HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Pharmacol Ther. 2020 January ; 205: 107415. doi:10.1016/j.pharmthera.2019.107415.

Modulation of retinoid signaling: therapeutic opportunities in organ fibrosis and repair

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Abstract

The vitamin A metabolite, retinoic acid, is an important signaling molecule during embryonic development serving critical roles in morphogenesis, organ patterning and skeletal and neural development. Retinoic acid is also important in postnatal life in the maintenance of tissue homeostasis, while retinoid-based therapies have long been used in the treatment of a variety of cancers and skin disorders. As the number of people living with chronic disorders continues to increase, there is great interest in extending the use of retinoid therapies in promoting the maintenance and repair of adult tissues. However, there are still many conflicting results as we struggle to understand the role of retinoic acid in the multitude of processes that contribute to tissue injury and repair. This review will assess our current knowledge of the role retinoic acid signaling in the development of fibroblasts, and their transformation to myofibroblasts, and of the potential use of retinoid therapies in the treatment of organ fibrosis.

Keywords

fibroblast; fibrosis; regeneration; retinoic acid; vitamin A

Introduction

Tissue injury triggers the process of wound repair which leads to the proliferation and activation of inflammatory and fibrogenic effector cells and the remodelling of the extracellular matrix (ECM). A successful repair process regenerates and restores the tissue to its original form and function. However, the process of wound healing often results in the

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deposition of excess amounts of ECM proteins, which cause scarring, increased tissue stiffness, and decreased elasticity. Increased tissue stiffness causes mechanical stress and promotes the activation of fibroblasts and myofibroblasts, thus perpetuating the process of fibrosis (Herrera, Henke, & Bitterman, 2018; Wells, 2013). Organ fibrosis is a hallmark and final outcome of many chronic disorders such as hypertrophic cardiomyopathy, heart failure, cirrhosis, and pulmonary and renal fibrosis (Ho et al., 2010; Rockey, Bell, & Hill, 2015; Wynn & Ramalingam, 2012).

Fibroblasts perform vital roles in multicellular organisms. Known for their ability to generate and remodel the ECM, fibroblasts are responsible for the stiffness and stromal architecture of tissues and organs. Fibroblasts also interact with parenchymal cells by secreting and responding to chemokines and growth factors. Tissue resident fibroblasts play important roles in the pathophysiology of wound repair and organ fibrosis. Fibroblasts can transform into myofibroblasts, which are the main fibrogenic effector cells during fibrosis. However, fibrogenic cells can also be derived via transdifferentiation of other cell types such as perivascular, epithelial, mesenchymal, and bone marrow cells. A better understanding of the cellular origins and development of fibroblasts, and of the signaling pathways that control their activity could lead to therapies to help reduce, or perhaps even reverse fibrosis.

The role of vitamin A in connective tissue function and in promoting the formation and turnover of the ECM has been appreciated since early days following its discovery (Wolbach & Howe, 1925). This wound-healing effect of vitamin A-based therapies is important in the treatment of various skin or epithelial disorders (Comptour et al., 2016; Fisher et al., 1996; Fisher & Voorhees, 1996; Griffiths et al., 1993). Vitamin A also influences fibroblast specification and differentiation and may also play a potentially important role in tissue repair and regeneration (Gudas, 2012; Maden, 2007). Alterations in vitamin A metabolism and/or signaling are frequently seen during the process of fibroblast activation in various organs. While some evidence suggests an anti-fibrotic effect of vitamin A in fibrotic conditions, there are also reports of profibrotic effects of vitamin A, as well as observations that changes in vitamin A metabolism or signaling are a consequence of fibroblast (or stellate cell) activation.

Vitamin A Uptake and Metabolism

Vitamin A is essential for a multitude of physiological processes in both fetal and postnatal life. The two main bioactive metabolites of vitamin A are all-*trans*-retinoic acid (atRA), which is a ligand of nuclear hormone receptors, and 11-*cis*-retinaldehyde, the photosensitive chromophore of rod and cone opsins required for vision (Dowling & Wald, 1960; Karrer, Morf, & Schöpp, 1931; Wald, 1933). Other pathways which will not be discussed here, lead to the formation of 13,14-dihydroretinoids or to *retro*-retinoids whose roles are currently less well understood (Buck et al., 1993; Derguini et al., 1995; Moise et al., 2008; Moise, Kuksa, Imanishi, & Palczewski, 2004). The term *retinoid* refers to either an endogenous vitamin A metabolite, or a synthetic analog that exhibits “vitamin A activity”, which initially concerned the ability to activate the retinoic acid receptor (RAR), but has more recently also included its function as a visual chromophore (Sporn, Roberts, & Goodman, 1994; Travis, Golczak, Moise, & Palczewski, 2007). AtRA is essential to ensure proper embryonic

development and a multitude of physiological processes which include reproduction, nervous system function, immune response, cell proliferation, differentiation, and apoptosis (Clagett-Dame & Knutson, 2011; Cunningham & Duester, 2015; Rhinn & Dolle, 2012; Ross, 2012). To explore the role of atRA in cell differentiation, we will first review the mechanisms by which atRA signals within target cells.

The activity of atRA is mediated through two subfamilies of nuclear receptors, RAR and its heterodimeric partner retinoid X receptor (RXR) (Giguere, Ong, Segui, & Evans, 1987; Kastner et al., 1997; Kliewer, Umesono, Mangelsdorf, & Evans, 1992; Mangelsdorf, Ong, Dyck, & Evans, 1990; Petkovich, Brand, Krust, & Chambon, 1987). AtRA only binds RAR with high affinity (low nM), however, 9-*cis*-retinoic acid (9cRA) displays high affinity for both RXR as well as RAR (Heyman et al., 1992; A. A. Levin et al., 1992). However, atRA is present in most fetal and postnatal tissues at various stages and levels, whereas 9cRA has a much more limited presence (Jones, Pierzchalski, Yu, & Kane, 2015; Kane, 2012; Kane, Chen, Sparks, & Napoli, 2005; Kane et al., 2010; Kane, Folias, Wang, & Napoli, 2008; Kane & Napoli, 2010). RAR and RXR are each encoded by three related genes (α, β, or γ). The resulting three different subtypes of RAR, or RXR, activate both overlapping as well as distinct sets of genes, and display significant redundancy *in vivo* (Ghyselinck et al., 1997; Lohnes et al., 1993; Lohnes et al., 1994; Lufkin et al., 1993). Unliganded RAR/RXR heterodimers are bound to retinoic acid response elements (RARE) found within enhancer regions of target genes. Ligand binding induces specific conformational changes within RAR/RXR to allow the dissociation of repressor complexes and the association of co-activator complexes (Chandra et al., 2017). Other atRA-signaling modes which have been proposed include both non-genomic signaling of atRA-RAR, as well as atRA-signaling through alternate nuclear hormone receptors (N. Chen & Napoli, 2008; N. Chen, Onisko, & Napoli, 2008; Kruse et al., 2008; Shaw, Elholm, & Noy, 2003; X. E. Zhou et al., 2011).

RAR/RXR signaling is governed by the availability of atRA ligand. We will briefly discuss the pathways that lead to the formation and breakdown of atRA and refer the reader to more in-depth recent reviews (Figure 1) (Napoli, 2017; Shannon, Moise, & Trainor, 2017). In brief, atRA is formed from dietary precursors consisting of preformed vitamin A (all-*trans*-retinol, or retinyl esters - REs) and provitamin A carotenoids defined as having at least one unsubstituted β-ionone ring. Dietary REs are hydrolyzed in the intestinal lumen and then re-esterified mainly by lecithin:retinol acyltransferase (LRAT), and to a lesser extent by enzymes with acyl CoA:retinol acyltransferase activity (Ables et al., 2012; Batten et al., 2004; L. Liu & Gudas, 2005; O'Byrne et al., 2005; Ong, Kakkad, & MacDonald, 1987; Ruiz et al., 1999; Wongsiriroj et al., 2008; Yen, Monetti, Burri, & Farese, 2005). Newly formed REs are then packaged in chylomicrons and secreted into the lymphatic system for distribution to peripheral sites such as adipose tissue where a percentage of REs are hydrolyzed and taken up via lipoprotein lipase (Blaner et al., 1994; van Bennekum et al., 1999). The bulk of REs remain associated with chylomicron remnants to be cleared by the liver and ultimately stored in hepatic stellate cells (HSCs) (Blaner et al., 2016).

Most of the absorbed provitamin A carotenoids are converted to retinol in the intestine and then follow the same fate as retinoids derived from preformed vitamin A. Intestinal absorption of provitamin A carotenoids requires the scavenger receptor B type 1 (SCARB1)

(Kiefer, Sumser, Wernet, & Von Lintig, 2002; Toomey et al., 2017; Voolstra et al., 2006). The enzyme beta-carotene dioxygenase 1 (BCO1) coverts both β-carotene and β-apo-10′-carotenal to all-*trans*-retinaldehyde via oxidative cleavage (Hessel et al., 2007; Kiefer et al., 2001; Lampert et al., 2003; von Lintig, Dreher, Kiefer, Wernet, & Vogt, 2001; von Lintig & Vogt, 2000; von Lintig & Wyss, 2001). Asymmetric cleavage via beta-carotene dioxygenase 2 (BCO2) permits the utilization of asymmetric provitamin A carotenoids for atRA production (Kelly et al., 2018; Kiefer et al., 2001). Intestinal absorption and conversion of provitamin A carotenoids is under tight regulation via feedback mechanisms. AtRA produced in enterocytes activates RAR/RXR which upregulates the expression of the intestinal-specific homeobox domain transcription factor (ISX). In turn, ISX suppresses the expression of *Bco1* and *Scarb1,* thereby restricting the absorption and conversion of provitamin carotenoids to vitamin A (Bachmann et al., 2002; Lobo et al., 2013; Lobo et al., 2010; Seino et al., 2008; M. A. Widjaja-Adhi, Lobo, Golczak, & Von Lintig, 2015; M. A. K. Widjaja-Adhi et al., 2017). A non-negligible amount of provitamin A carotenoids, however, enter the circulation and are delivered and stored in an uncleaved form in liver, fat and other organs. These carotenoids can be cleaved to retinal to sustain retinol or atRA production during both adult as well as fetal life (Y. K. Kim et al., 2011; Lampert et al., 2003; Mora et al., 2004; I. Shmarakov et al., 2010).

Uptake of retinol by intestinal and liver cells is facilitated by a cross membrane gradient established through the sequestration of retinol by intracellular retinol binding proteins and the esterification of retinol by LRAT. Intracellular retinol binding proteins also shield retinol (and retinal) from non-specific reactions (Boerman & Napoli, 1991; Lapshina, Belyaeva, Chumakova, & Kedishvili, 2003). Cellular retinol binding protein 1 (CRBP1; HUGO gene nomenclature committee (HGNC) approved symbol:RBP1) has been shown to be important in regulating the uptake, storage and metabolism of vitamin A in most tissues other than the intestine (Ghyselinck et al., 1999; W. Jiang & Napoli, 2012; Kane, Bright, & Napoli, 2011; Kane, Folias, et al., 2011; Matt et al., 2005; Pierzchalski et al., 2014; Pierzchalski, Yu, Norman, & Kane, 2013). Meanwhile, CRBP2 (HGNC:RBP2) is essential for vitamin A uptake and homeostasis in the intestine, and CRBP3 (HGNC: RBP5) has been reported to have functions in mammary metabolism of vitamin A and incorporation of REs in milk (E et al., 2002; Herr et al., 1993; Kakkad & Ong, 1988; M. S. Levin & Davis, 1997; McDonald et al., 2012; Piantedosi, Ghyselinck, Blaner, & Vogel, 2005; Vogel et al., 2001; Zizola, Schwartz, & Vogel, 2008). Unbound CRBP1 has been reported to have an additional regulatory influence on atRA homeostasis through inhibition and stimulation of specific enzymes in order to control flux through the vitamin A pathway (Boerman & Napoli, 1991; Herr & Ong, 1992; Lapshina et al., 2003). The enzymes, transporters and binding proteins responsible for the uptake, storage and conversion of retinol to atRA are regulated by vitamin A status and/or by retinoid signaling (Bouillet et al., 1995; Bouillet et al., 1997; Mangelsdorf et al., 1991; Sapin et al., 2000; Taneja et al., 1995; L. Wu & Ross, 2010; Zolfaghari & Ross, 2002).

Storage forms of vitamin A consist of retinyl esters found primarily in HSCs, and also in adipose tissue, lung, retinal pigmented epithelial cells and kidney. These stores are hydrolyzed to generate retinol to meet tissue demands. Retinol is secreted by hepatocytes bound to serum RBP4 which forms a complex with transthyretin (Kanai, Raz, & Goodman,

1968). RBP4 binds to its receptor, stimulated by retinoic acid 6 (STRA6), a membrane protein which mediates both the import and export of retinol from cells (Amengual et al., 2014; Y. Chen et al., 2016; Isken et al., 2008; Kawaguchi et al., 2007; Kawaguchi, Zhong, Kassai, Ter-Stepanian, & Sun, 2012; Muenzner et al., 2013). STRA6 is expressed in many important retinoid target tissues such as eye, choroid plexus, heart, and placenta but not by the liver which expresses an alternate RBP4-receptor (Alapatt et al., 2013).

Synthesis of atRA from retinol begins with the reversible oxidation of retinol to retinaldehyde mediated primarily by NAD(P) -dependent microsomal, short-chain retinol dehydrogenases/ reductases (SDR). Given the abundance of the NAD(P) dinucleotide cofactors under normal cellular conditions, SDR enzymes with NAD-specificity catalyze oxidation of retinol, while NADP-dependent enzymes catalyze reduction of retinaldehyde. SDR oxidoreductases are part of one of the largest superfamily of enzymes known, with over 70 members in the human genome, and are responsible for transformation of many endogenous and exogenous compounds (Persson et al., 2009). *In vitro*, many SDR enzymes show activity with retinoids, but relatively few have been shown to significantly affect retinoid metabolism or signaling when ablated in mice (Kedishvili, 2016; Parker & Crouch, 2010). The NAD-dependent retinol dehydrogenase 10 (RDH10) is the main enzyme responsible for the oxidation of retinol during development (Cunningham, Chatzi, Sandell, Trainor, & Duester, 2011; Rhinn, Schuhbaur, Niederreither, & Dolle, 2011; Sandell, Lynn, Inman, McDowell, & Trainor, 2012; Sandell et al., 2007). The NADP-dependent enzyme dehydrogenase/ reductase 3 is primarily responsible for the reduction of retinaldehyde to prevent excess formation of atRA (Billings et al., 2013; Feng, Hernandez, Waxman, Yelon, & Moens, 2010; Haeseleer, Huang, Lebioda, Saari, & Palczewski, 1998; Kam et al., 2013). Interestingly, RDH10 and DHRS3 form a functional heterodimer which by carrying out coupled antagonistic activities ensures atRA homeostasis (Adams, Belyaeva, Wu, & Kedishvili, 2014; Belyaeva, Adams, Wu, & Kedishvili, 2017). In addition to RDH10 and DHRS3, other SDRs acting on retinoids have been shown to affect retinoid metabolism *in vivo* in postnatal visual and non-visual tissues (Kedishvili, 2016; Parker & Crouch, 2010). It is also possible that other enzyme families such as medium-chain dehydrogenases and aldo-keto reductases (AKR) participate in retinol oxidation or retinal reduction, respectively, under some circumstances (Kumar, Sandell, Trainor, Koentgen, & Duester, 2012; Porte et al., 2013).

All-*trans*-retinaldehyde undergoes irreversible conversion to atRA by means of cytosolic retinal dehydrogenases (RALDH) enzymes, RALDH1, 2, and 3 of the aldehyde dehydrogenase 1A (ALDH1A) family. RALDH enzymes have distinct expression patterns and, consequently, have tissue specific roles in atRA production. RALDH2 (ALDH1A2) is the main enzyme responsible for atRA synthesis during early embryogenesis, in the fetal heart and liver, in the immune system and most tissues; meanwhile RALDH3 (ALDH1A3) is expressed in developing sensory systems (Dupe et al., 2003; Mic, Molotkov, Fan, Cuenca, & Duester, 2000; Niederreither, Subbarayan, Dolle, & Chambon, 1999; Paschaki et al., 2013; Romand et al., 2006). RALDH1, on the other hand, appears to play a role in testes and adipose tissue, however, the latter role may not be contingent on atRA synthesis (Arnold et al., 2015; Yang et al., 2017). Independently of ALDH1A enzymes, the cytochrome P450 enzyme CYP1B1 was also proposed to contribute to atRA production (Chambers, Wilson,

Maden, & Lumsden, 2007; F. Li, Zhu, & Gonzalez, 2017; Maguire, Larsen, Foong, Tanumihardjo, & Jefcoate, 2017).

Retinol or atRA are catabolized mainly by a number of cytochrome (Cyp) P450 enzymes found in microsomal membranes (S. S. Abu-Abed et al., 1998; MacLean et al., 2001; Taimi et al., 2004; Topletz, Zhong, & Isoherranen, 2019; J. A. White et al., 1997; J. A. White et al., 1996; J. A. White et al., 2000). Within cells, atRA is found bound to cellular retinoic acid binding proteins, CRABP1 or CRABP2 (Napoli, 2017). CRABPs play important roles in modulating atRA signaling by channelling atRA towards P450 enzymes for oxidation, or towards RAR for signaling (Cai et al., 2012; Delva et al., 1999; Fiorella & Napoli, 1994; Nelson et al., 2016; Zhong, Ortiz, Zelter, Nath, & Isoherranen, 2018). Oxidized atRA metabolites, such as 4-oxo-atRA, do not appear to play a role in activating RAR during embryonic development, but it is possible that they carry out signaling roles in other settings (Niederreither et al., 2002; Pijnappel et al., 1993; Topletz et al., 2015). Through their distinct expression profiles, P450 enzymes of CYP26 family, namely CYP26A1, B1 and C1 control signaling by atRA in various tissues (S. Abu-Abed et al., 2002; Pennimpede et al., 2010; Reijntjes, Gale, & Maden, 2004; Tahayato, Dolle, & Petkovich, 2003). CYP26 enzymes also display regio- and stereospecific preference for atRA oxidation. CYP26A1 and B1 carry out initial oxidation of atRA, while CYP26C1 carries out secondary oxidation reactions (Topletz et al., 2012; Zhong et al., 2018). *In vivo*, ablation of CYP26A1 or CYP26B1 leads to embryonic lethality, meanwhile, CYP26C1-deficient mice are viable (S. Abu-Abed, 2001; Uehara et al., 2007; Yashiro et al., 2004). Other P450 enzymes contribute to atRA metabolism including CYP3A7 which is expressed in the fetal liver (Shimshoni et al., 2012; Topletz et al., 2019). AtRA metabolism is extensively autoregulated to ensure its homeostasis. Enzymes involved in atRA synthesis, such as RDH10 and RALDH2 are downregulated by atRA, while those whose actions result in reduction in the levels of atRA, such as CYP26A1 and DHRS3, are upregulated by atRA (Loudig et al., 2000; Sandell et al., 2012; Strate, Min, Iliev, & Pera, 2009; J. A. White et al., 1997; R. J. White, Nie, Lander, & Schilling, 2007).

Role of AtRA in the Development and Function of Cardiac Fibroblasts

Cardiovascular disease including ischemic (coronary) heart disease, cerebrovascular disease (stroke), and hypertension affects 11.5% of American adults and is the leading cause of death (Benjamin et al., 2018). Despite gains in the prevention and survival following a myocardial infarct in the last few decades, there is increased prevalence of chronic heart conditions such as heart failure in our aging population. This trend is projected to increase by 46% from 2012 to 2030 resulting in >8 million Americans living with heart failure (Heidenreich et al., 2013). Excess deposition of ECM by cardiac fibroblasts is a prominent feature of heart failure. Given that treatment options for heart failure are still limited, it is important to explore the factors that control the formation and function of cardiac fibroblasts as potential therapeutic targets in heart disease.

As the first organ to form, the embryonic heart is required to accommodate the increasing needs of the embryo. The cardiac fibroblast, one of the predominant cardiac cell populations, carries out essential roles in the development and function of the vertebrate heart. Cardiac

fibroblasts ensure that the heart can meet these demands throughout the life of an organism by altering the cardiac ECM in response to changes in the mechanical load placed upon the heart. To further support heart function, fibroblasts promote cardiomyocyte proliferation (Ieda et al., 2009), reinforce the coronary vessels and restrict electrical conduction to allow for the sequential contraction of atria and ventricles (Gourdie, Dimmeler, & Kohl, 2016). Following injury, resident cardiac fibroblasts become activated (myofibroblasts) and protect the heart by creating a scar. However, this process can also lead to the increased stiffness, and reduced compliance associated with heart disease (Kanisicak et al., 2016; van Putten, Shafieyan, & Hinz, 2016). Despite their significant and multifaceted roles in heart biology, we still know very little regarding the mechanisms that guide the embryonic development of cardiac fibroblasts. We review recent studies that implicate atRA as an important signaling molecule in the development of cardiac fibroblasts.

The majority of adult cardiac fibroblasts and myofibroblasts are believed to be derived from the embryonic epicardium. The developmental origin of cardiac fibroblasts was demonstrated using dye- and retroviral labeling of the proepicardium in chicken embryos and further supported by the usage of lineage-tracing of epicardial-derived cells in transgenic mouse models (Mikawa & Fischman, 1992; Moore-Morris et al., 2018; Tallquist & Molkentin, 2017). The embryonic epicardium originates from the proepicardium, which forms transiently as an outgrowth of the septum transversum. Proepicardial cells migrate to envelope the heart and thereby establish the visceral pericardial layer, commonly referred to as the epicardium. Proepicardial cells also find their way into the mesenchymal subepicardial space. In response to various stimuli, epicardial cells and subepicardial cells undergo epithelial-to-mesenchymal transition (EMT), migrate and colonize the myocardium where some differentiate into interstitial fibroblasts, while others respond to endothelial-derived signals and transform into mural cells and perivascular fibroblasts (Sharma, Chang, & Red-Horse, 2017). Several factors have been identified as critical for epicardial EMT, including neurofibromin 1 (Nf1), Wilms tumour 1 (Wt1), transforming growth factor-β (TGF-β), platelet-derived growth factor receptor (PDGFR), as well as atRA (Baek & Tallquist, 2012; Mellgren et al., 2008; Smith, Baek, Sung, & Tallquist, 2011; von Gise & Pu, 2012; S. Wang, W. Huang, et al., 2018; S. Wang, J. Yu, et al., 2018).

AtRA-signaling plays critical roles during early heart development (Stefanovic & Zaffran, 2017; Xavier-Neto et al., 2015). Recently several lines of evidence suggest that atRA-signaling also plays a critical role in the regulation of epicardial development during late gestation. The embryonic epicardium expresses atRA metabolic enzymes, binding proteins and receptors such as *Rbp1*, *Rdh10*, *Raldh2* (*Aldh1a2*), *Cyp26a1*, *Dhrs3*, *Rara*, *Rarb*, *Rarg, Rxra,* and *Stra6*, and carries out active atRA-signaling (Brade et al., 2011; Guadix et al., 2011; Moss et al., 1998; Perez-Pomares et al., 2002; S. Wang, W. Huang, et al., 2018; S. Wang, J. Yu, et al., 2018; Xavier-Neto, Shapiro, Houghton, & Rosenthal, 2000). In mouse embryos excess or deficiency of atRA during late gestation, *Rxra*-deficiency or the expression of dominant-negative form of RAR caused similar defects in the development of the coronary vasculature and/or the growth of the myocardial compact zone (Gruber et al., 1996; Lin et al., 2010; Merki et al., 2005; Shen et al., 2015; Sucov et al., 1994; S. Wang, W. Huang, et al., 2018). It has recently been demonstrated that epicardial atRA-signaling promotes cytoskeletal rearrangement, EMT and migration of epicardial cells and we

identified the Ras homolog gene family, member A (RhoA)-signaling pathway to be required for the atRA-induced cytoskeletal remodeling of epicardial cells (Guadix et al., 2011; von Gise et al., 2011; S. Wang, W. Huang, et al., 2018; S. Wang, J. Yu, et al., 2018).

In addition to epicardial EMT, atRA also controls the differentiation of epicardial-derived precursor cells (EPDCs) into vascular smooth muscle cells and fibroblasts (Azambuja et al., 2010; Braitsch, Combs, Quaggin, & Yutzey, 2012; von Gise et al., 2011; S. Wang, W. Huang, et al., 2018; S. Wang, J. Yu, et al., 2018). Having migrated into the myocardium EPDCs differentiate primarily into coronary vascular smooth muscle cells (VSMCs) and fibroblasts with minor contributions to other lineages (Smits, Dronkers, & Goumans, 2018). The embryonic epicardium and the proepicardial organ from which it originates accommodate a heterogeneous population of progenitor cells which follow distinct signaling pathways to achieve various developmental fates (Katz et al., 2012; Plavicki et al., 2014). A subset of proepicardial, epicardial cells and EPDCs express the transcription factor 21 (Tcf21; also known as Pod1 or epicardin), a member of the basic helix-loop-helix (bHLH) family of transcription factors whose expression in the epicardium is induced by atRA (Braitsch et al., 2012; Quaggin, Vanden Heuvel, & Igarashi, 1998; Robb et al., 1998). TCF21 is important in proepicardial specification and cardiac fibroblast development (Acharya et al., 2012; Braitsch et al., 2012; Kanisicak et al., 2016; Tandon, Miteva, Kuchenbrod, Cristea, & Conlon, 2013; Xiang, Fang, & Yutzey, 2017). Like TCF21, atRA suppresses the expression of VSMC markers in cultured chick proepicardium and embryonic hearts (Azambuja et al., 2010; Braitsch et al., 2012). Therefore, atRA acting via TCF21, favors the formation of cardiac fibroblasts and thus plays an important role in the formation and fate specification of EPDCs. In addition to signaling through TCF21, atRA also interacts with fibroblast growth factor (FGF) signaling which regulates multiple aspects of cardiac development including epicardial EMT, and cardiac fibroblast development (Lavine et al., 2005; Pennisi & Mikawa, 2009; Vega-Hernandez, Kovacs, De Langhe, & Ornitz, 2011; S. Wang, W. Huang, et al., 2018).

Though, the epicardium constitutes the major source of ventricular fibroblasts, the endocardium also contributes to a significant percentage of cardiac fibroblasts (reviewed in (Y. Li, Lui, & Zhou, 2018). Similar to the epicardium, endocardial cells undergo endothelial-to-mesenchymal transition (endo-MT) and contribute to the formation of the atrioventricular valves. Using lineage tracing technique, Moore-Morris *et al.* reported that about 18% of fibroblasts in the myocardium originate from Tie2-positive endocardial population (Moore-Morris et al., 2014). These endocardial-derived fibroblasts primarily populate the interventricular septum. The exact influence of atRA on the formation of endocardial-derived fibroblasts has, so far, not been examined but atRA was previously reported to regulate endo-MT by regulating the expression of *Tbx2* and *Tgfβ2*, both known to be critical morphogens for endo-MT and valve formation (Sakabe, Kokubo, Nakajima, & Saga, 2012).

Extra-cardiac sources, such as the neural crest, also contribute to a small percentage of cardiac fibroblasts. Neural crest is a transient migratory cell population whose derivatives can be found in craniofacial cartilage and bone, muscles and connective tissues of the face and neck, heart and endocrine glands, skin and peripheral nervous system (Mayor & Theveneau, 2013). Following induction in the neural plate, neural crest cells undergo EMT

to migrate along specific paths to colonize target organs in response to guidance molecules and morphogens which include atRA. In the heart, cardiac neural crest cells contribute to the septation of the outflow tract, the aortic and pulmonary valves, sympathetic and parasympathetic innervation of the heart, and differentiate into VSMCs and cardiac fibroblasts found in the proximal coronary artery and outflow tract, respectively (Ali et al., 2014; Arima et al., 2012; Odelin et al., 2018). AtRA signaling plays critical roles in fate decision, migration and survival of neural crest cells (Uribe, Hong, & Bronner, 2018). Therefore, it is plausible that atRA may also regulate the formation of neural crest-derived cardiac fibroblasts *in vivo*.

Recently, a potential interaction of atRA- and the Hippo-signaling pathways during the development of cardiac fibroblasts has been revealed in studies by Xiao *et al.* (Y. Xiao et al., 2018) (depicted in Figure 2).. The evolutionarily conserved Hippo-signaling pathway controls organ size and patterning and plays important roles in heart development and regeneration (J. Wang, Liu, Heallen, & Martin, 2018). When the Hippo-pathway is activated (Hippo-ON), the mammalian STE20-like kinases (Mst1/2) and large tumor suppressor kinases (Lats) 1/2 cascade cause the phosphorylation, cytoplasmic retention, and degradation of the transcriptional regulators Yes-associated protein (Yap) and transcriptional coactivator with PDZ-binding motif (Taz). When the Hippo kinases are not active (Hippo-OFF), nuclear-localized Yap/Taz respond to mechanical tension by binding the transcriptional factors TEA-domain protein (TEAD) to activate gene expression programs associated with apoptosis, growth or differentiation. Mechanical stress is a major inducer of Yap/Taz-signaling and a physiologically relevant stimulus during heart development (Dupont et al., 2011; Majkut, Dingal, & Discher, 2014). In the embryonic epicardium ablation of Yap/Taz results in impaired epicardial EMT (Singh et al., 2016), meanwhile, constitutively active Yap blocks fibroblast differentiation (Y. Xiao et al., 2018). Fibroblast precursors that accumulate in the presence of active Yap express *Dhrs3*, which is a direct target of TEAD. In light of evidence that atRA promotes fibroblast differentiation (Azambuja et al., 2010; Braitsch et al., 2012), and that *Dhrs3* functions as a negative regulator of atRA synthesis (Billings et al., 2013; Feng et al., 2010; Kam et al., 2013), Xiao *et al.* proposed a model by which active Yap suppresses fibroblast differentiation of EPDCs by attenuating atRA signaling. Since Yap is activated by mechanical stress in epicardial cells (Y. Xiao et al., 2018), these results also imply that mechanical stress modulates atRA-signaling and consequently fibroblast differentiation in EPDCs (Fig. 2). This model provides a mechanistic explanation of how form follows function, whereby mechanical stress guides cell fate decisions that give rise to fibroblasts which shape the ECM of the heart. However, many of the details of the putative interaction of Yap/Taz and atRA-signaling remain to be elucidated.

The main role of cardiac fibroblasts being to form ECM and provide structural and mechanical support to the heart, it stands to reason that their development and ECM production is influenced by mechanical tension (Herum, Lunde, McCulloch, & Christensen, 2017; van Putten et al., 2016). Transduction of mechanical signals (mechanotransduction) controls the differentiation of many cell types including VSMCs and fibroblasts (Hinz, Celetta, Tomasek, Gabbiani, & Chaponnier, 2001), and plays a crucial role in both heart development and repair (Majkut et al., 2013; Poelmann & Gittenberger-de Groot, 2018; van Putten et al., 2016). Despite the long-established role of atRA-signaling as a differentiation

signal, its potential for involvement in ECM stiffness-dependent lineage specification has only recently come to light. In addition to aforementioned evidence that expression of retinaldehyde reductase *Dhrs3* is induced by the mechanoregulator Yap/TEAD (Y. Xiao et al., 2018), it has been shown that mechanical stress regulates the nuclear localization of RARγ via lamin-A (Swift et al., 2013). Reciprocally, atRA regulates the cellular response to mechanical stress by controlling the expression of lamin-A. This interaction is potentially relevant in heart disease since mutations in lamin-A are often associated with dilated cardiomyopathy (Tesson et al., 2014).

The regenerative capacity of heart after injury varies between species. In mammals, the heart is one of the least regenerative organs (Bergmann et al., 2009; Senyo et al., 2013). Cardiac injury such as myocardial infarction (MI) leads to ventricular remodeling, including ventricular hypertrophy, and myofibroblast pool expansion which causes deposition of collagen and scarring, reducing compliance and negatively affecting the conductive and contractile functions of the heart (Ongstad & Gourdie, 2016). However, in some cases, a robust cardiac regenerative capacity can be found. The hearts of zebrafish, and even mouse and pig neonates can regenerate with minimal scarring (Porrello et al., 2011; Poss, Wilson, & Keating, 2002; Zhu et al., 2018) by relying on cardiomyocyte regeneration from pre-existing diploid cardiomyocytes (Gonzalez-Rosa et al., 2018; Y. Li, He, et al., 2018; Patterson et al., 2017; Senyo et al., 2013), and by being sustained through collateral artery growth (Das et al., 2019; Marin-Juez et al., 2016). Based on limited evidence, it seems that the same is true in the case of human newborn hearts which are mitotically active and can regenerate (Haubner et al., 2016; Macmahon, 1937).

The cardiac repair program relies on cell precursors and trophic factors derived from the epicardium. In the healthy adult heart, the epicardium acts as a simple mesothelial layer of the serous pericardium that protects and reduces the friction of the heart (as reviewed in (Blom & Feng, 2018; Cao & Poss, 2018; Limana, Capogrossi, & Germani, 2011; Smits et al., 2018). Heart injury induces the reactivation of epicardial EMT to give rise to VSMCs to help restore vascularization and support heart repair (Braitsch, Kanisicak, van Berlo, Molkentin, & Yutzey, 2013; Kikuchi, Holdway, et al., 2011; Lepilina et al., 2006; Marin-Juez et al., 2016; Smart et al., 2011). Adult EPDCs generated in response to injury also contribute to the formation of new fibroblasts, which can differentiate to myofibroblast and lead to cardiac fibrosis (Duan et al., 2012; Ruiz-Villalba et al., 2015). However, the preponderance of activated myofibroblasts are derived from pre-existing resident cardiac fibroblasts developed from EPDCs during embryogenesis ((Ali et al., 2014; Kanisicak et al., 2016; Moore-Morris et al., 2018; Moore-Morris et al., 2014). Despite earlier reports that the epicardium also contributes to the formation of new cardiomyocytes in the regenerating heart, more recent studies suggest that adult EPDCs are limited to non-myocardial fates (Kikuchi, Gupta, et al., 2011; Y. Li, He, et al., 2018). Injury also induces the secretion of epicardial- and fibroblast-derived mitogens such as IGF2, thymosin-β4, follistatin-like 1 (Fstl1), which promote myocardial growth, VSMCs differentiation, fibroblast migration and proliferation (Y. Huang et al., 2013; Maruyama et al., 2016; Rossdeutsch, Smart, Dube, Turner, & Riley, 2012; Smart et al., 2011; Smart et al., 2007; K. Wei et al., 2015; B. Zhou et al., 2011).

There is emerging evidence of the involvement of atRA-signaling in epicardial activation and its response to injury. Like other epicardial developmental pathways, atRA production and signaling re-emerge in the epicardium activated by heart injury or disease (Bilbija et al., 2014; Bilbija et al., 2012; Kikuchi, Holdway, et al., 2011). In mice subjected to myocardial ischemia–reperfusion injury, there were increases in both cardiac retinol levels and in the levels of expression of RAR-target genes in cardiac fibroblasts from the peri-infarct area (Bilbija et al., 2012). *In vitro*, atRA also suppresses cardiomyocyte hypertrophic responses (J. Wu, Garami, Cheng, & Gardner, 1996; M. D. Zhou, Sucov, Evans, & Chien, 1995). In mouse models of obesity, atRA-treatment prevented fibrosis and cardiomyocyte apoptosis (Manolescu et al., 2014). Conversely, in rodent models of myocardial infarction, vitamin A insufficiency was associated with adverse ventricular remodeling (Asson-Batres et al., 2016; Minicucci et al., 2010). These observations are also supported by evidence that mice deficient in β-carotene-15,15'-dioxygenase (BCO1), the enzyme required to convert provitamin A carotenoids to retinol, also exhibit systolic dysfunction (Hessel et al., 2007; S. A. Lee et al., 2014).

It is difficult to establish the roles of atRA in heart regeneration in adult mice since this process is not efficient in adult mammals. However, a pro-regenerative role of atRA in the heart was demonstrated in zebrafish. Transgenic expression of *Cyp26a1*, or of a dominant-negative RAR in zebrafish led to decreased atRA-signaling and was associated with a dramatic reduction in cardiomyocyte proliferation during regeneration (Kikuchi, Holdway, et al., 2011). Interestingly, atRA production is rapidly initiated in both endocardium and epicardium in the injured zebrafish heart. However, in the injured mouse adult heart atRA production can only be detected in the epicardium. It is not clear if the absence of endocardial expression of *Raldh2* in mice has any bearing on their reduced cardiac regenerative capacity.

While epicardial reactivation contributes to heart regeneration in zebrafish, it may potentially have unfavourable consequences in other species. During both embryogenesis and epicardial reactivation, expression of *Raldh2* and *Wt1* is controlled by the transcription factor C/EBPβ which recruits the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex (G. N. Huang et al., 2012; Vieira et al., 2017). Interestingly, expression of a dominant negative C/ EBPβ in mouse epicardium not only abrogated the expression of *Raldh2* and *Wt1* but also led to increased ejection fraction and decreased fibrosis following ischemia-reperfusion (G. N. Huang et al., 2012). More recent evidence indicates that depletion of EPDCs in the adult mouse heart led to improved function and reduced fibrosis following myocardial infarction (Quijada et al., 2019). Similarly, inactivation of cardiac fibroblasts limited the extent of fibrosis following cryoinjury in zebrafish (Sánchez-Iranzo et al., 2018). Therefore, from a therapeutic standpoint, increased atRA signaling in adult epicardial cells following cardiac injury could have both positive effects by supporting neovascularization and myocardial growth, as well as negative effects in promoting cardiac fibrosis.

Role of AtRA in the Development and Function of Hepatic and Pancreatic Stellate Cells

The liver is the primary storage site for vitamin A in the body. REs accumulate in lipid inclusion bodies within HSCs (reviewed in (Friedman, 2008)). To meet tissue retinoid needs, REs are hydrolyzed and transferred to hepatocytes to be released in the circulation as retinol complexed with its serum binding protein (RBP4). Upon liver injury or disease, HSCs become activated and adopt a myofibroblast-phenotype (Kent et al., 1976). HSC-derived myofibroblasts are a major contributor to the process of liver scarring and fibrosis though secretion of ECM components (Iwaisako et al., 2014). Developmentally, HSCs originate from septum transversum mesenchyme (Asahina, Zhou, Pu, & Tsukamoto, 2011; Ijpenberg et al., 2007; Pérez-Pomares et al., 2004), that also gives rise to proepicardium and sinus venosus.

Vitamin A metabolism and atRA signaling play important roles in the development, function and pathology of HSCs. Coelomic epithelial progenitors lining the liver lobes, delaminate, migrate and differentiate into HSCs and liver VSMCs (Asahina et al., 2009; Pérez-Pomares et al., 2004). As in the case of epicardial development, this process requires Wt1, RXRa and atRA-signaling in both mice, and avian models (Ijpenberg et al., 2007). However, a chemical screen for disruptors of HSC differentiation identified RAR and RXR agonists as having opposite effects in preventing or promoting HSC formation in zebrafish, respectively (Yin, Evason, Maher, & Stainier, 2012). Therefore, more studies are needed to identify the exact mechanism by which atRA signaling affects the development of HSCs.

The most salient feature of quiescent HSCs is the presence of REs-containing lipid droplets recognized based on gold chloride staining and/or associated fluorescence (Nagy et al., 1997; Wake, 1971). LRAT is the main enzyme responsible for the esterification of retinol within HSCs and a specific marker of HSCs within the liver (Batten et al., 2004; Mederacke et al., 2013; O'Byrne et al., 2005). As HSCs become activated, they remodel their lipid pools of REs and triacylglycerols through cycles of hydrolysis and acylation. The net result of HSC activation is that lipid droplets become smaller, the levels of unesterified retinol increase, and the acyl composition of triacylglycerols shifts towards a higher percentage of polyunsaturated fatty acids (Ajat et al., 2017; Testerink et al., 2012; Tuohetahuntila et al., 2017). Consequently, during the progression of liver disease, hepatic retinoid stores diminish significantly (Leo & Lieber, 1982). Chronic alcohol consumption-induced loss of hepatic retinoid stores has been attributed to an initial mobilization of retinoid from hepatic towards extrahepatic storage sites followed by increased catabolism and excretion of retinoids (Clugston, Huang, & Blaner, 2015). A similar decrease in liver retinoids is associated with obesity and related conditions such as non-alcoholic fatty liver disease (NAFLD) (Trasino, Tang, Jessurun, & Gudas, 2015) reviewed in (Saeed, Dullaart, Schreuder, Blokzijl, & Faber, 2017).

It is not clear if loss of hepatic retinoids is a cause or consequence of HSC activation. While retinoid loss is invariably associated with HSC activation, a recent study suggests that loss of retinoid-laden lipid droplets occurs only after HSC activation and transdifferentiation into myofibroblasts, and more importantly, that the levels of REs within HSCs remain steady during the initial phase of HSC activation (Jophlin, Koutalos, Chen, Shah, & Rockey, 2018).

It is not clear whether atRA levels or atRA-signaling change during HSC activation since atRA levels do not mirror the changes in the concentrations of hepatic REs (Blaner, 2019).

There is evidence supporting an anti-fibrotic role of hepatic atRA. Pharmacological studies have shown that atRA or RAR agonists reduced HSC proliferation and activation and led to diminished steatosis in mice (Davis, Kramer, & Davidson, 1990; Trasino, Tang, Jessurun, & Gudas, 2016). Also, expression of a dominant negative RAR in hepatocytes is associated with steatohepatitis (Yanagitani et al., 2004). Given a better knowledge of HSC specific markers, the approach of specifically targeting a dominant negative RAR in activated HSCs is now feasible (Mederacke et al., 2013). However, the role of atRA-signaling in suppressing the activation of HSCs was questioned in some studies. For example, mRNA levels of RARs were undetectable in activated HSCs, meanwhile neither retinol nor atRA could prevent HSC activation (Milliano & Luxon, 2005). Moreover, RARα protein was largely found in insoluble aggregates in activated HSCs (Mezaki et al., 2009). At the same time, absence of REs within HSCs of *Lrat*-deficient mice does not promote HSC activation or liver fibrosis (Kluwe et al., 2011). The issue of whether retinoids promote or counteract HSC activation is made even more complicated by the fact that high doses of dietary vitamin A and retinoid-based therapies carry a known risk of hepatotoxicity characterized by HSC activation and fibrosis (Nollevaux et al., 2006). At the same time, dietary vitamin A and hepatic retinyl ester stores are vital for liver health (Aguilar et al., 2009).

While we still have a limited understanding of the involvement of atRA in HSC activation, several studies suggest that atRA might play a role in the response of HSCs to mechanical stress. HSCs activation and transdifferentiation to myofibroblasts is influenced by matrix stiffness (Olsen et al., 2011). In turn, liver fibrosis is associated with significant increase in tissue stiffness. Similar to the effects of mechanical stress on epicardial cells, there is evidence that HSCs exposed to mechanical stress undergo changes in retinoid gene expression which are consistent with decreased atRA-signaling (Yi, Zhang, Tang, & Zhu, 2015). Reciprocally, atRA signaling downregulates the expression of myosin light chain 2 (MLC-2) and negatively regulates myosin-driven migration of HSCs towards substrates of higher stiffness (durotaxis) (Cortes, Lachowski, et al., 2019). Yap-mediated mechanotransduction plays a role in multiple liver pathologies associated with HSCs activation, liver fibrosis and tumorigenesis as well as liver regeneration (Cox et al., 2016; Lu et al., 2010; Zhubanchaliyev, Temirbekuly, Kongrtay, Wanshura, & Kunz, 2016). Given the potential crosstalk of Yap and atRA-signaling observed in epicardial cells, and of the central role for Yap in the mechano-regulation, it would be important to further explore the role of atRA in Yap-mediated activation of HSCs (Cortes, Sarper, et al., 2019; Mannaerts et al., 2015).

HSC activation and fibrosis can in many instances resolve through senescence or apoptosis of activated HSCs, or through reversion of myofibroblasts to an inactive state (Cordero-Espinoza & Huch, 2018; Kisseleva et al., 2012; Krizhanovsky et al., 2008). It was observed that hepatic retinoid stores, atRA-signaling and RXRα were positively correlated with hepatocyte proliferation and liver regeneration following hepatectomy (Imai, Jiang, Kastner, Chambon, & Metzger, 2001; H. X. Liu, Ly, Hu, & Wan, 2014; I. O. Shmarakov, Jiang, Yang, Goldberg, & Blaner, 2013). Potential roles of atRA-signaling in the resolution of fibrosis

have also been proposed by others, therefore, this exciting possibility will require more studies (Panebianco, Oben, Vinciguerra, & Pazienza, 2017).

Pancreatic stellate cells (PSCs) are important in the processes of lipid metabolism and tissue repair occurring in the pancreas. The embryonic source(s) of PSCs are not clearly defined, though it appears that their origin includes the embryonic coelomic mesothelium and that their development requires Wt1 signaling similar to (pro)epicardial cells and HSCs (Ariza, Cañete, Rojas, Muñoz-Chápuli, & Carmona, 2018). Several features of adult PSCs also resemble those of HSCs. Like HSCs, quiescent PSCs store REs within lipid droplets (Apte et al., 1998; N. Kim et al., 2009) which become depleted in activated PSCs (Bachem et al., 1998). Injury causes the activation of PSCs which transdifferentiate to myofibroblasts and contribute to pancreatic fibrosis (reviewed in (Bynigeri et al., 2017; Sherman, 2018; Xue et al., 2018).

There is evidence that atRA plays an important role in the maintenance of normal function of the pancreas (reviewed in (Brun, Wongsiriroj, & Blaner, 2016)). Focusing on the role of atRA in the activation of PSCs and pancreatic fibrosis, there is evidence that PSCs express RARs and RXRs and that retinoids inhibit the proliferation and migration, and induce the quiescence of PSCs (Chronopoulos et al., 2016; Froeling et al., 2011; McCarroll et al., 2006; W. Xiao et al., 2015). The exact mechanism of atRA modulation of PSC activation is not known, but there is evidence that implicates atRA modulation of TGF-β. TGF-β is an important mediator of myofibroblast differentiation, which is released from latent ECM-associated complexes by myofibroblast-induced contractions (Wipff, Rifkin, Meister, & Hinz, 2007). AtRA-signaling promotes the quiescence of PSCs by inhibiting PSC-mechanosensing and suppressing ECM remodeling necessary to release TGF-β from its latency complex (Chronopoulos et al., 2016; Sarper, Cortes, Lieberthal, & Del Rio Hernandez, 2016). Accordingly, atRA attenuates pancreatic fibrosis in experimental models (W. Xiao et al., 2015).

Aside from manipulating atRA-signaling to reduce fibrosis, several interesting approaches rely on the retinol storage property of HSCs and PSCs to efficiently deliver antifibrotic drugs and siRNAs to HSCs and PSCs (El-Mezayen et al., 2018; Okimoto et al., 2019; Qiao et al., 2018; Sato et al., 2008; Y. Zhang et al., 2018; Z. Zhang et al., 2015). The exact mechanism responsible for the targeted delivery of retinol-conjugated drugs to HSCs is not clear. It was suggested that the uptake of retinol-coupled liposomes by HSCs is dependent on serum RBP4 (Sato et al., 2008). RBP4 is taken up by parenchymal liver cells and is also proposed to transfer retinol from hepatocytes to stellate cells (Alapatt et al., 2013; Blomhoff, Berg, & Norum, 1988; Gjoen et al., 1987; Malaba, Kindberg, Norum, Berg, & Blomhoff, 1993; Senoo et al., 1993). Nevertheless, more studies are needed to establish the factors that control the distribution and uptake of retinol-coupled drugs by the liver.

Role of AtRA in Pulmonary Fibrosis

Retinoid signaling is essential for lung development as well as maintenance of alveolar architecture and regeneration (F. Chen et al., 2010; Chytil, 1996; Gudas, 2012; Maden & Hind, 2004; D. Massaro & Massaro, 2002). During development, endogenously produced atRA controls the formation of lung primordium from the primitive foregut (F. Chen et al.,

2010). AtRA plays a particularly important role in regulating alveologenesis (Hind, Corcoran, & Maden, 2002a, 2002b; Maden, 2000; Maden & Hind, 2004). AtRA synthesizing enzymes, retinoid receptors, and retinoid-binding proteins are present during development and display dynamic regulation during alveologenesis (Hind et al., 2002a, 2002b; Maden & Hind, 2004; S. E. McGowan, Harvey, & Jackson, 1995; Ong & Chytil, 1976; Whitney, Massaro, Massaro, & Clerch, 1999). Through studies in mutant mice, it has been shown that atRA, acting through specific RAR isoforms, can be both a positive and negative regulator of alveologenesis (Desai et al., 2006; G. D. Massaro, Massaro, & Chambon, 2003; G. D. Massaro et al., 2000; S. McGowan et al., 2000; Mollard, Ghyselinck, Wendling, Chambon, & Mark, 2000; Snyder et al., 2005; Wongtrakool et al., 2003). RARγ functions as a positive regulator of alveologenesis, where Rarg-mutant mice fail to form alveoli (S. McGowan et al., 2000). Meanwhile, RARα has been shown to be required for the proper number of alveoli to develop after the perinatal period (G. D. Massaro et al., 2003). In contrast, RARβ functions as a negative regulator of alveologenesis, where RARβ mutant mice form too many alveoli (G. D. Massaro et al., 2000). It is thought that reawakening of developmental pathways occurs in tissue regeneration as an evolutionary efficiency without requiring separate regenerative signaling pathways; these concepts have been reviewed in detail (Hind & Maden, 2011; Maden & Hind, 2004). Chronic vitamin A deficiency (VAD) in both humans and animal models has been associated with lung functional defects and pulmonary diseases, including pulmonary fibrosis (Baybutt, Hu, & Molteni, 2000; Baybutt & Molteni, 2007; Biesalski & Nohr, 2003; Maden & Hind, 2004; G. D. Massaro & Massaro, 2000; S. E. McGowan et al., 2002; Morabia, Menkes, Comstock, & Tockman, 1990; Sommer, Katz, & Tarwotjo, 1984). VAD has also been associated with reduced immune response and increased risk of respiratory infections, asthma, and emphysema (Arora, Kumar, & Batra, 2002; Baybutt & Molteni, 2007; F. Chen et al., 2014). VAD results in squamous cell metaplasia with a reduced proportion of ciliated and mucous-producing cells, reduced number and surface of alveoli, alveolus septum thickening (Biesalski & Nohr, 2003; H. Wei et al., 2009). Additionally, in VAD, thickening of the alveolar basement membrane (BM) is accompanied by an increase in collagen I and collagen IV and the deposition of ectopic collagen fibrils in the BM (Esteban-Pretel, Marin, Renau-Piqueras, Barber, & Timoneda, 2010).

Type 1 epithelial cells form the surface barrier in the lung where gas exchange takes place. Type II cells are epithelial cells thought to act as progenitors for Type I cells and are, thus, involved in regeneration of the alveolar epithelium after injury. Type II cells make surfactant and atRA has been shown to regulate surfactant protein synthesis in fetal lung explants (Baybutt et al., 2000). Additionally, surfactant synthesis was lower in Type II pneumocytes isolated from VAD rats (Barber, Esteban-Pretel, Marin, & Timoneda, 2014). Type II pneumocytes are in close proximity to the connective tissue layer comprised of lipofibroblasts. It is believed that lipofibroblasts may transfer neutral lipids to Type II cells to support surfactant and phospholipid synthesis (S. E. McGowan & Torday, 1997). The size of lipofibroblasts can be increased by vitamin A feeding suggesting that they are a significant storage site for retinoids in the lung (Okabe, Yorifuji, Yamada, & Takaku, 1984; Spit, 1983). Whereas α-SMA expression has been widely used to identify myofibroblasts, it has recently been shown that Tcf21 expression may identify the lipofibroblast lineage (distinct from

myofibroblasts, interstitial fibroblasts, or adventitial fibroblasts) (Park et al., 2019). These lipid-laden fibroblasts participate in the synthesis of structural proteins such as collagen and elastin (Okabe et al., 1984).

Upon pulmonary injury, myofibroblast accumulation in the lung is the major contributor to the excessive collagen deposition and inflammation that causes a replacement of normal lung parenchyma with fibrotic tissue (F. Jiang, Yang, Xue, Li, & Zhang, 2017; Song et al., 2013; T. B. Zhou, Drummen, & Qin, 2012). Pulmonary fibrosis eventually yields an irreversible decrease in oxygen diffusion capacity of the lung. The pathogenesis of the progressive impairment of pulmonary function is not well understood and there are currently few therapeutic options. Fibrosis of the lung can occur without any known cause (idiopathic pulmonary fibrosis; IPF) or can be a secondary injury resulting from viral infections, sarcoidosis, environmental and occupational inhaled exposures, radiation exposure (either from radiotherapy for cancer or accidental/intentional exposures to ionizing radiation), or as a side effect of certain drugs (Timoneda et al., 2018; T. B. Zhou et al., 2012).

Lung is the second largest source of retinoids in the body where retinoids are stored as retinyl esters in intracellular lipid droplets (L. Liu & Gudas, 2005; O'Byrne et al., 2005; Okabe et al., 1984; Schmitz, Poor, Wellman, & Erdman, 1991). Storage of vitamin A in the lung is regulated by its active metabolite, where exogenous atRA can stimulate vitamin A uptake and storage in the lung (L. Wu & Ross, 2010). Retinoid metabolism has been shown to be altered in a number of lung disorders, including fibrosis. Endogenous atRA in lung was found to be reduced in several different strains of mice typically used as models of radiation-induced lung injury, in which fibrosis is a main injury endpoint. AtRA was reduced 24h after radiation exposure and the reduction in atRA persisted and continued to decline in fibrotic lung up to 180 days post-radiation (Jones et al., 2014). This observation shows that atRA is reduced by the initial insult prior to the onset of clinical symptoms. The degree of depletion of atRA at 180 days appears to be consistent with fibrosis severity, however, a systematic study to establish this relationship is needed. In addition to the observation that atRA levels are reduced after radiation exposure prior to the onset of clinical symptoms, a number of atRA-regulated proteins were observed to be changed after radiation exposure in a proteomic analysis of radiation-induced lung injury during the first week after radiation exposure, several months before clinical symptoms develop (W. Huang et al., 2019). These proteomic changes which may represent initiating molecular events towards the development of fibrosis included Rho GTPase signaling; kinase-related canonical pathways associated with cell migration, proliferation, and adhesion; and retinoid receptor dysregulation that has been reported to impact atRA biosynthetic enzyme expression (W. Huang et al., 2019). Similarly, observations have been reported where enzymes for biosynthesis and metabolism are altered after exposure to cigarette smoke before clinical symptoms of emphysema manifest (Quinn, Harvey, & Penning, 2008; R. Wang et al., 2010). Exposure to cigarette smoke or benzo[a]pyrene results in depletion of retinol in lung where the severity of emphysema was correlated with the degree of retinol deficiency in lung (Baybutt et al., 2000). The observed retinoid depletion in radiation-induced lung injury and emphysema models supports the postulate that depletion of retinoid signaling may be an initiating event in the development of pulmonary fibrosis and other lung dysfunction, which

with persistence of local deficiency of endogenous atRA, presents a permissive environment for fibrotic transformation.

A common feature of pulmonary fibrotic conditions is persistent alveolitis, accumulation of myofibroblasts, and the deposition of excessive amounts of ECM (Inage et al., 2009; T. B. Zhou et al., 2012). Fibroblasts are tissue-resident mesenchymal cells that produce ECM. ECM normally functions to maintain tissue integrity and homeostasis and contributes to the regulation of alveolarization, tissue stiffness/elasticity, as well as tissue remodeling and repair (Pelosi, Rocco, Negrini, & Passi, 2007; Timoneda et al., 2018). Retinoid signaling regulates the expression of ECM proteins dysregulated in fibrosis including collagen, laminin, fibronectin, elastin, and proteoglycans (Aguilar et al., 2009; Axel et al., 2001; Barber et al., 2014; Y. S. Lee & Jeong, 2012; Matsui, 1996). Many ECM proteins are directly regulated by retinoid signaling through their gene promoters however, retinoid signaling can also regulate the expression of cell membrane ECM receptors. Chronic VAD has been reported to be associated with morphological changes to ECM in lung which was related to fibrogenic activation and deterioration of lung parenchyma (Timoneda et al., 2018). Many of the VAD-induced alterations of ECM can be reversed by atRA, yielding promise for potential therapeutic utility of retinoids against pulmonary fibrosis (Esteban-Pretel et al., 2010; Marin et al., 2005; D. Massaro & Massaro, 2006; S. E. McGowan, Holmes, & Smith, 2004; Morath et al., 2001; Takahashi & Takasu, 2011).

Myofibroblasts are a distinct cell population that expresses α-SMA and possesses contractile microfilamentous apparatus (stress fibers) (Di Carlo & Peduto, 2018). Multiple progenitor cell populations have been proposed to contribute to the formation of lung myofibroblasts including pericytes and fibroblasts, resident mesenchymal cells, bone marrow progenitors, and epithelial cells (Di Carlo & Peduto, 2018; F. Jiang et al., 2017; Song et al., 2013; T. B. Zhou et al., 2012). Polarized epithelial cells differentiate into contractile, motile mesenchymal cells via EMT. The process of EMT is critical during lung development and contributes to lung disease including fibrosis, COPD and cancer (Bartis, Mise, Mahida, Eickelberg, & Thickett, 2014; Sung, Kim, & Park, 2016). In the lung, EMT is triggered by local microenvironmental factors and signals including cytokines, growth factors, inflammation, hypoxia, disrupted cell-cell contact, and/or contact with aberrant ECM components. Particularly, TGF-β, Smad, and β-catenin signaling have been implicated as inducers of EMT in lung disease (Kage & Borok, 2012). EMT is characterized by a loss of expression of E-cadherin accompanied by increases in mesenchymal markers including vimentin, fibronectin, α-SMA, and N-cadherin (Beck, Chikwem, Solanki, & Golemis, 2014; Gonzalez & Medici, 2014; Kourtidis, Lu, Pence, & Anastasiadis, 2017). AtRA regulates a number of these markers of fibroblast activation; atRA represses TGF-β, activates E-cadherin, and regulates α-SMA, vimentin, calponin, and MMP9 (F. Chen et al., 2007; Gong et al., 2018; Hu et al., 2010; Langton & Gudas, 2008; Papi et al., 2007; Woo & Jang, 2012).

AtRA biosynthesis and signaling has been previously shown to influence microenvironmental events such as cell fate, cell homing, cell migration, and protein secretion (Fu et al., 2010; Jones et al., 2014; Kane, Folias, et al., 2011; Kane et al., 2010; Pierzchalski et al., 2014; Pierzchalski et al., 2013; Sidell et al., 2010; Siegenthaler et al., 2009; Villablanca et al., 2011; C. Wang, Kane, & Napoli, 2011; S. Wang, J. Yu, et al., 2018;

Williams et al., 2009). Endogenous atRA is depleted in pre-fibrotic and fibrotic tissue that displays characteristics typical of an activated microenvironment including increased stromal collagen as well as epithelial and stromal hypercellularity (Pierzchalski et al., 2014; Pierzchalski et al., 2013). Deposition of fibrillary collagens (especially collagen I, collagen III) occurs in pulmonary fibrosis and adds stiffness to tissues. Mechanical forces have been shown to be important to myofibroblast activation and matrix deposition in lung (Balestrini, Chaudhry, Sarrazy, Koehler, & Hinz, 2012; X. Huang et al., 2012; F. Liu et al., 2010; Wells, 2013). The resulting matrix stiffness from the deposition of fibrillary collagens increases α-SMA expression and matrix deposition. Fibronectins are mechanosensitive and among the first to be upregulated after injury (Wells, 2013). TGF-β, an important and potent pro-fibrotic factor and inducer of EMT also undergoes activation as a result of mechanical tension (Wells, 2013). However, in a bleomycin model of lung fibrosis, lineage tracing analysis of alveolar epithelial cells showed that resident mesenchymal cells, and not cell populations derived by EMT of other cell types, were the major source of matrix producing fibroblasts and myofibroblasts (Rock et al., 2011).

Treatment with atRA reversed pulmonary fibrosis in a number of models. AtRA attenuated both radiation-induced and bleomycin-induced pulmonary fibrosis in mouse lung by inhibiting proliferation and reducing collagen synthesis (Tabata, Kadokawa, et al., 2006; Tabata, Kubo, et al., 2006). In their studies, Tabata et al. demonstrated that atRA inhibited IL-6 production through a protein kinase C (PKC)-δ / NF-κB-mediated mechanism. They also reported atRA reduced radiation-induced increases in TGF-β1 production through the p38MAPK/NF-κB pathway. Based on *in vitro* studies, Tabata *et al.* also reported that atRA reduced radiation-induced production of IL-6, TGF-β1, α-SMA, collagen 1A1, and activated NF-κB p65 in lung fibroblasts (Tabata, Kadokawa, et al., 2006; Tabata, Kubo, et al., 2006). AtRA-treatment of oxygen-induced lung injury reduced the degree of fibrosis and α-SMA expression (Ozer et al., 2005). In bleomycin-induced lung injury, atRA was able to decrease the expression of IL-17A, IL-6, and TGF-β1 (Dong et al., 2012). AtRA also blocked bleomycin-induced changes in EMT by preventing the increase in α-SMA and reduction in E-cadherin (Song et al., 2013). The atRA-mediated attenuation of EMT involved inhibition of bleomycin-induced Snail and Twist expression, where Snail expression is essential for TGF-β1 –induced EMT of alveolar epithelial cells (Song et al., 2013). Administration of atRA to VAD animals restored the concentration of parenchymal elastic fibers and lung mechanical properties (S. E. McGowan & Holmes, 2007; S. E. McGowan, Takle, & Holmes, 2005). AtRA administration has also been shown to be protective towards cell injury and ECM accumulation by reducing collagen I mRNA, and inhibiting TGF-β and CTGF expression (Davis et al., 1990; Ye & Dan, 2010). Additionally, atRA treatment reduced the amount of collagen IV and downregulated inflammatory cytokine expression, including IL-1α, IL-1β, and TNFα in VAD animals (Esteban-Pretel et al., 2010).

Animal models and *in vitro* experiments have shown encouraging potential for retinoid-mediated attenuation of fibrosis. Additional *in vivo* animal experimentation and clinical trials will be needed to determine the therapeutic utility of retinoid therapy for pulmonary fibrosis. Challenges in clinical trials of retinoids in lung diseases may arise from the differing effects of retinoids on mature differentiated cells and progenitor cells in lung (Ng-

Blichfeldt et al., 2018). Inhibition of retinoid signaling was needed for *in vitro* expansion of lung epithelial progenitor cells that are important to regeneration whereas atRA signaling promoted differentiation of alveolar and airway epithelial cells consistent with atRA's well characterized role as an essential differentiation cue for both embryonic and adult stem/progenitor cells (Jacobs et al., 2006; Lasagni et al., 2015; Ng-Blichfeldt et al., 2018; Okada, Shimazaki, Sobue, & Okano, 2004; Peired et al., 2013; Schuldiner, Yanuka, Itskovitz-Eldor, Melton, & Benvenisty, 2000). A differing effect of retinoids in diseased lung may occur due to, in part, differing stem cell populations. Whereas cells with stem/progenitor properties have been isolated from lung, full characterization stem cell populations in the lung and elucidation of their lineages is still in need of further attention (Fujino et al., 2011; Kajstura et al., 2011; C. F. Kim et al., 2005). AtRA treatment of patients in clinical trials for emphysema demonstrate some of the potential challenges of treating with atRA (Hind & Maden, 2011; Mao et al., 2002; Roth et al., 2006). AtRA induces its own degradation, limiting the effective therapeutic drug levels that can be achieved. The oral atRA treatment in emphysema patients resulted in compensatory enzyme induction that caused a significant reduction in plasma atRA levels over time (Hind & Maden, 2011; Mao et al., 2002; Roth et al., 2006). Only the highest doses appeared to have any biological effect, where clinical improvements correlated with plasma drug levels (Mao et al., 2002; Roth et al., 2006). Increased degradation of endogenous atRA by CYP26A1 in emphysema (similar to what has been observed in some cancers) is an additional factor limiting clinical success where deficient retinoid-driven angiogenesis was reported to impair endothelial cell repair and suggested to contribute to chronic lung disease (Ng-Blichfeldt et al., 2018). RAR isoform-specific agonists have also replicated the therapeutic effects of atRA in models of alveolar regeneration (Belloni, Garvin, Mao, Bailey-Healy, & Leaffer, 2000; Garber et al., 2006; Ishizawa et al., 2004; Kaza et al., 2001; G. D. Massaro et al., 2000; Ozer et al., 2005; Perl & Gale, 2009; Tepper et al., 2000; Veness-Meehan, Bottone, & Stiles, 2000)

Conclusions and Future Directions

We summarized observations that suggest that atRA is required for the development of (pro)fibroblast cell populations in the heart, liver, pancreas and lung. The pervasive occurrence of atRA-signaling during the formation of fibroblasts hints at the existence of shared developmental pathways for fibroblasts associated with internal organs. Indeed, a growing number of studies indicate that cardiac fibroblasts, HSCs, PSCs and lipofibroblasts are derived from precursors initially found within the embryonic mesothelium covering the heart (i.e. the epicardium), lung (pleura) and GI tract (septum transversum and visceral peritoneum) (Koopmans & Rinkevich, 2018; Rinkevich et al., 2012; Wilm, Ipenberg, Hastie, Burch, & Bader, 2005). Furthermore, these mesothelial precursor cell populations employ a related set of developmental programs to give rise to fibroblasts and smooth muscle cells. For example, WT1 is expressed by EPDCs as well as by coelomic precursors that give rise to HSCs, lung fibroblasts, hepatic smooth muscle cells, and PSCs (Asahina et al., 2011; Carmona, Barrena, & Munoz-Chapuli, 2019; Ijpenberg et al., 2007; Perez-Pomares et al., 2002; Sontake et al., 2018; Takeichi, Nimura, Mori, Nakagami, & Kaneda, 2013 Ariza, 2018 #4540). In comparison to WT1, TCF21 is expressed in both overlapping as well as distinct subsets of mesothelial precursors that give rise to cardiac fibroblast and lung lipofibroblast

populations (Acharya et al., 2012; Braitsch et al., 2012; Braitsch et al., 2013; Kikuchi, Gupta, et al., 2011; Park et al., 2019; Tandon et al., 2013; Vicente-Steijn et al., 2015 Kanisicak, 2016 #4022). Meanwhile, AtRA-signaling intersects with the multiple developmental programs that guide mesothelial-to-mesenchyme transitions such as WT1, TGF-β, TCF21, Rho and WNT-signaling pathways (Braitsch et al., 2012; F. Chen et al., 2010; F. Chen et al., 2007; Guadix et al., 2011; Ijpenberg et al., 2007; Lin et al., 2010; Sarper et al., 2016; von Gise et al., 2011; S. Wang, J. Yu, et al., 2018; W. Xiao et al., 2015).

Though studies highlighted in this review suggest a link between tissue fibrosis and vitamin A there is still much to be learnt about the role of atRA in various fibrotic processes before it can be realistically considered as a therapeutic target in fibrosis. While a case can be made for the importance of atRA in the developmental processes that give rise to tissue resident fibroblasts in many organs, the role of atRA in the fibroblast-myofibroblast transformation is not as clear. The most conflicting findings have been in regard to the effect of atRA in liver fibrosis, which some have argued could be a result of the dose and timing of atRA agonist employed (T. B. Zhou et al., 2012). This is certainly an important consideration given the evidence that atRA regulates its own metabolism and that a pharmacological dose of atRA can be followed by lasting atRA deficiency due to compensatory responses (L. M. Lee et al., 2012; Rydeen et al., 2015). To achieve an efficient activation of RAR in a specific tissue we need to overcome an exquisitely complex feedback regulatory system which has evolved since the beginning of the vertebrate diversification as a way to prevent the teratogenic effects caused by variations in the intake of dietary vitamin A. For this to happen, we first need to have a comprehensive understanding of factors that control the distribution and metabolism of atRA or synthetic RAR agonists. Future studies should also focus on the development of isoform-specific agonists, or RAR-agonists that resist catabolism by CYP26 enzymes and have a longer half-life; properties making them more pharmacokinetically favorable and potentially translatable.

One of the main obstacles in conclusively establishing the effect of atRA in fibrosis is that atRA influences a multitude of cellular processes such as differentiation, ECM deposition, metabolism and inflammation. It is possible that atRA may have some beneficial effect in one process but cause detrimental effects in another. One very important aspect of fibrosis is the inflammatory response and as there is considerable evidence of atRA being an important factor in immunity, it will be important to carefully assess the role of atRA in the innate immune response that promotes fibrosis (Brown & Noelle, 2015; Wynn & Ramalingam, 2012). In one such example, atRA produced by dendritic cells in the ocular mucosa promotes the activation of conjunctival fibroblasts (Ahadome, Abraham, et al., 2016; Ahadome, Mathew, et al., 2016). Therefore, in the future, it would be useful to study and refer to the effects of atRA on a specific profibrotic mechanism, as opposed to its effects on organ fibrosis in the broader sense.

Acknowledgements

This work was supported in part by the grant R01HD077260 from the National Institutes of Health (M.A.K., A.R.M.) and by Discovery Grant RGPIN-2019-04002 from the Natural Sciences and Engineering Research Council of Canada to ARM. Additional support was provided by startup funds to A.R.M. from the Northern Ontario School of Medicine. Conflicts of interest: none.

Funding Information

• NIH Grant Number: R01HD077260. Sponsor: NIH, Eunice Kennedy Shriver National Institute of Child Health and Human Development

• Discovery Grant Number RGPIN-2019-04002. Sponsor: Natural Sciences and Engineering Research Council of Canada

ABBREVIATIONS

atRA	all-*trans*-retinoic acid
CRABP	cellular retinoic acid binding protein
CRBP	cellular retinol binding protein
DHRS3	dehydrogenase/reductase superfamily member 3
DGAT1	diacylglycerol O-acyltransferase 1
EMT	epithelial-to-mesenchymal transition
EPDCs	epicardial-derived precursor cells
LC-MS/MS	liquid chromatography-tandem mass spectrometry
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
RBP	(serum) retinol binding protein 4
RDH10	retinol dehydrogenase 10
REs	retinyl esters
RhoA	Ras homolog gene family, member A
RXR	retinoid X receptor
SDR	short-chain dehydrogenase/reductase
SMAα	smooth muscle α-actin
SRF	serum response factor
TCF21	transcription factor 21
VSMC	vascular smooth muscle cells

WT1	Wilms-tumor 1

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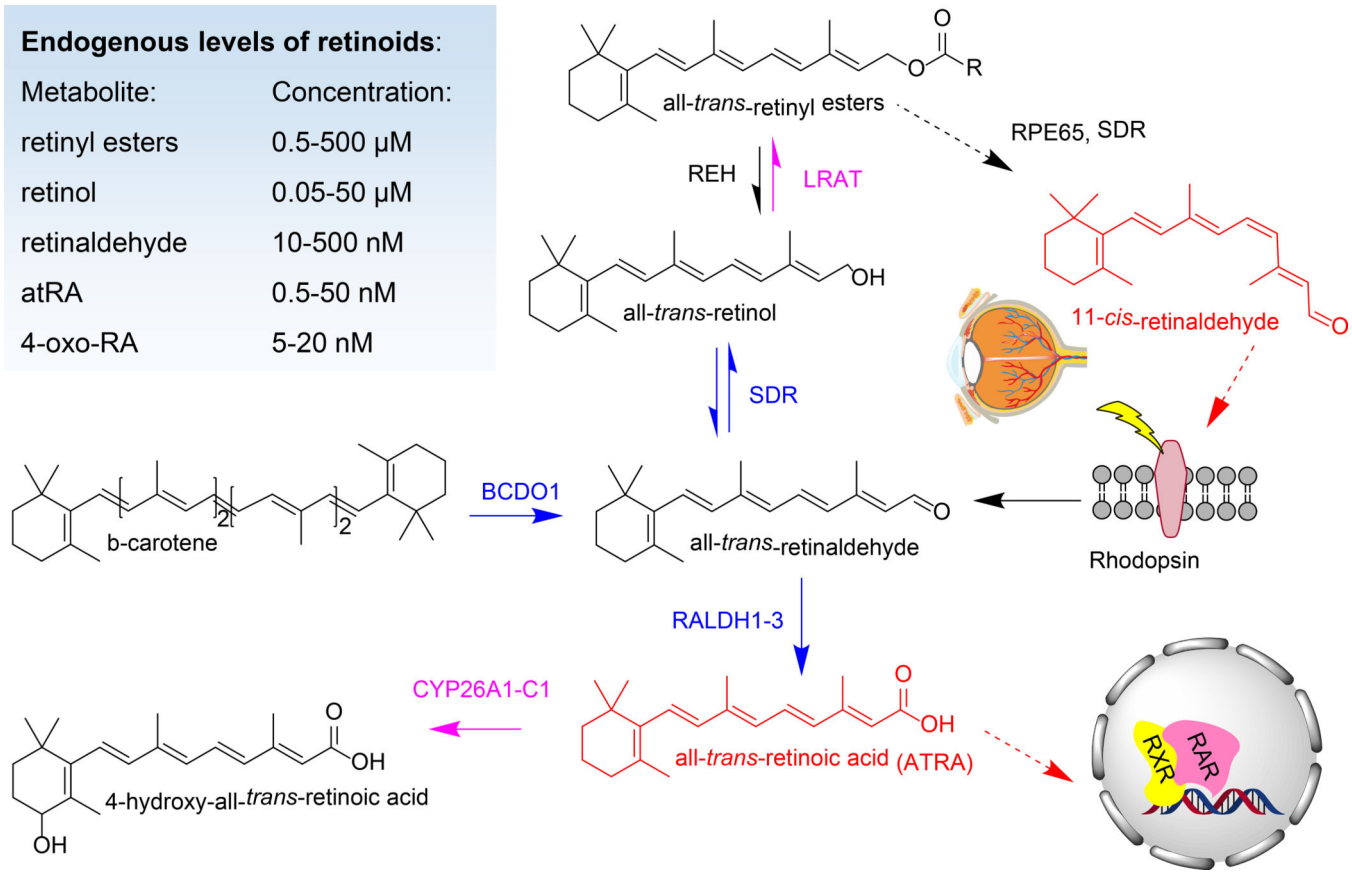

Figure 1.

Schematic representation of vitamin A metabolism leading to the formation of bioactive metabolites indicated in red, namely, all-trans-retinoic acid, a ligand for RAR/RXR nuclear hormone receptors involved in gene transcription, and 11-cis-retinaldehyde, the visual chromophore which binds rod and cone opsins. The dietary sources of vitamin A are either preformed retinol and retinyl esters or provitamin A precursors, such as all-*trans*-β-carotene. Enzymes involved in retinoid metabolism include: beta-carotene dioxygenase 1 (BCDO1), cytochrome P450 family 26 subfamily A1, B1 or C1 (CYP26A1-C1), lecithin:retinol acyltransferase (LRAT), retinaldehyde dehydrogenases (RALDH), retinyl ester hydrolases (REH), retinal pigment epithelium-specific 65 kDa protein (RPE65), short chain dehydrogenase reductases (SDR) such as DHRS3 and RDH10. The endogenous serum or tissue levels of various retinoid metabolites are shown inset (Arnold, Amory, Walsh, & Isoherranen, 2012; Kane & Napoli, 2010).

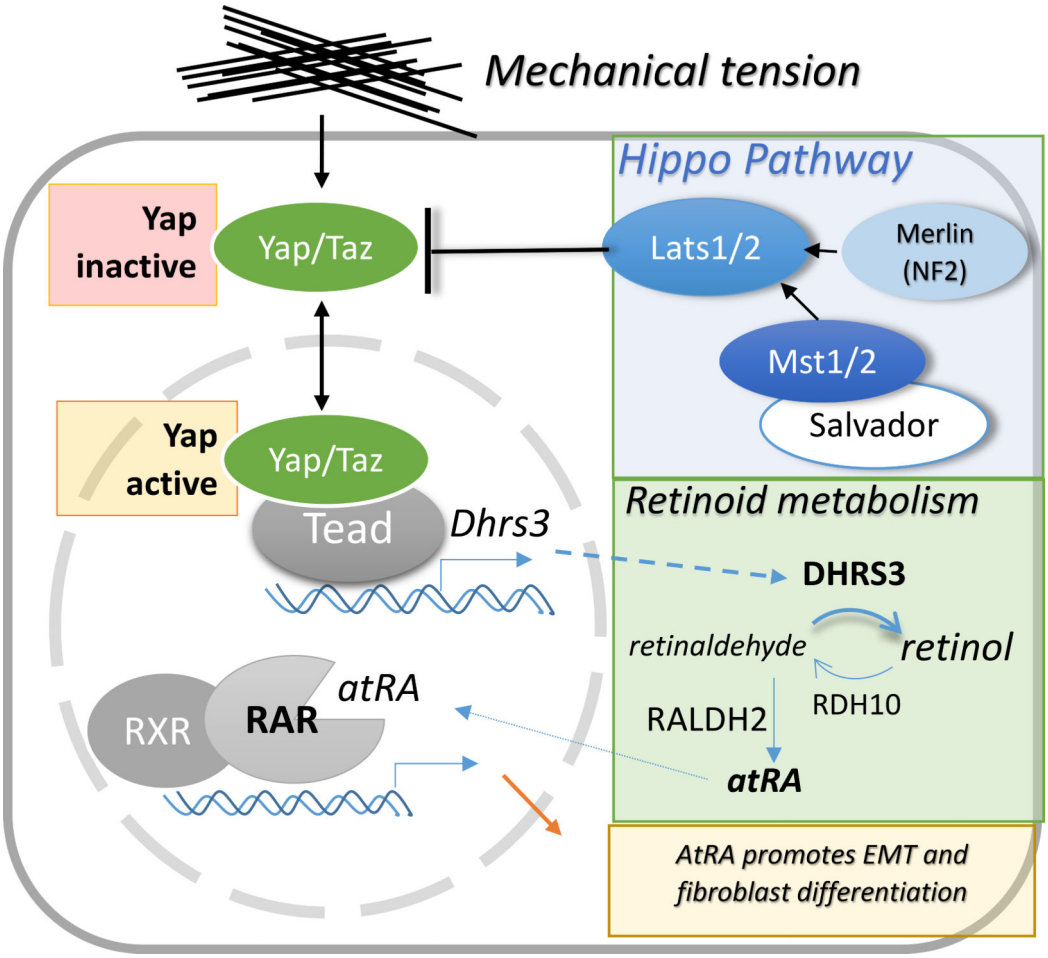

Figure 2.

Schematic representation of the proposed interaction of the Yap/Taz and atRA-signaling pathways during fibroblast development (adapted based on findings presented by Xiao *et al.* (Y. Xiao et al., 2018). Yap/Taz transduce mechanical stress and are regulated by the Hippo kinase cascade including Merlin, Salvador, Mst1/2 and Lats1/2 and the upstream regulators Merlin (Mer, or Nf2), and Salvador. Active Yap/Taz inhibits fibroblast differentiation potentially by inducing the expression of *Dhrs3*, a retinaldehyde reductase that restricts atRA synthesis.