of cells that vary in both marker expression and developmental potential [235–238]. Like other coelomic epithelial cells, a large subset of proepicardial cells express the transcription factor Wilms' tumour 1 (*Wt1*), which controls (among others) the expression of *Raldh2* [239]. Proepicardial cells also express the T-box transcription factor *Tbx18* often but not exclusively in conjunction with *Wt1* [240]. A subpopulation of proepicardial cells which gives rise to cardiac fibroblasts expresses the transcription factor *Tcf21* (also known as Capsulin, Epicardin or POD1), whose expression is retained in migrating epicardial progenitors and adult cardiac fibroblasts [241–243]. In fact, the majority of resident cardiac fibroblasts and injury-derived myofibroblasts in the adult heart express *Tcf21* and *Wt1*, the rest being derived from an endocardial *Tie2*+ progenitor population [244, 245]. *Tcf21*+ epicardial cells also express *Pdgfrα* and *periostin* markers shortly before epicardial EMT [246–250]. Meanwhile, another distinct subpopulation of proepicardial cells, which express *Scleraxis* (*Scx*) and *Semaphorin3D* (*Sema3D*), give rise to a subset of coronary endothelial cells [238]. The proepicardial precursors of pericytes and coronary vascular smooth muscle (VSMC) are currently not distinguished by a specific marker but as epicardial-derived cells (EPDCs) they begin to express *Pdgfrβ* [251–253].

After myocardial investment is complete, some epicardial and subepicardial cells undergo EMT to invade and colonize the myocardium with EPDCs. This process is influenced by the mitotic spindle orientation of individual epicardial cells with regards to the epicardial basement membrane [254]. Epicardial EMT is also governed by a multitude of extracellular transduction pathways which include TGF, FGF, PDGF, Prokineticin receptor 1 and Wnt, in coordination with regulators of cytoskeleton dynamics, such as the Ras homolog gene family, member A (RhoA) pathway, and with transcriptional regulators RAR, WT1, LEF1, Myocardin-related transcription factor (MRTF), YAP/TAZ, and NFATC1 [246, 250, 252, 254–262]. EPDCs seeding the myocardium contribute primarily to two cardiac cell populations, namely VSMCs and cardiac fibroblast populations, but also give rise to a small percentage of coronary endothelial cells (reviewed in [263–266]. EPDC-derived VSMCs and pericytes play important roles in regulating vascular tone, while EPDC-derived cardiac fibroblasts provide mechanical support for the myocardium (interstitial fibroblasts) and coronary vessels (adventitial fibroblasts) as well as the fibrous skeleton of the heart (fibroblasts of the annulus fibrosus and parietal AV leaflets) [247, 248, 267–269]. Epicardial-derived cells play crucial roles in the maturation and remodeling of the coronary vasculature, therefore defects in epicardial-development often result in impaired coronary development. Epicardial derived, resident VSMCs and fibroblasts also play an important role in pathological processes of atherosclerosis and cardiac fibrosis, therefore, understanding the factors that guide EPDC differentiation and proliferation could inform the development of better therapies for cardiovascular diseases [270–272].

Embryonic epicardial cells express a full complement of metabolic enzymes, retinoid binding proteins and transporters required for the regulated production of RA from all-*trans*-retinol. *Raldh2* is robustly expressed in the avian proepicardial and embryonic epithelial epicardial cells, however, in mouse, the expression of *Raldh2* is not significantly seen in the epicardium till after investment of the myocardium is complete (E12) [76, 229, 273–275] The expression of *Raldh2* becomes extinguished in migrating EPDCs and in the postnatal epicardium [239, 257, 273]. The embryonic epicardium also expresses *Rbp4* and its membrane receptor *Stra6*, components of the ROC complex, i.e. *Dhrs3*/*Rdh10*, the RA-synthetic enzyme *Raldh2,* and the catabolic enzymes, *Cyp26a1* and *Cyp26b1* [229, 262, 276]. The additional expression of RA-receptors, *Rar* and *Rxr*, grants the embryonic epicardium the capacity to control expression of various genes via RAR-signaling.

## RA-Signaling and Epicardial EMT

RA-signaling plays an important role in **epicardial EMT and the migration of EPDCs into the myocardium**. The evidence to support this role includes the observation that mice lacking *Rxr* expression in the epicardium have a coronary vascular defect and exhibit impaired epicardial EMT [230]. Similar coronary defects were observed in RA-rescued *Raldh2*-deficient mice [277]. Additionally, RA administration was observed to rescue a defect in epicardial EMT related to *Wt1*-deficiency [257]. More recently, it was shown that administration of a chemical inhibitor of RALDH2 caused reduced EMT and impaired migration of primary embryonic epicardial cells in response to PDGFBB [262]. RALDH2 inhibition in fetal mouse hearts also resulted in a reduced number of EPDCs infiltrating the myocardium. Conversely, RA excess resulting from *Dhrs3*-ablation was associated with increased rate of EMT and of epicardial migration and an increase in the number of EPDCs in the myocardium [262]. Several potential mechanisms by which RA promotes epicardial EMT have been proposed, such as induction of FGF- and canonical and non-canonical Wnt-signaling, and through promoting cytoskeletal reorganization via the RhoA pathway [230, 257, 262]. RA-signaling also induces the expression of other factors that have been implicated in epicardial EMT, such as as *Tcf21*, *Pdgfra*, and *Wt1* [243, 246, 252, 278, 279].

## RA-Signaling and the Cellular Fate of EPDCs

In addition to regulating the migration of EPDCs, **RA-signaling influences the differentiation of EPDCs towards either a VSMC or fibroblast fate**. Studies by Azambuja *et al*. indicated that RA represses the expression of VSMC markers in proepicardial explants and suggested that epicardial RA delays VSMC formation to allow the endothelial plexus to form before being reinforced by mural cells [280]. Braitsch *et al* confirmed these findings and showed that RA inhibits VSMC differentiation by inducing the expression of *Tcf21* (Pod1) [279]. TCF21 was suggested to induce the EMT of cardiac fibroblast precursors and the proepicardial cell fate specification towards a fibroblast fate [242, 243]. In the case of *Wt1*-ablated epicardial cells mentioned previously, RA was shown to rescue the expression of *Pdgfra*, which marks fibroblast precursor cells [239]. Other reports also indicate that RA can inhibit the proliferation of human coronary smooth muscle cells [281]. Therefore, several independent lines of investigation support a role for RA-signaling in promoting the formation of cardiac fibroblasts at the expense of VSMCs. However, it is not currently clear at which developmental stage this regulation occurs, or if

the effects of RA on epicardial EMT and epicardial cell fate are mediated through common or independent pathways.

The Hippo/Yap pathway is an important developmental pathway that controls organ size and patterning and also plays a role in the differentiation and repair of adult tissues [282, 283]. The Hippo kinase cascade is triggered by various extracellular cues including mechanical strain, GPCR activation, Wnt-signaling, cytoskeletal reorganization, or loss of cell polarity, to phosphorylate and inactivate the YAP/TAZ effectors (reviewed in [284–286]. In the absence of Hippo-signaling, YAP/TAZ translocate to the nucleus where they associate with TEAD (TEA/ATTS domain) transcription factors to control gene expression. Recently, Hippo-YAP/TAZ signaling has emerged as an important pathway in heart development, fibrosis and regeneration [287–289]. In studies investigating the effect of *Lats1*/*2* deficiency on heart development through single-cell transcriptomics, Xiao *et al.* found that in the presence of constitutively active Yap, EPDCs undergo differentiation arrest at a prefibroblast stage [290]. This population of arrested prefibroblast cells express *Tcf21* along with YAP target genes including the retinaldehyde reductase *Dhrs3* whose activity limits the formation of RA. This observation led Xiao *et al.* to propose that YAP, known to respond to mechanical strain, causes a reduction in RA-signaling (via *Dhrs3*) and blocks the formation of cardiac fibroblasts. YAP was also shown to affect epicardial EMT, however, it is not clear if RA mediates the effects of YAP on epicardial EMT [291]. These findings suggest that the effects of RA on epicardial differentiation may act downstream of YAP in the Hippo signaling pathway to affect epicardial development and perhaps heart repair.

## Cardiac and Extracardiac RA in Promoting Myocardial Expansion

To meet the nutrient and oxygen demands of the growing embryo, the heart needs to grow in both capacity and strength. This is particularly evident during late gestation, when the heart undergoes a phase of rapid growth and consolidation resulting in the loss of ventricular trabeculations and the formation the myocardial compact zone. Given the density and size of the newly formed compact myocardium, oxygen can no longer diffuse from the ventricular lumen to reach the entire myocardium, which now requires the development of a specialized coronary vasculature. A primary coronary plexus formed by endothelial differentiation of precursor cells derived from the sinus venosus, epicardium and endocardium, connects to the circulation via the coronary ostia and becomes reinforced with VSMCs and adventitial fibroblasts (reviewed in [265]). The formation of the coronary vasculature and myocardial growth must be closely coordinated.

In addition to acting as a source of progenitor cells, the embryonic epicardium also secretes trophic factors which induce cardiomyocyte proliferation and **RA-signaling exerts a regulatory influence on the secretion of epicardial mitogens** (reviewed in [292]). After an early observation that myocardial expansion relies on RXRα [21], further studies demonstrated that RXRα and RA generated by RALDH2 act in an extracardiac fashion to affect epicardial mitogen secretion, by activating expression of hepatic erythropoietin that is secreted and travels to the epicardium to stimulate secretion of IGF2 [229, 293–295]. First seen in original studies by Warkany *et al.* in vitamin A-deficient rat fetuses, a thin ventricular myocardium was also observed in mouse models with reduced RA synthesis,

such as RA-rescued *Raldh2*$^{-/-}$ mice or in mouse embryos exposed to a RALDH2 inhibitor [108, 229, 276]. Paradoxically, mouse models of RA excess such as *Dhrs3*$^{-/-}$ embryos also have a thin-walled myocardium, evoking a commonly observed phenomenon where too little or too much RA often cause a similar effect [67, 276, 296]. Hypoplasia of the ventricular myocardium is often observed in mouse models with altered RA receptor signaling, such as mice expressing a dominant negative RARα receptor (RAR303E) in the epicardium, RARα/γ double knockout mice, and in mice with global or epicardial-specific RXRα-ablation [21, 216, 230, 297]. In conclusion, RA-signaling is found at the crux of regulatory pathways that coordinate myocardial growth, the differentiation of VSMCs and fibroblasts and coronary remodeling. Integration of these pathways allows for the correct timing and coordination of vascular and morphological changes necessary for the growth and maturation of the heart.

## CONCLUSIONS AND FUTURE PERSPECTIVES

Cardiovascular disease is the leading cause of death worldwide and despite gains in the prevention and treatment of acute myocardial events, the rates of myocardial fibrosis and heart failure continue to increase [298]. A few weeks after birth, the regenerative capacity of the mammalian heart becomes greatly reduced. As a result, the adult heart cannot adequately replace cardiomyocytes lost in case of a myocardial infarct. Instead, the injured area elicits inflammatory cells which secrete cytokines, and activated myofibroblasts which induce extracellular matrix remodeling [299, 300]. The scar tissue created negatively affects the contractile, conductive and mechanical properties of the heart leading to reduced compliance and hypertrophic remodeling. Given the poor therapeutic options currently available, there is great interest in harnessing the tools created by studying cardiac developmental pathways to enhance the scar-free repair of the heart.

Zebrafish are capable of effective regeneration following cardiac resection through a process that requires the epicardium and a sustained neovascularization response [301–304]. Along with other known epicardial developmental pathways such as FGF, PDGF IGF2, RA-signaling also plays a role in sustaining zebrafish heart regeneration [305–307]. Is it potentially feasible that cardiac injury evokes similar, albeit much less attenuated, epicardial responses in mammals? There is, indeed, evidence that RA-signaling is activated in the mouse heart following injury, and during coronary artery disease [308, 309]. However, decreased liver retinoid stores in mice were seen to correlate with a better myocardial response to cardiac injury [310]. Meanwhile, inhibition of the CCAAT/enhancer binding protein (C/EBP), which is responsible for the induction of the expression of *Wt1* and *Raldh2* in the epicardium in response to injury, led to improved function, and reduced fibrosis and inflammation after a cardiac insult [311]. In fact, the potent inflammatory and fibrotic response to cardiac injury seen in mammals is suppressed by YAP/TAZ-signaling, which also suppresses the formation of RA [290, 312]. Therefore, in the heart as in other organs, RA-signaling or vitamin A status have both positive and negative effects on different aspects of heart repair and fibrosis (reviewed in [313]). Finally, one potential immediate use of RA-based cardiogenic signaling is in the differentiation of pluripotent stem cells. RA in conjunction with BMP promotes the differentiation of pluripotent stem cells towards an epicardial lineage [314–318]. Such cells could be an effective tool to model human disease or to support regenerative therapies.

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## ABBREVIATIONS:

| | |
|---|---|
| **RA** | all-*trans*-retinoic acid |
| **CRABP** | cellular retinoic acid binding protein |
| **CRBP** | cellular retinol binding protein |
| **DHRS3** | dehydrogenase/reductase superfamily member 3 |
| **EMT** | epithelial-to-mesenchymal transition |
| **EPDCs** | epicardial-derived cells |
| **LRAT** | lecithin:retinol acyltransferase |
| **PDGF** | platelet-derived growth factor |
| **PDGFRA** | platelet-derived growth factor receptor A |
| **PDGFRB** | platelet-derived growth factor receptor B |
| **RALDH** | retinaldehyde dehydrogenase |
| **RAR** | retinoic acid receptor |
| **RBP4** | (serum) retinol binding protein 4 |
| **RDH10** | retinol dehydrogenase 10 |
| **RhoA** | Ras homolog gene family, member A |
| **RXR** | retinoid X receptor |
| **SDR** | short-chain dehydrogenase/reductase |
| **STRA6** | stimulated by retinoic acid 6 |
| **TCF21** | transcription factor 21 |
| **VSMC** | vascular smooth muscle cells |

| | |
|---|---|
| **WT1** | Wilms-tumor 1 |

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## Highlights

- Embryonic retinoic acid synthesis and catabolism need to be carefully orchestrated
- Retinoic acid is required for the developmental processes that control cardiogenesis
- Both excess and deficiency of retinoic acid is associated with developmental defects

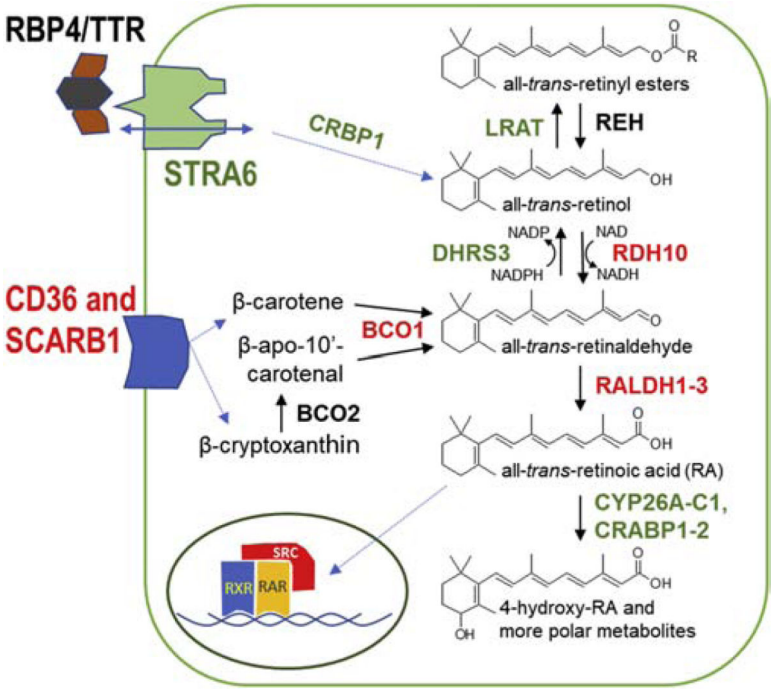


**Figure 1.**

Vitamin A uptake and metabolism. All-*trans*-retinol is transported in the circulation by serum retinol binding protein (RBP4) in association with transthyretin (TTR) and as retinyl esters incorporated in lipoproteins (not shown). In target cells, RBP4/TTR-bound retinol is taken up via the bidirectional cellular receptor STRA6 and delivered to the cellular cytosol where it binds cellular retinol binding proteins (CRBP1 shown). Provitamin A carotenoids circulating in association with lipoproteins are taken up via scavenger receptors class B CD36 (also known as SCARB3) or by the related receptor SCARB1. Provitamin A carotenoids that contain substituted rings such as β-cryptoxanthin are cleaved by the asymmetric beta-carotene-dioxygenase 2 (BCO2) to produce β−10'-apocarotenal, which together with β-cryptoxanthin can be converted by beta-carotene-dioxygenase 1 (BCO1) to all-*trans*-retinaldehyde. All-*trans*-retinaldehyde is reduced to all-*trans*-retinol via the NADPH dependent dehydrogenase reductase 3 (DHRS3). Alltrans-retinol can be esterified by lecithin:retinol acyltransferase (LRAT) and stored in intracellular lipid droplets, or it can be secreted for use by other cells, or it can be oxidized to all-*trans*-retinaldehyde by the NAD+ dependent retinol dehydrogenase 10 (RDH10) which associates with DHRS3. RA is produced by the oxidation of all-*trans*-retinaldehyde by retinaldehyde dehydrogenases 1–3 (RALDH1–3). RA then binds cellular RA binding proteins (CRABP1–2) and is transported to the nucleus to activate RAR/RXR, or it can be oxidized to 4hydroxy-RA and other oxidized metabolites by CYP26A1-C1. Feedback regulation by RA leads to downregulation of the expression of genes whose activity lead to increased RA production (proteins indicated in red font) and the upregulation of the expression of genes whose activity could limit RA production or catalyze its degradation (proteins shown in green font).

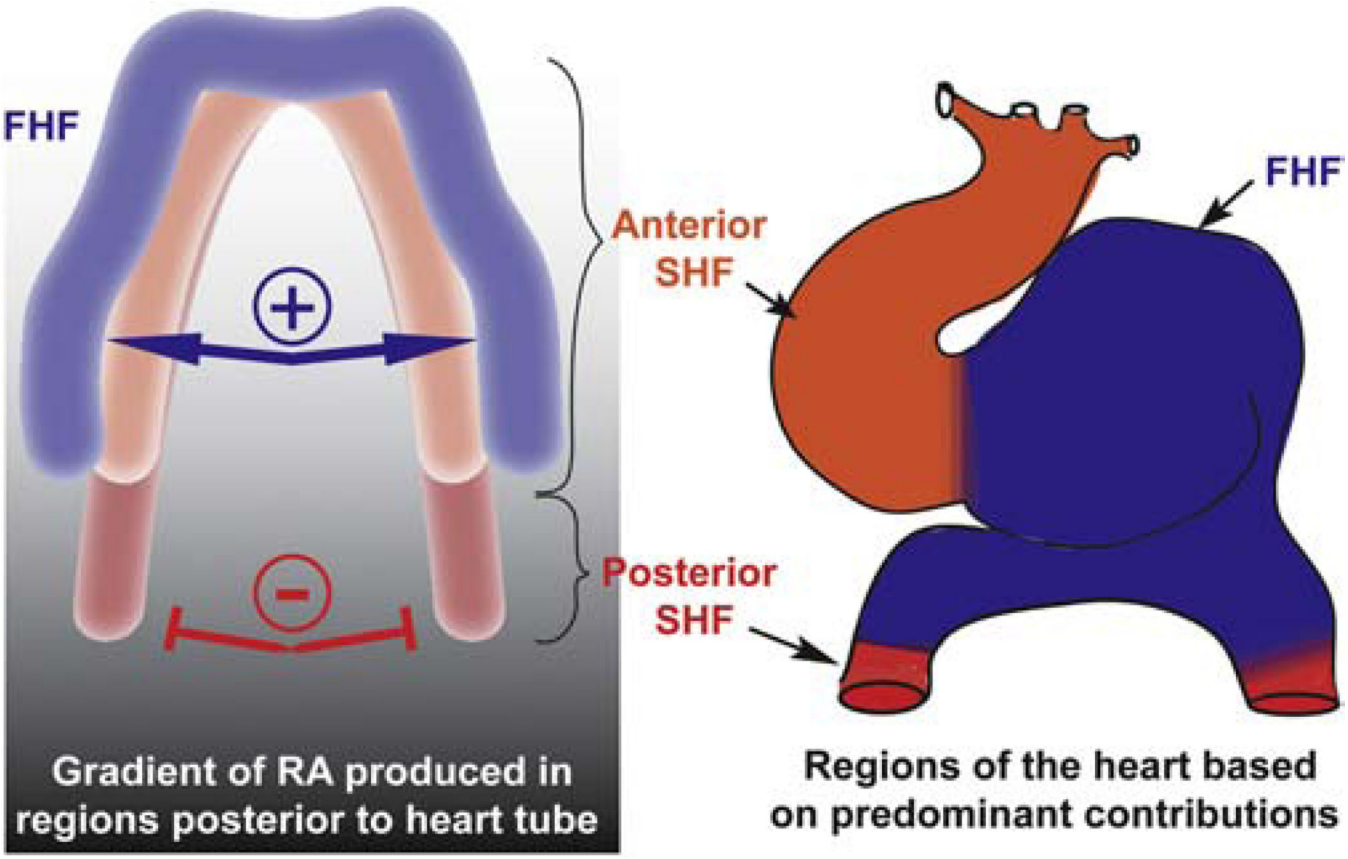


**Figure 2.**

Role of RA during early cardiogenesis (up to early somite stage). Left, cardiogenic regions of the HH7–8 chick embryo (E7.5 in mouse) include the cardiac crescent, first heart field (FHF) shown in blue, and the second heart field (SHF) which is further subdivided in anterior (orange) and posterior (red) domains. RA production by regions posterior to the heart tube and then later by cardiac precursors themselves generates a caudo-rostral gradient of RA [78]. RA signaling defines the posterior border of the SHF and the ratio between FHF and SHF and pattern the inflow/outflow tract. Right, the regionalization of the looped heart tube based on the contributions of the FHF and the anterior and posterior SHF (image adapted from [435]).

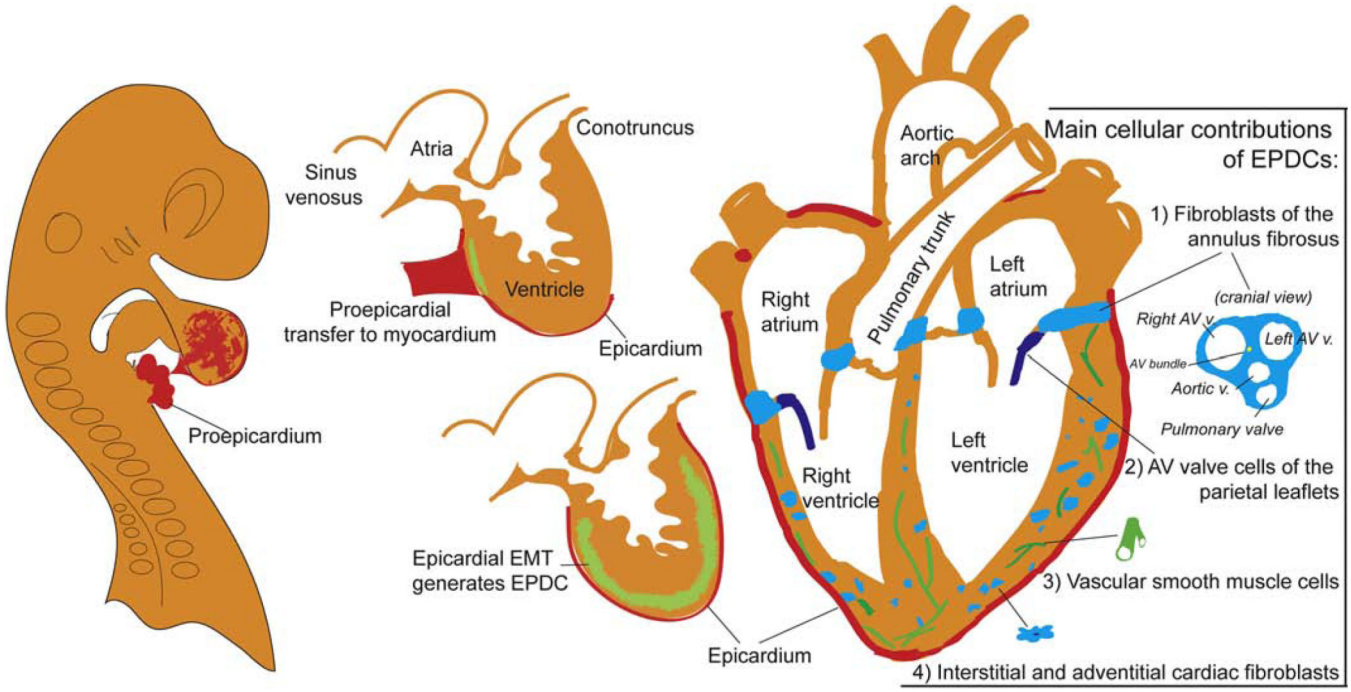


**Figure 3.**

The role of the epicardium in heart development. Left, HH17–18 chicken embryo (equivalent to E9.5–10 mouse) showing the proepicardium (red) making villous projections towards the dorsal myocardium. Middle top, shows the epicardium migrating ventrally to envelop the myocardium to establish the epithelial epicardium (red) and subepicardium (green). Middle bottom, by HH20 (E10.5–11 in mouse, Carnegie Stage 15 human) the epicardium has completely enveloped the heart and epicardial and subepicardial cells begin to undergo EMT to infiltrate the myocardium as epicardial-derived cells (EPDCs green). Right, EPDCs give rise to various epicardial derivatives, chiefly of which coronary vascular smooth muscle cells (VSMCs, green) and fibroblasts (blue) that contribute to the adventitial layer of vessels, the interstitium and annulus fibrosus as well as the parietal leaflet of the antrioventricular valves (purple).

## Table 1

Association of variations in genes involved in retinoid metabolism or signaling with inherited disorders and other diseases.

| Gene HGNC approved name (common name) | Chromo some position | Function in carotenoid/retinoid metabolism or signaling | Disease association (mutations associated with cardiovascular disease in bold font) | References |
|---|---|---|---|---|
| ABCA4 | 1p22.1-p21 | Clearance of all-*trans*-retinal in RPE | • Stargardt disease | [319] |
| ALDH1A1 (RALDH1) | 9q21.13 | RA synthesis | • Cancer (melanoma endometrial, bladder, cervical, colorectal) | [320–324] |
| ALDH1A2 (RALDH2) | 15q21.3 | RA synthesis | • Congenital diaphragmatic hernia, anencephaly, neural tube defects, renal agenesis | [325–329] |
| | | | • **Tetralogy of Fallot,** | |
| | | | • **Pentalogy of Cantrell ectopia cordis and omphalocele, a defect of the lower sternum, a deficiency of the anterior diaphragm, a defect in the diaphragmatic pericardium and cardiac defects (ventricular septal defects, tetralogy of Fallot)** | |
| | | | • Increased newborn kidney size (due to higher RA levels associated with rs7169289(G) | |
| ALDH1A3 (RALDH3) | 15q26.3 | RA synthesis | • Anophthalmia and microphthalmia | [330–337] |
| | | | • Hypoplasia of the optic nerve and optic chiasm | |
| | | | • Autism | |
| BCO1 (BCDO1) | 16q21-q23 | Conversion of β-apocarotenals and provitamin A carotenoids to retinaldehyde | • Hypercarotenemia and hypovitaminosis A | [338–341] |
| | | | • Kabuki-like syndrome | |
| CD36 | 7q11.2 | Uptake of carotenoids and other lipids | • CD36 deficiency ischemic heart disease, hypertension, and congestive heart failure | [342, 343] |
| CD×1 | 5q32 | Retinoid signaling | • Anorectal malformation | [344, 345] |
| CD×2 | 13q12.3 | Retinoid signaling | • Persistent cloaca (C132Stop and R237H CDX2 cause increased Cyp26A1) | [346, 347] |
| CRABP1 | 15q25.1 | RA binding | • **Moyamoya Disease** | [348, 349] |
| CYP1B1 | 2p21 | RA synthesis both retinol and retinal oxidation to RA | • Primary congenital glaucoma | [350–353] |
| CYP26A1 | 10q23–24 | RA oxidation | • Neural tube defects | [354–357] |
| | | | • Hirschsprung disease | |
| | | | • Developmental disorder | |
| CYP26B1 | 2p13.2 | RA oxidation | • Skeletal and craniofacial anomalies, including fusions of long bones (multisutural synostosis, radiohumeral synostosis), calvarial bone hypoplasia, and craniosynostosis. | [358–361] |
| | | | • Neural tube defects | |
| | | | • Elevated RA, hypervitaminosis A | |
| | | | • Intellectual disability | |

| Gene HGNC approved name (common name) | Chromosome position | Function in carotenoid/retinoid metabolism or signaling | Disease association (mutations associated with cardiovascular disease in bold font) | References |
|---|---|---|---|---|
| CYP26C1 | 10q23.33 | RA and 4-oxo-RA oxidation | • Focal facial dermal dysplasia (FFDD) Type IV | [360, 362- 364] |
| | | | • Short stature | |
| | | | • Craniosynostosis | |
| CYP27C1 | 2q14.3 | Conversion of all-*trans*-retinol to all-*trans*-3,4-didehydro- retinol (vitamin A2), but also in other metabolic pathways | • Autism | [356, 365, 366] |
| | | | • Neurodevelopmental disorder | |
| DHRS3 | 1p36.21 | Retinaldehyde reductase | • Altered optic nerve cup area | [367–369] |
| | | | • Intellectual disability | |
| | | | • Ectrodactyly, ectodermal dysplasia, | |
| LRAT | 4q32.1 | Esterification of retinol in retinoid metabolism and visual cycle | • Retinal dystrophy, retinitis pigmentosa, Leber Congenital Amaurosis | [370–375] |
| | | | • Usher Syndrome | |
| MEIS2 | 15q14 | Retinoid target | • Orofacial clefting & delayed motor development | [376] |
| NAA10 | Xq28 | Involved in Nα-terminal acetylation as catalytic subunit of N(alpha)-acetyltransferase 10. Mutations in NAA10 affect expression of Stra6 and retinol uptake by cells. | • Lenz microphthalmia syndrome | [377] |
| NRIP1 (RIP140) | 21q11.2 | Retinoid and other nuclear receptor signaling | • Congenital anomalies of the kidney and urinary tract via impaired RA-signaling | [378] |
| POR | 7q11.2 | Electron donor to cytochrome P450 enzymes | • Anorectal and urogenital anomalies similar to Antley-Bixler syndrome caused by FGFR deficiency | [379] |
| | | | • Craniofacial defects (craniosynostosis evokes CYP26 mutations) | |
| | | | • Skeletal malformations | |
| | | | • Limb malformations | |
| | | | • Congenital adrenal hyperplasia (CAH) most likely due to steroid signaling | |
| RARA | 17q21.2 | RA receptor | • Acute promyelocytic leukemia | [365, 380– 385] |
| | | | • Autism | |
| | | | • Cleft lip and cleft palate (inconsistent) | |
| RARB | 3p24.2 | RA receptor | • **PDAC (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect) (GOF R387S or R387C mutations)** | [386–388] |
| | | | Intellectual Disability with Progressive Motor Impairment (with Chiari type I) (GOF G296A and L213P mutations) | |
| | | | • **Matthew-Wood syndrome** | |
| RARG | 12q13 | RA receptor | • Schizophernia | [389, 390] |
| | | | • **Susceptibility to anthracyclineinduced cardiotoxicity in childhood cancer** | |

| Gene HGNC approved name (common name) | Chromo some position | Function in carotenoid/retinoid metabolism or signaling | Disease association (mutations associated with cardiovascular disease in bold font) | References |
|---|---|---|---|---|
| RBP1 (CRBP1) | 3q23 | Intracellular retinol binding protein | • Retinal disease | [391] |
| RBP3 (IRBP) | 10q11.2 | Intra and extracellular retinal binding protein | • Retinitis pigmentosa | [347, 392– 394] |
| | | | • Leber Congenital Amaurosis | |
| | | | • Persistent cloaca | |
| RBP4 (SERUM RBP) | 10q23q24 | Serum retinol binding protein | • Night blindness, hypovitaminosis A, ocular coloboma | [40–43, 395–397] |
| | | | • Retinal Dystrophy and coloboma | |
| | | | • Familial amyloid polyneuropathy as a | |
| | | | • Coloboma, microphthalmia and anophthalmia (in the case of dominant-negative A73T, A75T mutations or if both mother and fetus are homozygous mutant as in affected canines) | |
| | | | • Coloboma, microphthalmia and anophthalmia (in the case of dominant-negative A73T, A75T mutations or if both mother and fetus are homozygous mutant as in affected canines) result of deposition of transthyretin (TTR) protein the binding partner of RBP4 | |
| RBP5 (CRBP3) | 12p13.31 | Intracellular retinol binding protein | • **Total Anomalous Pulmonary Venous Return** | [398] |
| RDH10 | 8q21.11 | Retinol oxidase | • **Total Anomalous Pulmonary Venous Return** | [398, 399] |
| | | | • Choanal atresia in mouse model | |
| RDH11 | 14q24.1 | Retinaldehyde reductase | • Atypical retinitis pigmentosa accompanied by facial dysmorphologies, psychomotor developmental delays | [400] |
| RDH12 | 14q24.1 | Retinaldehyde reductase | • Retinal dystrophy, retinitis pigmentosa, Leber Congenital Amaurosis | [401–406] |
| RAI1 | 17p11.2 | RA responsive; thought to function in transcriptional regulation; more studies are required to assess role in RA signaling | • Smith-Magenis syndrome | [407– 413] |
| | | | • Autism | |
| RPE65 | 1p31 | All-*trans*-retinyl ester isomerization to 11-*cis*retinaldehyde, key step in visual cycle | • Leber congenital amaurosis | [414–417] |
| | | | • Retinitis pigmentosa | |
| RXRB | 6p21.32 | Homomer or heterodimeric partner of RAR and other NRs; activated by 9-*cis*- retinoic acid and 9-cis-4oxo-13,14-dihydroretinoic acid | • Neurodevelopmental Disorders | [418] |
| RXRG | 1q22-q23 | Homomer or heterodimeric partner of RAR and other NRs; activated by 9-*cis*- retinoic acid and 9-cis-4oxo-13,14-dihydroretinoic acid | • Familial combined hyperlipidemia | [419–421] |
| | | | • Diabetes | |
| | | | • Intellectual and developmental disabilities | |
| SCARB1 | 12q24.31 | Uptake of carotenoids and other lipids | • Increased HDL cholesterol | [56, 422] |
| SDR16C5 (RDHE2) | 8q12.1 | Retinol oxidase | • Psoriasis | [423, 424] |

| Gene HGNC approved name (common name) | Chromosome position | Function in carotenoid/retinoid metabolism or signaling | Disease association (mutations associated with cardiovascular disease in bold font) | References |
|---|---|---|---|---|
| SP110, (SPECKLE D) | 2q37.1 | Retinoid signaling transcriptional regulator component of PML bodies, represses RARa signaling | • **Hepatic venoocclusive disease with immunodeficiency** | [425, 426] |
| STRA6 | 15q24.1 | Receptor for RBP4 | • Anophthalmia Microphthalmia, coloboma | [44–49, 427–431] |
| | | | • Diaphragmatic hernia | |
| | | | • **PDAC (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect)** | |
| | | | • severe short stature, and profound mental retardation, diaphragmatic eventration | |
| | | | • **Matthew-Wood syndrome** | |
| STRA8 | 7q33 | RA-responsive protein involved in gametogenesis | • Azoospermia | [432] |
| TBX1 | 22q11.21 | Retinoid signaling and regulation of RA metabolism; RA downregulates the expression of Tbx1, Loss of Tbx1 extinguishes Cyp26a1 expression | • Congenital heart defects present in del22q11.2 DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS) patients | [433] |
| | | | • Nonsyndromic patients Tetralogy of Fallot | |
| TFAP2A | 6p24 | Retinoid signaling RA-inducible member of the AP-2 family of transcription factors involved in neuronal differentiation | • Branchio-oculofacial syndrome | [434] |