Connective tissue remodeling in myopia and its potential role in increasing risk of glaucoma

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Abstract
Myopia and glaucoma are both increasing in prevalence and are linked by an unknown mechanism as many epidemiologic studies have identified moderate to high myopia as an independent risk factor for glaucoma. Myopia and glaucoma are both chronic conditions that lead to connective tissue remodeling within the sclera and optic nerve head. The mechanobiology underlying connective tissue remodeling differs substantially between both diseases, with different homeostatic control mechanisms. In this article, we discuss similarities and differences between connective tissue remodeling in myopia and glaucoma; selected multiscale mechanisms that are thought to underlie connective tissue remodeling in both conditions; how asymmetric remodeling of the optic nerve head may predispose a myopic eye for pathological remodeling and glaucoma; and how neural tissue deformations may accumulate throughout both pathologies and increase the risk for mechanical insult of retinal ganglion cell axons.

Keywords
Myopia, Glaucoma, Ocular biomechanics, Remodeling, Optic nerve head, Mechanobiology.

Introduction
The link between myopia (nearsightedness) and glaucoma has been recognized, at least, since the early 20th century [1]. High myopia is a major risk factor for glaucoma in various ethnic groups, and even low levels of myopia have a significant effect on glaucoma risk [2]. The prevalence of myopia has been increasing worldwide over the past 60 years, with epidemic levels higher than 80% in some East Asian populations [3], increasing the vision-related health care burden and the risk for associated blinding diseases such as glaucoma and retinal detachment. Globally, glaucoma is the second leading cause of blindness with an estimated 65 million people suffering from primary open-angle glaucoma, one of the most common forms of the disease [4,5]. The growing prevalence of myopia and glaucoma makes these ocular diseases a significant global health concern; therefore, it is critical to gain an understanding of the interrelated pathophysiologic mechanisms of both conditions.

Connective tissue remodeling is thought to play a key role in both conditions [6,7]. However, the mechanobiology of remodeling differs significantly between myopia and glaucoma. Because elevated intraocular pressure (IOP) is the primary risk factor of glaucoma, connective tissue remodeling in glaucoma is thought to be load-driven and to involve connective tissue turnover to maintain mechanical homeostasis [7]. In this sense, glaucoma-related remodeling has similarities to other load-driven remodeling processes, such as those associated with vascular hypertension [8]. Significant progress has been made over the last couple of decades in deciphering the fundamental mechanisms underlying load-driven remodeling. The remodeling mechanisms involved in eye development and myopia, however, are to some extend unique to the eye and not common across other organs, as they are not driven by load but by visual cues [6]. In the following section, we discuss why, despite the differences, connective tissue remodeling is a plausible link between both pathologies, and how connective tissue remodeling that leads to myopia early in life may increase the risk for pathologic connective tissue remodeling and vision loss in glaucoma later in life.
maintain clear vision (emmetropia) using visual cues that are locally detected by the retina [9,10]. The retina is thought to send biochemical signals to the fibroblasts of the sclera, altering its composition, biomechanical properties and remodeling rate, and ultimately the eye’s axial length [6]. Figure 1 illustrates the multiscale mechanisms that are involved in scleral remodeling in myopia.

There is a fascinating multiscale dilemma inherent in the emmetropization process. Visual cues such as defocus, light intensity, contrast, and light chromaticity alter axial eye elongation [6,11]. Some visual cues lead to signals that accelerate scleral remodeling, whereas others slow it down. These competing visual cues can vary across the retina (tissue level) and overtime. Based on the local visual cues, a photoreceptor cell, or a small collection of cells have to determine if the organ has to elongate faster or slower. This difficult decoding and decision-making task is even more astonishing because it functions without a connection to the brain and is, therefore, thought to solely occur at the cellular level of the retina [9,10]. However, the homeostatic control mechanism aims to match the organ-level size of the eye with its optics. This discrepancy between length scales presents a potential explanation for continued scleral remodeling and myopia progression in children that receive common lens correction (single-vision lenses). Single-vision lens are designed to correct defocus along the central axis but not in the periphery. Typically, myopic eyes have a hyperopic shift in the periphery, which remains after single-vision correction. Consequently, a peripheral photoreceptor cell will continue to receive local visual cues that suggest the eye is too short, accelerating scleral remodeling while the eye is already too long.

Abundant evidence suggests that axial elongation in myopia involves accelerated connective tissue remodeling and not accelerated tissue growth of the posterior sclera [12–14,6]. Although some remodeling mechanisms are thought to be universal across soft tissues and organs, scleral remodeling during eye development and myopia is unique in at least two ways: (i) remodeling is driven by visual cues, as described previously; and (ii) may be modulated by aggrecan. Aggrecan is a major structural proteoglycan (PG) that is found in cartilage but not in soft collagenous tissues except the sclera.

Figure 1

Multiscale mechanisms of scleral remodeling in myopia. The green boxes represent structural and material alterations owing to remodeling; the blue box represents the primary stimulus; and the orange box represents stimulus detection and signaling pathways. Scleral remodeling during eye development is driven by visual cues and a homeostatic control mechanism that matches the eye’s axial length to its focal length at the organ scale. Visual cues are detected by the retina, which sends signals through the choroid to the sclera to alter the scleral remodeling rate. Scleral remodeling in myopia leads to axial elongation at the organ scale, scleral thinning, increased creep rate, and cyclic softening at the tissue scale. We propose that scleral remodeling involves lamellar sliding at the lamellae scale, and fibril sliding and adaptation of the collagen fibril crimp at the fiber scale. The colors at the lamellae scale indicate the local fiber orientation, whereas the intensity is proportional to the collagen fiber density.
Multiple studies have concluded that PGs and glycosaminoglycans (GAGs) play no significant role in the elastic and viscoelastic response of soft tissues [15,16]. This may be different in the sclera owing to its aggregan content. Indeed, Murienne et al. [17] have shown in porcine sclera that enzymatic digestion of GAGs leads to a similar shift in the stress-strain response that was seen tree shrews when comparing control eyes to those developing myopia [13]. The composition of the sclera has been shown to change during experimental myopia with a reduction in aggregan and sulfated GAG levels [18,19]. During myopia development, several changes in scleral material properties and microstructure have been reported, including changes in the elastic, viscoelastic, creep, cyclic softening, and collagen fiber crimping response [20,13,21]. Interestingly, these material property changes seem to prevail as long as scleral remodeling is accelerated and myopia progresses but return to normal levels once remodeling stabilizes (Figure 2).

Based on the aforementioned evidence, it seems plausible that connective tissue remodeling in myopia is a creep-like deformation response. Scleral fibroblasts receive biochemical signals from the retina to accelerate or slow scleral remodeling by altering the composition and biomechanical properties of the sclera. Initial mechanistic theories assumed that the scleral collagen architecture consisted of lamellae and collagen fibers with distinct endings. In this case, connective tissue remodeling can be imagined as collagen sliding or relative deformations between neighboring lamellae and/or fibers within each lamella [23]. This theory of scleral remodeling is based on a highly simplified view of the hierarchical structure of the sclera and does not consider that lamellae are highly interwoven (see lamellae scale in Figure 1). Neither scleral lamellae nor their collagen fibers show clear endings. In contrast, scleral lamellae are tightly interwoven with each other, where lamellae split and merge, and collagen fibers can be connected to multiple lamellae. Although the highly interwoven lamellar structure of the sclera may limit relative microdeformations, the collagen sliding theory is still plausible but likely more complicated than originally thought. If collagen fibers have no endings, collagen fiber elongation could lead to a sliding-like mechanism at higher length scales. Indeed, experimental results in tree shrews indicate that the collagen fiber diameter decreases in myopia [12]. Lower scale mechanisms may allow for a continuous and permanent elongation of collagen fibers by adding new monomers to existing fibrils as they are being stretched [24]. Aggrecan is reduced during accelerated sclera remodeling, suggesting that its removal may promote collagen sliding and/or collagen fibril stretching. This perspective counters observations in tendon, where the removal of PGs and GAGs is thought to inhibit collagen fibril sliding [25]. However, the architecture of tendons is fundamentally different from that of the sclera.

Figure 2

![Time-dependent changes in scleral biomechanics during experimentally induced myopia using a -5D lens in tree shrews. Plotted are the differences between lens treated and control eyes, showing a similar time-dependent trend for all of the study variables. The axial elongation rate (red curve [20]) increases rapidly after lens placement, followed by a decline to normal levels as the eye adapted its axial length to the new focal length. The creep rate (green curve [20]) and the collagen fiber crimp angle (blue curve [13]) show a similar time-dependent trend compared with the axial elongation rate. Based on the model assumptions, the computationally predicted remodeling rate (magenta curve [22]) predicts an immediate increase in the remodeling rate after lens placement, followed by a gradual decrease that is consistent with the time-dependent biomechanical changes seen in the other curves.](image-url)
Connective tissue remodeling in glaucoma

The optic nerve head (ONH) is of particular interest in glaucoma as it is thought to be the primary site of retinal ganglion cell (RGC) axonal injury in glaucoma [26]. From the biomechanical perspective, the ONH is generally thought to be a weak spot within the otherwise relatively strong collagenous corneo-scleral shell [27]. Progressive remodeling of the ONH connective tissues is the defining feature of glaucoma as compared with other optic neuropathies [28]. Figure 3 illustrates the multiscale mechanisms hypothesized to be involved in ONH remodeling in glaucoma. The connective tissues of the ONH include the peripapillary sclera (PPS) and lamina cribrosa (LC), which are mainly composed of Type I collagen. The LC is thought to mechanically protect RGC axons from organ scale pressure loads as the axons pass from a relative higher pressure environment within the eye (IOP) to a lower pressure region in the retrobulbar cerebrospinal space [29]. The LC consists of a complex, load-bearing, three-dimensional network of collagenous beams, nourished by a capillary bed primarily arising from the short posterior ciliary arteries penetrating the PPS. The anatomy of the LC and sclera raises several considerations regarding the etiology of pathologic remodeling and bowing of the LC in glaucoma and implies that the classic mechanical and vascular mechanisms of axonal insult are inseparably intertwined [30].

At the tissue scale, early experimental glaucoma in nonhuman primates shows a thicker LC [31,37] that is bowed posterior [31,39] than contralateral control eyes. Structural changes at the ONH occur before any detectable loss of retinal nerve fiber layer thickness, suggesting that pathologic ONH remodeling precedes axonal insult [40]. Computational and experimental studies based on experimental glaucoma in monkeys suggest that these morphologic changes result from connective tissue remodeling owing to increased collagen synthesis in the retrolaminar septa [37,41]. Furthermore, initial bowing of LC may be caused by elastic deformations, but these deformations are thought to become permanent and progress owing to...
connective tissue turnover [7]. Recent findings by Fazio et al. [36] suggest that scleral remodeling in glaucoma follows a connective tissue wound healing response, where the sclera becomes more compliant initially, followed by a scarring period in which the sclera progressively stiffens. A similar process has been proposed for the LC, where after an initial thickening, the LC becomes thinner with associated scar formation at the advanced stage of glaucoma [7]. Although the scarring response remains poorly understood, the primary remodeling response is thought to be load-driven, involving a mechanical homeostatic control mechanism that modulates collagen turnover.

Several findings suggest that connective tissue remodeling in glaucoma is driven by a homeostatic control mechanism at the fiber scale. Fiber scale strain was identified as a critical stimulus in mechanotransduction pathways of LC cells and scleral fibroblasts [42]. Camp et al. [43] have shown that the fiber scale strain protects fibrillar collagen against enzymatic degradation. Computational models suggest that the LC thickens in early experimental glaucoma to maintain a homeostatic strain level at the fiber scale [41]. Brazile et al. [38] found that collagen fibers are less wavy in thin LC beams than in their thicker counterparts. This difference may allow thin beams to support similar amounts of IOP-induced force as thicker beams at physiologic IOP, despite the differences in beam width (Figure 4). A remodeling mechanism that alters the collagen fiber crimp can maintain a homeostatic strain condition without changing the LC beam diameter. In addition, studies of the distribution of collagen crimp characteristics throughout the globe show well-defined regional patterns consistent across eyes and between sheep [44] and human [45], suggesting that the mechanisms regulating these parameters might be shared across species and act at multiple scales.

### Connective tissue remodeling linking myopia and glaucoma

Connective tissue remodeling in myopia leads to profound morphological changes of the posterior pole and the ONH, which alters the biomechanical environment of the RGC axons permanently. Recent advancements in optical coherence tomography (OCT) allow in vivo assessment of ONH remodeling. Here, we present characteristic morphological changes that occur at the ONH in myopia, and how these changes might increase the risk for glaucoma development. Figure 5 presents a summary of the interacting mechanisms.

During development of myopia, the ONH shape becomes more elliptical at multiple depths, including the...
BMO and the scleral canal opening [48]. The increased BMO and scleral canal opening areas in myopia suggest that myopic remodeling leads to an overall expansion of the ONH [48]. In monkeys, this expansion process involves thinning of the PPS and LC [49]. Tissue thinning supports the notion that connective tissue remodeling in myopia involve microdeformations (e.g. collagen sliding) that are mostly volume-preserving at the tissue level. Age-dependent tissue stiffening may play a critical role in deciphering the interaction between connective tissue remodeling in myopia and glaucoma. The human sclera was shown to stiffen with age owing to increased shear stiffness and a reduction collagen fiber crimp [45,46]. Using computational modeling, Sigal [50] predicted that a stiffer sclera and increased scleral canal opening (i.e. LC diameter) lead to an increase in peak LC strain, which can result in load-driven remodeling. When the sclera is compliant (as it is in children), LC radius had no influence on the peak LC strain [50]. This finding supports the idea that scleral stiffening due to
aging may be an important aspect of the increased susceptibility to glaucoma of highly myopic eyes that typically have a larger scleral canal opening. Furthermore, a thinner LC was found to be more sensitive to IOP-induced posterior displacement of the LC (LC bowing) and this effect increased with scleral canal size [51]. Consequently, both the thinning of the LC and the expansion of the scleral canal in myopia may promote pathologic ONH remodeling that leads to LC bowing and mechanical insult to the RGC axons passing through the LC, even at normal IOP.

In contrast to a normal eye, the myopic ONH is characterized by an asymmetric morphology [52]. Besides the already mentioned elliptical shape of the ONH, this asymmetric changes involve a vertical tilting and tissue-level deformations that make the ONH appear as if it was rotated (also called ONH torsion) [53]. This asymmetric morphology suggests that scleral remodeling in myopia is heterogeneous and/or anisotropic. If scleral remodeling involves collagen fiber sliding, the collagen fiber architecture will impact the tissue-level deformations that result from such a remodeling mechanism. Consequently, the complex collagen fiber architecture of the sclera, with radial, circumferential, interweaving and tangential fibers [54,55] may explain the asymmetric morphological changes of the ONH observed in myopia.

As connective tissue remodeling in myopia is driven by visual cues and not by mechanical stimuli, an asymmetric ONH remodeling will likely cause local and/or regional deviation from the mechanical homostatic state. These deviations can lead to overloaded and underloaded connective tissues and may change the principal stress/strain directions, which may lead to secondary load-driven remodeling. Changes in principal stress directions are thought to alter the anisotropic collagen architecture in the LC and the sclera [56]. Indeed, Markov et al. [57] have found notable alterations in the collagen architecture of the PPS in highly myopic eyes. We have two hypotheses to explain these microstructural changes in the PPS. First, it is possible that microstructural changes are the result of load-driven remodeling secondary to the asymmetric vision-guided remodeling of the ONH in myopia. Alternatively, the microstructural changes may be a direct consequence of vision-driven remodeling of collagen fibers in the posterior sclera. Fibers and fiber bundles in the sclera are several orders of magnitude longer than their diameter. Thus, they may interact with cells and other fibers at small scales, for example by interweaving, but can also transmit forces across long distances. In this perspective, vision-guided remodeling that increases the length of scleral fibers far away from the ONH may still impact the biomechanics and microstructure of the ONH. The exact implications of anisotropic and heterogenous vision-guided and load-driven remodeling interactions on glaucoma risk are unclear at this point.

Anatomically, the retina is thought to be fully developed between 15 and 45 months of age [58,59], which is also the age rage at which scleral growth ceases [60]. Typically, connective tissue remodeling that leads to high myopia occurs at young age, but still long after the retina has fully developed. Consequently, the retina is stretched as it deforms with the remodeling sclera during the development of myopia. At the ONH, the interaction between neural and connective tissues is more complex as the ONH remodels into an asymmetric shape with relative deformations between the connective and neural tissues (see tissue scale in Figure 5). Lee et al. [61] provided longitudinal evidence that the LC is shifted or ‘dragged’ nasally relative to the prelaminar tissue and BMO during axial elongation in myopic children. These relative deformations are likely involved in the tilted and rotated appearance of the ONH in high myopia and in the development of peripapillary atrophy often seen at the temporal side of the myopic optic disc [61]. The myopia-associated deformations of the prelaminar tissues will likely remain or worsen with age. As mentioned previously, pathologic ONH remodeling in glaucoma typically involves posterior deformations or bowing of the LC, which pulls the prelaminar tissues posteriorly. In addition, patients with glaucoma also have peripapillary changes that can be seen in clinic [62,63]. Beta-zone atrophy associated with glaucoma corresponds to loss of retinal pigment epithelium cells and photoreceptors, as well as changes in the choriocapillaris. Consequently, stretching and shearing of the prelaminar tissues may accumulate with age due to vision-guided ONH remodeling during childhood myopia and load-driven remodeling in glaucoma later in life. This age-dependent accumulation of prelaminar deformation in myopic eyes may lead to mechanical axonal insult at lower levels of pathological ONH remodeling than nonmyopic eyes. If this is true, more severe levels of ONH remodeling owing to myopia should lead to more profound vision loss in glaucoma with otherwise comparable conditions (e.g. IOP). Sawada et al. [64] investigated this idea using a clever study design based on paired eyes of patients with open-angle glaucoma whose IOP was similar. The study revealed that myopic papillary and parapapillary deformations (more elliptical ONH, larger peripapillary atrophy area without Bruch’s membrane), rather than the refractive error, were related to the visual field loss in open-angle glaucoma, which supports our speculation.

**Discussion**

We have presented an opinion about connective tissue remodeling in myopia and glaucoma. We suggest that the primary remodeling mechanisms are substantially different between these two comorbidities. Differences
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Our opinions are based on the data and models available to date. To the best of our knowledge, no longitudinal data set exists that encompasses the development of both conditions, which is critical for clarifying the interactions between myopia and glaucoma. Acquiring these data presents a significant challenge as it would require longitudinal data collection from childhood until late adulthood to realistically capture the development of childhood myopia and glaucoma later in life. Another challenge is rooted in the limitations of current imaging techniques that are insufficient to characterize all aspects of connective tissue remodeling in response to IOP changes, with age and disease in humans or typical animal models. Specialized animal models, such as the tree shrew (tupaia belangeri), may provide unique advantages for this purpose. Tree shrews have been used as a model of myopia for decades [67,68], but more recently a glaucoma model has been established in these animals [69]. The tree shrew eye has inherent magnification and appears to have little corneal or lenticular aberration as spectral domain optical coherence tomography (SD-OCT) images are astonishingly clear. SD-OCT imaging of the ONH reveals exceptional detail of the collagenous LC, including microstructural beam definition. Furthermore, tree shrew eye ages rapidly, where 20 weeks of eye development correlate to 20 years in humans [70]. This animal model may provide a special opportunity to identify and follow collagen remodeling throughout both conditions in vivo.

Connective tissue remodeling is a promising and underutilized treatment target for both, myopia and glaucoma. In myopia, collagen cross-linking has been proposed as a potential treatment modality for slowing scleral remodeling by inhibiting collagen sliding and biomechanically strengthening the sclera [21]. Scleral cross-linking may also inhibit asymmetric remodeling of the ONH in myopia. Animal studies confirmed that scleral cross-linking can inhibit myopia progression but with some controversial results [71,72]. As ONH remodeling in glaucoma is thought to be driven by load, surgical or pharmaceutical interventions that alter the biomechanical state of the ONH could not only reduce the mechanical insult to the RGC axons but also guide and potentially reverse pathologic ONH remodeling. This may be of particular interest in patients with glaucoma with myopia and asymmetric ONH morphology. Personalized alterations in the stress—strain environment of the myopic ONH may be needed to effectively prevent or reverse pathologic load-driven ONH remodeling. The best approaches for these treatments will depend on whether the changes in the ONH and PPS associated with myopia are primary or secondary. Although IOP-lowering drugs can slow glaucoma progression, the load reduction occurs globally, which may be insufficient in high myopic eyes. Scleral cross-linking was also proposed for glaucoma treatment [73,74]. However, cross-linking the entire sclera will increase the scleral stiffness overall (similar to aging), which may explain the increased glaucomatous damage in mouse experiments conducted by Kimball et al. [73]. Coudrillier et al. [74] demonstrated ex vivo that localized cross-linking of the PPS reduces LC strains, supporting our opinion that localized biomechanical treatment could be used to guide load-driven
remodeling. The asymmetric shape of the ONH in high myopic eyes may require a personalized treatment strategy to effectively control load-driven remodeling at the ONH. Predictive computational simulations could be used to guide biomechanical interventions at the ONH. Simulation-based diagnostic and treatment planning is being tested for anterior segment interventions [75] but has not been applied to the posterior segment.

In our opinion, significant progress toward the effective treatment of myopia and glaucoma could be made as follows: (i) by gaining a deeper understanding of the interacting remodeling mechanisms through longitudinal animal experiments where both conditions can be induced; (ii) development of treatment strategies that can locally alter ONH biomechanics and guide load-driven remodeling; and (iii) development of eye-specific computational models that can predict the progression of connective tissue remodeling and be used to personalize ONH biomechanics interventions.

**Conflict of interest statement**

Nothing declared.

**Acknowledgements**

This work was supported in part by the National Institutes of Health Grants R01-EY027759, R01-EY026508, R01-EY026662 and R01-EY023966 (Bethesda, Maryland); EyeSight Foundation of Alabama (Birmingham, Alabama); and Research to Prevent Blindness (New York, New York).

**References**

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest


This article summarizes optic disc changes in myopia and provides evidence that these changes are secondary to changes of the posterior globe.


This article provides insight into the complex collagen fiber architecture of the sclera, with radial, circumferential, interweaving and tangential fibers, which may play a critical role in the asymmetric morphological changes of the ONH observed in myopia.


This article provides longitudinal evidence that the lamina cribrosa is shifted or “dragged” nasally relative to the prelaminar tissue and BMO during axial elongation in myopic children. These relative deformations are likely involved in the tilted and rotated appearance of the ONH in high myopia, and in the development of peripapillar atrophy often seen at the temporal side of the myopic optic disc.


This article provides insight into the special opportunity of using tree shrews as glaucoma model.


