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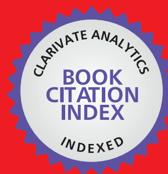

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Chapter

Retinoic Acid in Ocular Growth Regulation

Jody A. Summers

Abstract

All-*trans*-retinoic acid (atRA) is a metabolite of vitamin A (retinol) and is required for growth and development of a variety of organ systems in all higher animals from fish to humans. Evidence is accumulating to suggest that atRA may also be an important molecular signal in the postnatal control of eye size. Choroidal synthesis of atRA is modulated during periods of visually-induced changes in ocular growth and has pronounced effects on eye growth and refraction in several animal models of myopia. Choroidal atRA synthesis is exclusively regulated by expression of the enzyme, retinaldehyde dehydrogenase 2 (RALDH2). In chicks and humans, RALDH2 is synthesized by a unique population of uncharacterized extravascular stromal cells concentrated in the proximal choroid. The identification of choroidal atRA and RALDH2 as visually induced ocular growth regulators provides the potential for new therapeutic targets for the treatment of childhood myopia. The objective of this chapter is to discuss what is presently known about atRA biosynthesis and transport in the eye during visually guided eye growth and how this research can contribute to a better understanding of the mechanisms underlying the development of myopia.

Keywords: retinoic acid, choroid, myopia, sclera, RALDH2, emmetropization

1. Introduction

All-*trans*-retinoic acid (atRA) is the transcriptionally active derivative of vitamin A. atRA is an essential signaling molecule for developmental processes of numerous organ systems including those of the brain, limbs, lungs, pancreas, heart, and eye in many organisms from fish to humans [1, 2]. With the advent of increasingly sensitive methods to measure endogenous concentrations of atRA, data is accumulating to suggest that atRA is also important in the growth and maintenance of a number of organ systems during postnatal and adult life [3–7]. Within the postnatal eye, atRA has been detected in the retina, where its synthesis was shown to be mediated by oxidation of the chromophore all-*trans*-retinaldehyde, released from bleached rhodopsin in the photoreceptor outer segments following exposure to light [8]. More recently, the choroid (the highly vascular layer between the retina and the sclera) has been shown to synthesize and accumulate high levels of atRA [9, 10]. A number of studies in several animal models suggest that choroidal atRA may be an important molecular signal for the control of postnatal ocular growth [9, 11–13]. We and others have demonstrated that in response to visual stimuli, ocular atRA synthesis is regulated exclusively via choroidal expression of the atRA synthe sizing enzyme, retinaldehyde dehydrogenase 2 (RALDH2) by a unique population of cells [10, 14]. Furthermore, choroidally derived retinoic acid is transported to the

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sclera (the outer connective tissue shell of the eye) by apolipoprotein A-1 (ApoA-1) which functions as a specific extracellular atRA-binding and transport protein in the eye [15, 16]. Once delivered to the sclera, we speculate that atRA regulates the transcription of many genes in the sclera to effect changes in scleral extracellular matrix remodeling, ocular size, and refraction.

This chapter therefore focuses primarily on the potential role of atRA on the control of postnatal growth of the eye, and implications for the development of new therapies for the control of myopia in children.

2. Retinoic acid is a vitamin A derivative

atRA is synthesized in two steps from vitamin A (all-*trans*-retinol). The first step produces all-*trans*-retinaldehyde from all-*trans*-retinol through the action of cytosolic or membrane bound alcohol dehydrogenases (ADH). The second, irreversible, step in atRA synthesis involves the oxidization of all-*trans*-retinaldehyde to atRA through the actions of the cytosolic retinaldehyde dehydrogenases (RALDH1, RALDH2, RALDH3; a.k.a. Aldh1α1, Aldh1α2, Aldh1α3) [16, 17]. Tissue concentrations of atRA are regulated by the activities of these synthesizing enzymes, as well as the atRA-metabolizing enzyme CYP26, a member of the cytochrome P450 family [17]. Cyp1B1 may also contribute to atRA synthesis in the chick embryo [18] via synthesis of all-*trans*-retinaldehyde and atRA from all-*trans*-retinol. Furthermore, the rate of these reactions is regulated by the availability of the substrates, the accessibility of the enzymes to their substrates, and the catalytic activity of the enzymes [19]. Once synthesized, atRA can act within its own cell of synthesis (autocrine signaling) or be transported to nearby cells (paracrine signaling) and bind with nuclear retinoic acid receptor complexes to directly control the transcriptional activity of more than 100 target genes [20].

3. Visual regulation of intraocular retinoic acid synthesis

3.1 Emmetropization: vision-dependent ocular growth regulation

Clinical and experimental evidence have indicated that postnatal eye growth is regulated, at least in part, by a vision-dependent "emmetropization" mechanism that acts to minimize refractive error through the coordinated regulation of the growth of the ocular tissues [21, 22]. Interruption of emmetropization in animal models, such as the chick, primate, and guinea pig, through the application of translucent occluders (form deprivation) causes a distortion in visual quality, which results in ocular growth and myopia through changes in the regulation of scleral extracellular matrix (ECM) remodeling [23–27]. Form deprivation-induced myopia is reversible; removal of the occluder and subsequent detection of myopic defocus results in a rapid cessation of axial growth and the eventual reestablishment of emmetropia (recovery) [24]. Even stronger evidence for the presence of an emmetropization mechanism comes from studies in which animals are fitted with either concave (minus) lenses or convex (plus) lenses that shifts the focal plane behind (hyperopic defocus) or in front of (myopic defocus) the retinal photoreceptors, respectively. In animals with functional emmetropization, the axial length of the lens-treated eye will increase or decrease until the retinal location has shifted to match that of the new focal plane [28–31]. The emmetropization mechanism does not require the central nervous system and appears to be regulated by locally produced chemical signals within the eye itself. When visual form deprivation is restricted to nasal or temporal visual

fields, excessive growth of the sclera is limited to that portion corresponding to the visually deprived part of the retina [32, 33]. Furthermore experimental myopia can be induced animals lacking a functional optic nerve [34–36], suggesting that the central nervous system is not required for the development of myopia. It is now generally accepted that visually guided eye growth is regulated by a series of locally generated chemical events that begin in the retina in response to specific visual stimuli and terminate in the sclera where they result in scleral extracellular matrix (ECM) remodeling, changes in ocular length and refractive status [37–42]. Therefore the elucidation of the chemical events responsible for visually-induced changes in ocular growth is of great interest as it may provide new avenues for the development of therapies to slow or prevent the progression of myopia.

3.2 Choroidal retinoic acid: a potential ocular growth regulator

Several studies in a variety of animal models indicate that all-*trans*-retinoic acid (atRA) may be one of the chemical signals required for the regulation of eye growth during emmetropization [9, 11–13]. Mertz and Wallman [9] were the first to show that choroidal synthesis of atRA was increased in chick eyes during recovery from form deprivation myopia and following application of positive lenses (imposed myopic defocus), two visual conditions that cause a deceleration in ocular growth rates. Moreover, atRA was shown to be decreased in eyes undergoing form deprivation myopia and compensation for hyperopic defocus compared with the fellow control eye, conditions that stimulate ocular elongation. It was therefore suggested that choroidal atRA could act as a locally produced (within the eye) scleral growth modulator during visually guided ocular growth. atRA is an attractive candidate for a visually regulated ocular growth regulator because it is readily diffusible, has pronounced effects on scleral extracellular matrix metabolism, and exerts its effects through highly regulated, locally controlled synthesis and degradation.

Studies by Simon et al. [43] and Rada et al. [10] identified transcriptional changes in choroidal *RALDH2* in response to imposed defocus or recovery from in induced myopia. RALDH2 mRNA concentration was found to decrease in the choroid following treatment with negative lenses and to increase with positive lenses or during recovery from induced myopia. No changes were observed in the expression of the atRA metabolizing enzymes, *RALDH3*, *RDH10*, *CYP1B1*, *CYP26*, and transcript levels of choroidal *RALDH1* were undetectable [10]. Additionally, changes in choroidal RALDH2 protein concentrations and enzymatic activity in recovering eyes were reflective of the transcriptional changes in choroidal RALDH2 [14] suggesting that, in response to myopic defocus or recovery from induced myopia, the concentration of choroidal RALDH2 increases which, in turn, results in increased production of atRA. No RALDH activity was detected in the sclera or retina/RPE of control or treated chick eyes, indicating that the choroid is responsible for the majority of atRA synthesized in the chick eye [14].

3.3 Choroidal RALDH2+ cells: a novel cell type

In chicks and humans, RALDH2 is synthesized by a population of extravascular choroidal stromal cells, some of which are closely associated with blood vessels (**Figure 1**) [10, 14, 44]. In chicks, RALDH2+ cells increase in number markedly over 1–7 days of recovery due, in part, to cellular proliferation (**Figure 1F** and **G**) and become concentrated on the proximal (RPE) side of the choroid [14]. Immunohistochemical analyses of chick choroids indicate that many of RALDH2+ express pro-collagen type IA (**Figure 1B** and **C**), similar to activated pericytes (a.k.a. perivascular stromal cells) within the CNS perivascular space [45]. Additionally RALDH2 is expressed in the chick

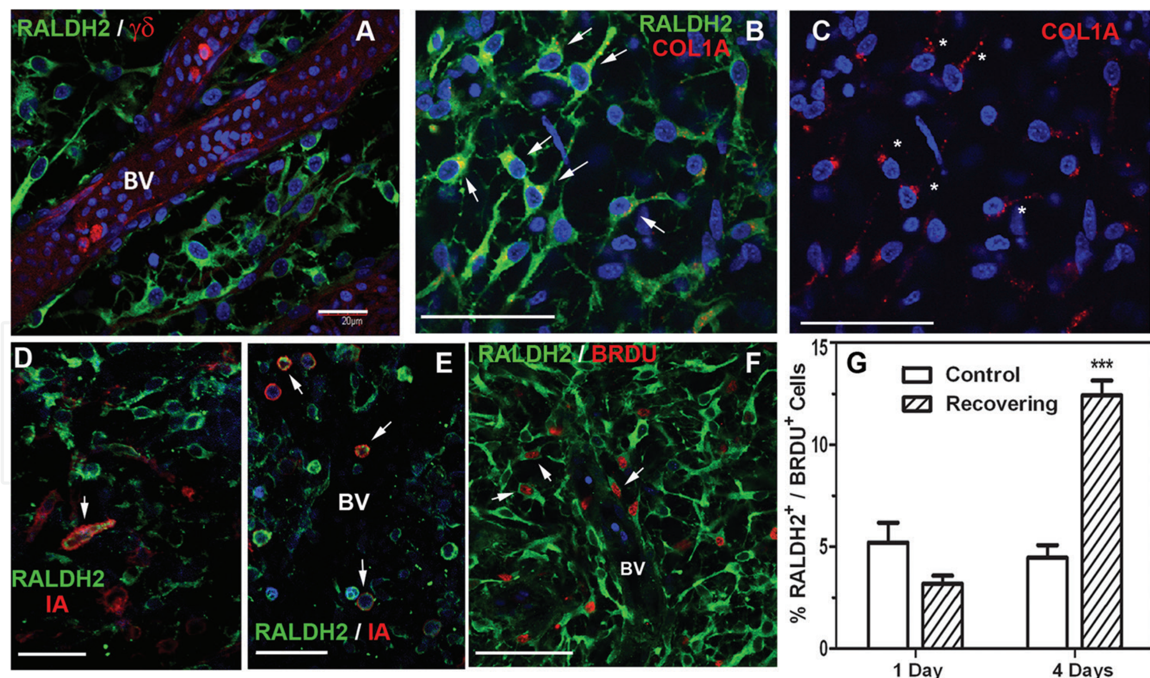

Figure 1.
*Choroidal RALDH2 positive (+) cells are heterogeneous. (A–E) RALDH2+ cells (green) are identified following labeling of 4 day recovering choroids with anti-RALDH2, together with anti-TCRγδ (γδ), pro-collagen IA (COL1A), or Ia antigen (IA) (red). Double-labeled cells are indicated by arrows. Asterisks in (C) indicate RALDH2+ cells that co-express Col1A. (F) Proliferating RALDH2+ cells were labeled with BrdU and identified with anti-BRDU (red). (G) Percentage of RALDH2+/BRDU+ cells is ≈ 3× higher in 4 day recovering choroids, suggesting that RALDH2 activity is partially controlled by proliferation of RALDH2+ cells. Bar = 20 μM in A, 40 μM in B–F. ***Student's t test, $p < 0.0001$. Error bars = SEM. Nuclei in A–F are stained with DAPI. BV, blood vessel.*

choroid by a small population of round cells that are positive for the Ia antigen [46, 47], indicating similarities with thymic macrophages/dendritic cells (**Figure 1D** and **E**), but are negative for the macrophage markers KuL01, MHC-II, and IgY [48]. A subpopulation of RALDH2+ cells also express α-smooth muscle actin (αSMA) [10, 14], but are negative for the smooth muscle/myofibroblast proteins, smoothelin, desmin and myocardin. RALDH2+ cells do not co-localize with CD-45 [14], TCRδγ (**Figure 1A**), CD5, or GRL(2) positive cells [49, 50], indicating they are not of hematopoietic origin. RALDH2+ cells also do not co-localize with neuron-specific beta III tubulin, NOS (pan), or tyrosine hydroxylase, indicating they are not of neuronal origin. Negative results were also obtained using anti-NG2 (a pericyte marker), vimentin, and PECAM-1 (an endothelial marker). Similarly, RALDH2+ cells in the human choroid were negative for the endothelial cell marker, CD31, the pericyte markers, NG2 and CD146, α-smooth muscle actin, the macrophage markers CD68 and LYVE1, IBA1 (microglia) and the pan-neuronal marker PGP9.5 [51]. Unlike results in the chick, some RALDH2+ cells in the human choroid co-localized with vimentin, suggesting a mesenchymal origin [51]. Based on the markers used in these studies, RALDH2+ cells seem to represent an independent cell-population. Studies are in progress using additional markers as well as transcriptome analyses on RALDH2+ cells isolated from chick and human choroids to further classify this new cell-population as this cell type may represent a potential target for therapies to slow or prevent myopia in children.

4. Retinoic acid on scleral proteoglycan synthesis

The retina, choroid and sclera are three possible tissue targets for choroidally generated atRA within the eye. Of these three targets, the sclera is a leading candidate. Based on results using a specific inhibitor of proteoglycan synthesis

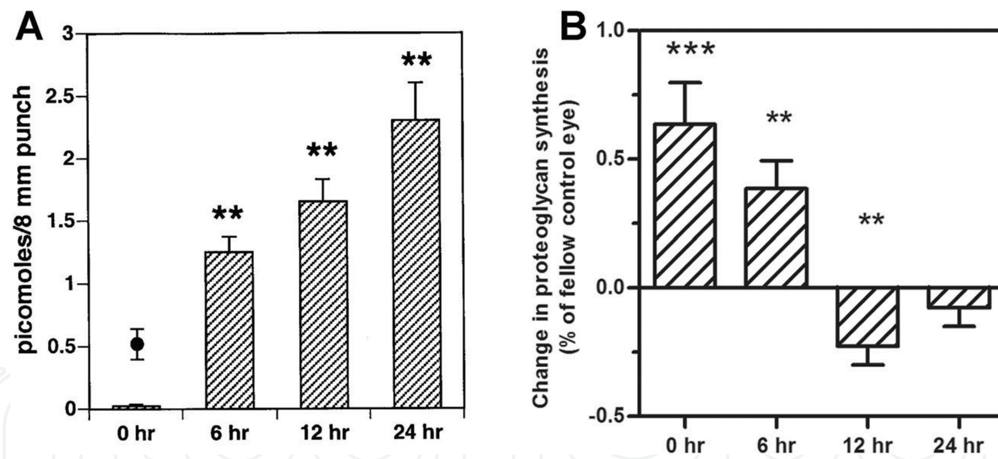

Figure 2.
Choroidal retinoic acid synthesis and scleral proteoglycan synthesis during recovery from form deprivation myopia. (A) Changes in choroidal all-trans-retinoic acid (atRA) synthesis during recovery from experimental myopia. (B) Changes in scleral proteoglycan synthesis in during recovery from experimental myopia. A from: Mertz and Wallman [9]. B adapted from: Summers and Hollaway [53]. Reproduced with permission © Elsevier.

(*p*-nitrophenyl-beta-D-xylopyranoside), we previously demonstrated that the rate of proteoglycan synthesis in the cartilaginous layer of the chick sclera is largely responsible for visually guided changes in eye size [27, 52]. Moreover, proteoglycan synthesis is rapidly upregulated in the sclera in response to visual form deprivation and is rapidly downregulated in the posterior sclera to levels significantly below those of fellow controls within 12 hours upon restoration of unrestricted vision (=recovery from induced myopia) [53, 54]. Interestingly, the time course of the increase in choroidal atRA synthesis during recovery from induced myopia [9] was remarkably similar to that of the decrease in rate of sclera proteoglycan synthesis observed in the early phase of recovery from induced myopia [53] suggesting a causal relationship between choroidal atRA synthesis and scleral proteoglycan synthesis (**Figure 2**). Moreover, *RALDH2* mRNA pools in the chick choroid were shown to increase and decrease in a manner that inversely correlated with changes in scleral proteoglycan synthesis in recovering eyes [10], suggesting that RALDH2 gene expression in the choroid regulate choroidal atRA synthesis during visually induced ocular growth. It is well known that atRA is a potent inhibitor of proteoglycan biosynthesis by chondrocytes [55, 56] and that it facilitates cartilage catabolism through the increased synthesis of matrix-degrading enzymes [55, 57, 58]. atRA inhibits scleral proteoglycan synthesis in a dose-dependent manner with an IC_{50} of 8×10^{-9} M, which is similar to the measured endogenous levels of atRA in choroid organ cultures (4×10^{-9} to 7×10^{-9} M) [10]. At this concentration, atRA would be able to regulate scleral growth matrix remodeling through the stimulation or repression of transcription factors, extracellular matrix constituents, and MMPs or TIMPs.

5. Identification of apolipoprotein A-1 as a retinoic acid binding protein

Due to its hydrophobicity, atRA cannot diffuse freely in the hydrophilic extracellular microenvironment. Therefore, the requirement for carrier proteins capable of forming a soluble complex with atRA and transporting atRA to target cells is necessary to achieve high efficiency and specificity while avoiding toxicity associated with random diffusion. Mertz and Wallman [9] and our lab [15] identified a secreted protein of *M*r = 27,000 that was the major atRA binding protein present in choroid and sclera conditioned medium. This *M*r 27,000 protein did not correspond in size to any of the previously identified atRA binding proteins [59]. We subsequently determined that the *M*r 27,000 protein was apolipoprotein a-1 (ApoA-1) [15] (**Figure 3**).

We have also shown that choroidal expression of ApoA-1 is transcriptionally regulated by atRA, *and* choroidal ApoA-1 mRNA and protein synthesis are upregulated during recovery from induced myopia, suggesting the presence of a regulatory feedback mechanism to regulate atRA transport and activity [15]. We postulate that ApoA-1 functions to transport atRA from its site of synthesis by RALDH2+ cells in the proximal choroid to the sclera for the regulation of scleral ECM remodeling. This idea is supported by our observation that the chick sclera (which is avascular) also releases significant amounts of ApoA-1 into culture medium, despite undetectable *de novo* protein synthesis [15]. These data provide further evidence that choroidally derived ApoA-1 accumulates in the sclera, presumably as a consequence of retinoid transport.

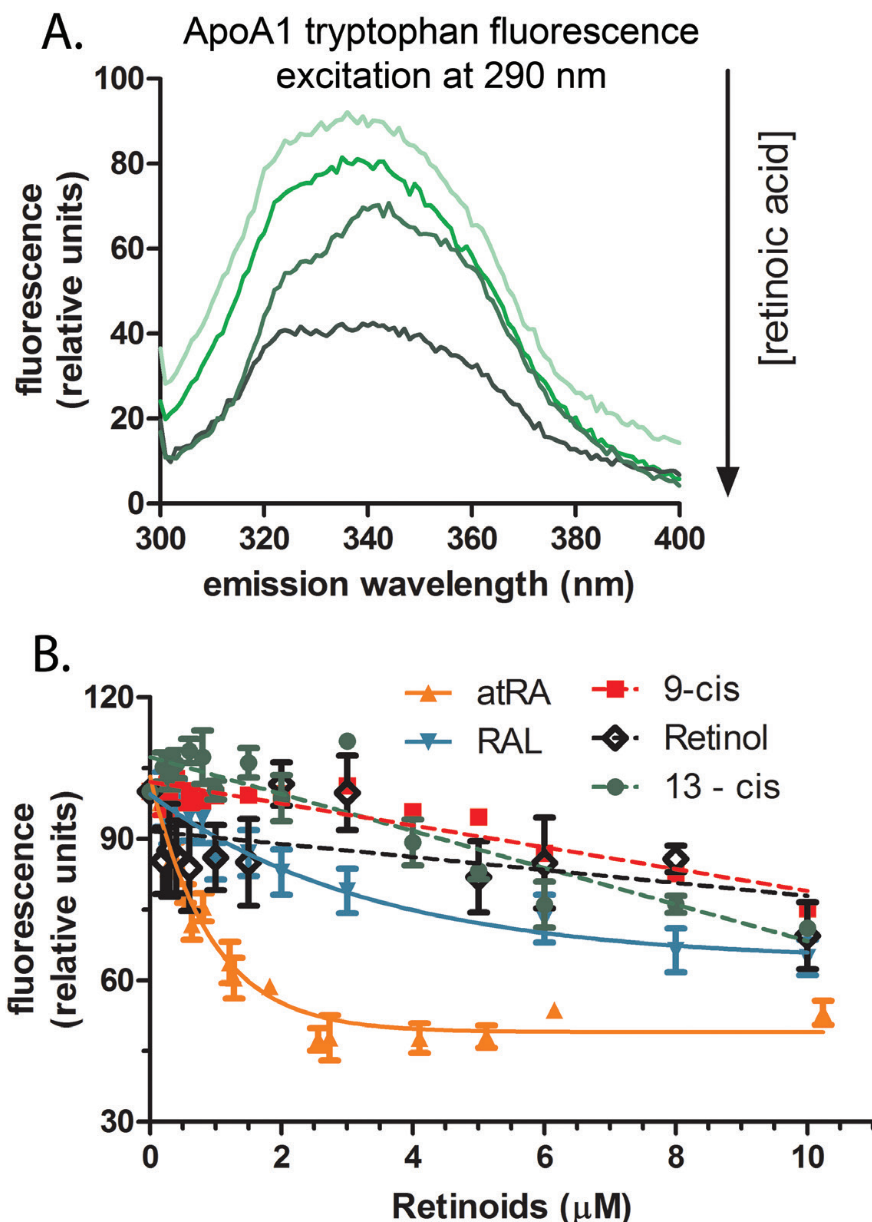

Figure 3.
ApoA-1 is a specific atRA-binding protein. (A) Retinoic acid (atRA) lacks intrinsic fluorescence (not shown), but can quench intrinsic protein fluorescence excited at 290 nm due to energy transfer from tryptophan residues on ApoA-1. Increasing atRA concentrations cause decreased fluorescence emission following excitation at 290 nm. (B) Titration of ApoA-1 with various retinoids by measuring quenching of protein fluorescence (emission = 340 nm). Significant quenching of protein fluorescence was observed only for atRA, indicating that ApoA-1 is a specific atRA-binding protein. atRA, all-trans-retinoic acid; RAL, all-trans-retinaldehyde; 9-cis, 9-cis-retinoic acid; 13-cis, 13-cis-retinoic acid. This research was originally published in the Journal of Biological Chemistry [70]. © The American Society for Biochemistry and Molecular Biology.

6. Role of retinoic acid in postnatal ocular growth

To elucidate the role of atRA in the regulation of postnatal ocular growth, several studies have been carried out in which either atRA or non-specific atRA synthesis inhibitors (i.e., citral, disulfiram) were administered either systemically or locally in several animals undergoing visually induced changes in eye growth [12, 60, 61]. Results of studies using chicks and mammals to examine the role of atRA in emmetropization, myopia development and postnatal ocular growth are difficult to interpret due to species differences in the processes of scleral remodeling and in the mechanisms by which ocular length and refraction are modulated by visual stimuli [62]. Moreover, these studies are further complicated by the multiple targets of atRA within the eye and pleiotropic cellular responses to retinoid signaling [63]. The mammalian sclera consists of a single fibrous layer that undergoes scleral thinning, and increased distensibility during periods of ocular elongation and myopia development. Scleral thinning during myopia development in mammals is the consequence of decreased sulfated glycosaminoglycan and collagen synthesis [11, 64, 65]. In contrast, the chick sclera consists of both cartilaginous and fibrous scleral layers. Ocular elongation during induced myopia in chicks is the result of growth of the cartilaginous sclera, with increases in sulfated glycosaminoglycan synthesis, increased protein synthesis, and increased total scleral mass [27, 66–68]. In chicks, increased choroidal synthesis of atRA during recovery from form deprivation myopia results in inhibition of scleral proteoglycan synthesis and slowing of the rate of ocular elongation. In primates [11] and guinea pigs [12], choroidal atRA synthesis is increased in treated eyes following induced myopia, a condition that is also associated with decreased proteoglycan synthesis in the posterior sclera but, in contrast to chicks, results in increased ocular elongation and myopia due to weakening of the fibrous sclera and localized ectasia at the posterior ocular pole. Considering the negative effect of atRA on scleral proteoglycan synthesis in animals containing either a single fibrous sclera (i.e., guinea pigs, primates) as well as chicks that contain both cartilaginous and fibrous scleral layers [9, 11], choroidally derived atRA represents a mechanism to regulate ocular length and refraction common to multiple species.

Furthermore, interpretation of experiments in which atRA agonists and atRA synthesis inhibitors are delivered either systemically or intraocularly is complicated by the widespread multicellular effects of atRA. Eye growth is increased following dietary delivery of atRA to chicks and is decreased after oral delivery of citral, a non-specific inhibitor of atRA synthesis [61]. Similarly, intraocular delivery of the non-specific atRA synthesis inhibitor, disulfiram, inhibited the development of form-deprivation myopia in chicks [60], a result generally opposite of what would be predicated if atRA acted to inhibit ocular elongation in chicks. It is likely that untargeted administration of atRA or use of non-specific atRA synthesis inhibitors that also inhibit other aldehyde dehydrogenases lead to multicellular effects that may differ from those mediated by endogenous atRA. We have recently developed a small molecule inhibitor, dichloro-all-*trans*-retinone (DAR) that is an irreversible inhibitor of RALDH1, 2, and 3 that effectively inhibits RALDH1, 2, and 3 in the nanomolar range but has no inhibitory activity against mitochondrial ALDH2 [69]. It is hoped that DAR, or similar compounds can be used to modulate endogenous concentrations of atRA through specific inhibition of the RALDH isoenzymes within the eye for future experimental and clinical studies to elucidate the role of atRA on postnatal ocular growth and myopia development.

7. Conclusions

Although the cause of myopia in humans is complex, clinical and experimental studies indicate that failure of the emmetropization process often leads to the development of myopia. It has been well-established that visually induced changes in ocular length are the result of altered extracellular matrix remodeling of the scleral shell. However no therapeutic targets have been identified and no pharmaceutical or optometric approaches have proven effective for the treatment of high myopia. The increasing prevalence of myopia and earlier age of onset emphasize the need for the development of an effective therapy. The identification of choroidal atRA, RALDH2, and the choroidal cells responsible for atRA synthesis, may provide new targets for the development of effective myopia therapies. Moreover the development of small molecule inhibitors specifically targeting RALDH2 would greatly expand our basic understanding atRA's role in postnatal growth and development as well as provide potential new therapies to slow or prevent the progression of myopia.

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Conflict of interest

The author certifies that she has no conflicts of interest and no affiliations with or involvement in any organization or entity with any financial interest.

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