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Glaucomatous cupping of the lamina cribrosa: A review of the evidence for active progressive remodeling as a mechanism

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ABSTRACT

The purpose of this review is to examine the literature in an attempt to elucidate a biomechanical basis for glaucomatous cupping. In particular, this work focuses on the role of biomechanics in driving connective tissue remodeling in the progression of laminar morphology from a normal state to that of an excavated glaucomatous state. While there are multiple contributing factors to the pathogenesis of glaucoma, we focus on laminar extracellular matrix (ECM) remodeling in glaucoma and the feedback mechanisms and signals that may guide progressive laminar cupping. We review the literature on the potential mechanisms of glaucomatous changes in the laminar ECM at the anatomic, structural, cellular and subcellular levels in the context of the biomechanical paradigm of glaucomatous onset and progression. Several conclusions can be drawn from this review. First, extensive remodeling of the lamina cribrosa ECM occurs in primary open angle glaucoma. Second, there is surprisingly little evidence to support acute mechanical damage to the lamina as the principal mechanism of cupping. Third, ONH astrocytes and lamina cribrosa cells can sense their mechanical environment and respond to mechanical stimuli by remodeling the ECM. Fourth, there is evidence suggesting that chronic remodeling of the lamina results in a progressive posterior migration of the laminar insertion into the canal wall, which eventually results in the posterior lamina inserting into the pia mater. Finally, modeling studies suggest that laminar remodeling may be a biomechanical feedback mechanism through which cells modify their environment in an attempt to return to a homeostatic mechanical environment. It is plausible that biomechanics-driven connective tissue remodeling is a mechanism in the progression of laminar morphology from a normal state to that of a cupped, excavated glaucomatous state.

1. Introduction and scope

Lowering intraocular pressure (IOP) remains the only proven method of preventing the onset and progression of glaucoma. The role of IOP in the disease, however, remains controversial. This largely arises from the wide spectrum of individual susceptibility to IOP wherein a significant number of patients with normal IOPs develop glaucoma (e.g. normotensive glaucoma), and other individuals with elevated IOP show no signs of the disease. It is therefore important to understand the relationship between glaucomatous optic neuropathy and IOP, an inherently mechanical phenomenon.

One common clinical feature of glaucoma is ONH cupping. This cupping can be described as having two components: prelaminar and laminar (Yang et al., 2007a,b; Burgoyne and Downs, 2008). Prelaminar cupping of the ONH surface is characterized by progressive loss of the prelaminar neural tissues, which serves to increase both the depth and width of the cup, thereby increasing the cup-to-disk ratio. Laminar cupping is connective tissue-based, with the lamina cribrosa progressively moving posteriorly and excavating beneath the anterior scleral canal. In most cases, glaucomatous cupping is a combination of these two components, reflecting both damage to and remodeling of the laminar connective tissues and progressive loss of retinal ganglion cell (RGC) axons.

The purpose of this review is to examine the literature in an attempt to elucidate a biomechanical basis for glaucomatous cupping. In particular, this work will focus on the role of biomechanics in driving cell-mediated connective tissue remodeling in the progression of laminar morphology from a normal state to that of an excavated glaucomatous state (Fig. 1) While we acknowledge that there are multiple contributing factors to the pathogenesis of glaucoma (Fig. 2) we will focus on laminar extracellular matrix (ECM) remodeling in glaucoma and the feedback mechanisms and signals that may guide progressive laminar cupping. We review the

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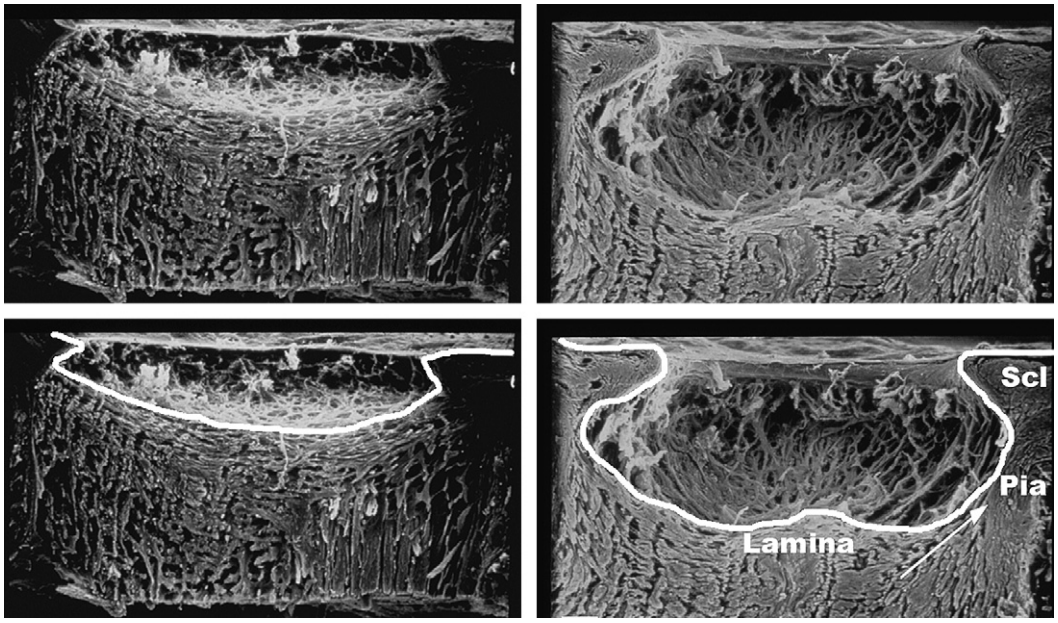

Fig. 1. Scanning electron micrographs of trypsin-digested optic nerve heads from normal (left) and advanced glaucoma (right) human eyes. The lamina cribrosa is cupped and excavated beneath the scleral canal rim in the glaucomatous eye. The connective tissue cups of both eyes are delineated in the lower panels. Note the thick pia mater, the laminar insertion into the pia (arrow), and the difficulty in distinguishing between the lamina and the retrolaminar septa in the glaucomatous eye. Scl, sclera. Images courtesy of Harry A. Quigley, MD.

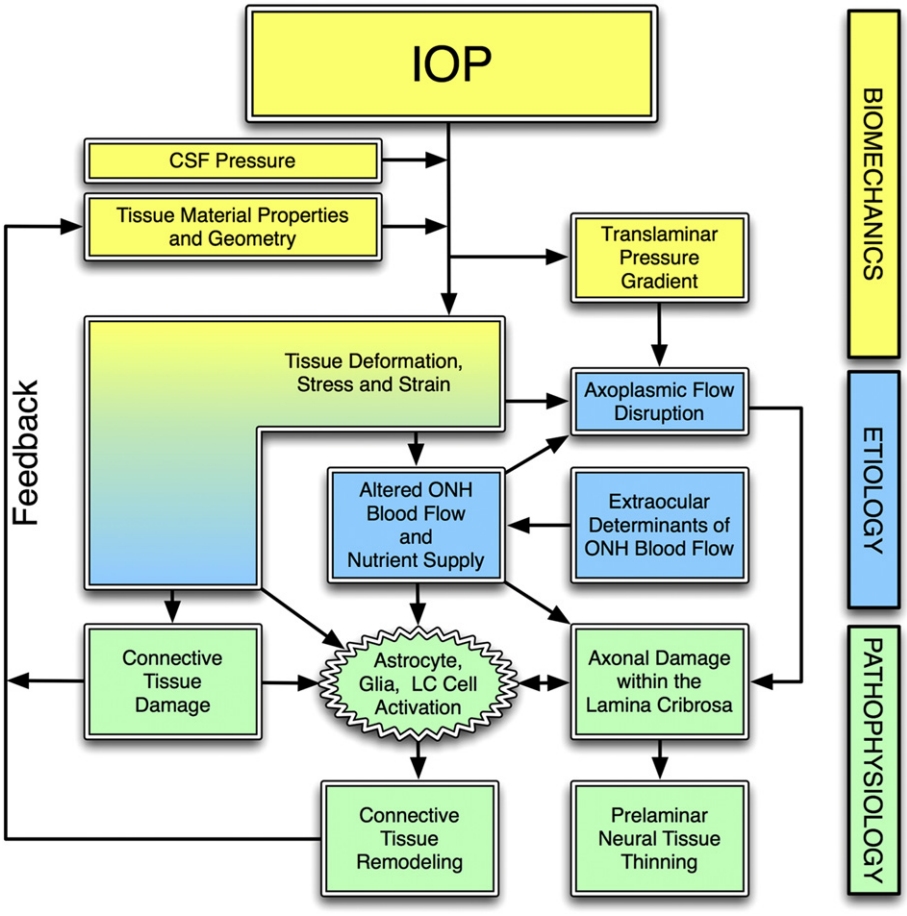

Fig. 2. The biomechanical paradigm of glaucomatous pathophysiology. IOP acts mechanically on the tissues of the eye, producing deformations, strain and stress within the tissues. These deformations depend on the particular tissue geometry and material properties of an individual eye. IOP-induced stress and strain could acutely alter blood flow in the laminar region, and/or delivery of nutrients (secondarily) through chronic alterations in connective tissue. IOP-related stress and strain could also induce alterations in the connective tissues directly (collagen or elastin fiber yield or failure), or indirectly. Indirect effects could include cell-mediated ECM remodeling or non-cell mediated alterations in laminar collagen (Ruberti and Hallab, 2005). These changes in the ONH connective tissues alter their geometries and mechanical responses to loading, which feeds back directly into the mechanical effects of IOP on the ONH. Adapted from Fig. 1 in Sigal et al. (2010b).

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literature on the potential mechanisms of glaucomatous changes in the laminar ECM at the anatomic, structural, cellular and subcellular levels in the context of the biomechanical paradigm of glaucomatous onset and progression.

2. A biomechanical perspective of glaucoma

It is generally accepted that the laminar region of the ONH is the principal site of RGC axonal insult in glaucoma, and therefore a natural site of interest when studying glaucoma (Quigley, 2005). In addition, the region is also interesting from a biomechanical perspective because it is a discontinuity in the corneo-scleral shell. Such discontinuities are often considered weak spots in mechanically loaded systems as they can sometimes be the site of substantial stress concentrations.

The biomechanics of the tissues includes both the acute mechanical response of tissues to mechanical load (i.e., how they deform under load) and the longer term changes in morphology, microstructure, and material properties that are driven by the mechanical environment. In a biomechanical paradigm of glaucomatous optic neuropathy, an ONH's susceptibility to IOP insult is a function of both the acute and long-term response of the constituent tissues to elevated IOP (Burgoyne et al., 2005). Tissue biomechanics can modulate ischemic, cellular, and other events in the ONH. Eyes with a particular combination of connective tissue geometry and stiffness, blood supply, and cellular reactivity may be more susceptible to damage at normal levels of IOP, whereas others may have a combination of these factors that can withstand prolonged periods of relatively high levels of IOP without clinically significant deleterious effects.

Our group (Burgoyne et al., 2005; Downs et al., 2008; Sigal and Ethier, 2009) and others (Levy and Crapps, 1984; Radius, 1987; Zeimer, 1995; Albon et al., 2000; Edwards and Good, 2001; Jonas et al., 2004; Quigley, 2005; Wells et al., 2008; Ren et al., 2009) have hypothesized that IOP-related deformations cause acute yield and/or failure of the anterior laminar beams, thereby transferring load to adjacent beams in a cascade of damage that results in glaucomatous connective tissue cupping. While this seems plausible, there is surprisingly little evidence to support acute mechanical damage to the lamina as the principal mechanism of cupping. We are not aware of any studies that have reported IOP-induced yield or failure of the laminar beams, although this may be due to the lack of appropriate experimental assessment methods. Several studies have indicated that optic disk hemorrhages are a risk factor for focal glaucomatous progression (Leske et al., 2003). These hemorrhages could arise from rupture of prelaminar capillaries or failure of capillary-containing laminar beams, although this association is speculative.

Recent experiments in monkeys have shown that the lamina cribrosa did not deform posteriorly (cup) in response to acute IOP increases (or deformed minimally), while the scleral canal expanded in most eyes (Yang et al., 2009) (Fig. 3). In vivo OCT imaging in the human has yielded similar laminar displacement results, but scleral canal expansion data was not reported (Agoumi et al., in press). In a separate study, Poostchi et al. showed that optic disc diameter is significantly increased in humans after acute IOP elevations (Poostchi et al., 2010). Modeling studies have shown that even if the lamina does not displace posteriorly, laminar stress and strain are significantly elevated compared to that at normal IOP (Sigal et al., 2009a,b; Roberts et al., 2010, in press). This arises from the tensile stretch imposed on the lamina by the acutely expanding scleral canal.

If elevated IOP does not cause appreciable acute laminar cupping, then it is reasonable to regard the connective tissue deformation and cupping typically seen in human and experimental glaucoma as a chronic phenomenon. Early glaucomatous damage has not been rigorously studied in humans because human cadaver eyes with well-characterized early damage are rare. In monkey eyes exposed to chronically elevated IOP, the lamina cribrosa thickens and cups (Yang et al., 2007a,b; Roberts et al., 2009) (Fig. 4). This change in laminar morphology has occurred at the onset of confocal scanning laser tomography-detected ONH surface change, the earliest detectable stage of glaucomatous damage in the monkey.

3. Laminar connective tissue remodeling

Roberts and coworkers have shown that in a monkey model of early experimental glaucoma, the volume of the laminar connective tissues is approximately 80% larger in glaucoma eyes compared to their contralateral controls (Roberts et al., 2009), but that the relative proportion of connective to neural tissue within the laminar region changed minimally. This study also showed that the early glaucoma eyes had an average of 27% more horizontally oriented laminar beams through the thickness of the lamina than their contralateral controls. One interpretation of these results is that in the experimental glaucoma eyes, the immediate retrolaminar septa synthesized connective tissue and were essentially recruited into the 3D load-bearing structure of the lamina. These changes may be driven by responses to the altered biomechanical environment (see below), and we propose that the lamina cribrosa be viewed as a portion of the larger 3D glial structure of the ONH

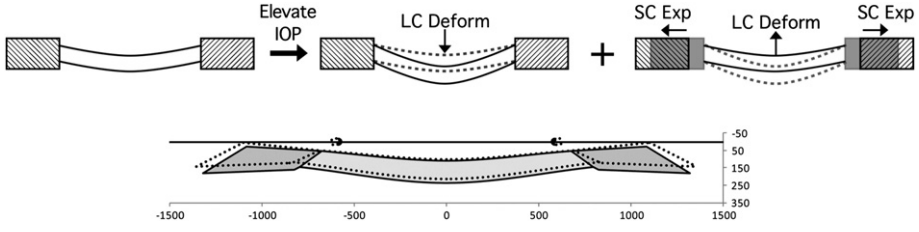

Fig. 3. From a mechanical perspective it is useful to recognize two components of IOP-induced deformation of the lamina cribrosa (top row). One component is the effect of IOP on the anterior laminar surface, which deforms the lamina posteriorly (top middle). Another component is the effect of IOP on the sclera, which causes an expansion of the canal (top right). The deformations are transmitted to the lamina through its insertion into the canal wall, resulting in a lamina that pulls "taut" thereby displacing anteriorly. As IOP increases, both components act simultaneously. The magnitudes of the components of deformation depend on both the material stiffnesses of the lamina and sclera (Sigal et al., 2005; Roberts et al., 2010, in press). Interestingly, models (Roberts et al., 2007; Sigal et al., 2007, 2009a,b, 2010c,d) and recent experimental evidence in both monkeys (Yang et al., 2009) and humans (Agoumi et al., in press) suggests that often the two components of laminar deformation combine to produce a very small (under 10 μm) net anterior–posterior laminar displacement (bottom). The bottom panel shows a schematic representation of the lamina cribrosa and peripapillary sclera of contralateral eyes of a monkey, fixed at low (10 mmHg, solid colors) or high (45 mmHg, dotted lines) IOP (adapted from Yang et al., 2009). It is important to note that even under a very small net anterior–posterior laminar displacement, the IOP-related strains and stresses within the lamina and peripapillary sclera may be substantial.

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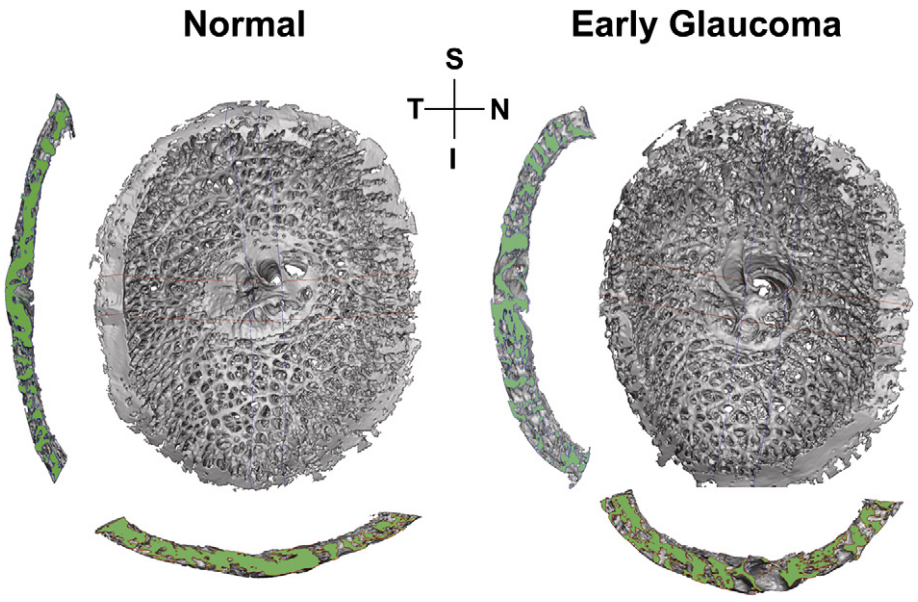

Fig. 4. 3D reconstructions of the laminar connective tissues of a monkey, with one eye having early experimental glaucoma. Shown are en face views of the laminar reconstructions, as well as views of the central vertical (left) and horizontal (below) sections. Note the thicker and deeper (cupped) lamina in the early glaucoma eye (Roberts et al., 2009). Both eyes are shown in OD configuration. S, superior; I, inferior; N, nasal; T, temporal.

(Oyama et al., 2006) that has synthesized the additional connective tissue components necessary to bear the forces of IOP.

There is also evidence suggesting that remodeling of the lamina results in a progressive posterior movement of the laminar insertion into the canal wall. Such a migration eventually results in the posterior lamina inserting into the pia mater. This has been observed in ostensibly healthy human eyes (Sigal et al., 2010a) (Fig. 5), and more recently in monkey eyes with experimental glaucoma (Yang et al., 2010). Careful inspection of the glaucoma eye in Fig. 1 suggests that the lamina may partially insert into the pia.

Extensive remodeling of the lamina cribrosa extracellular matrix (ECM) occurs in primary open angle glaucoma. For example, in

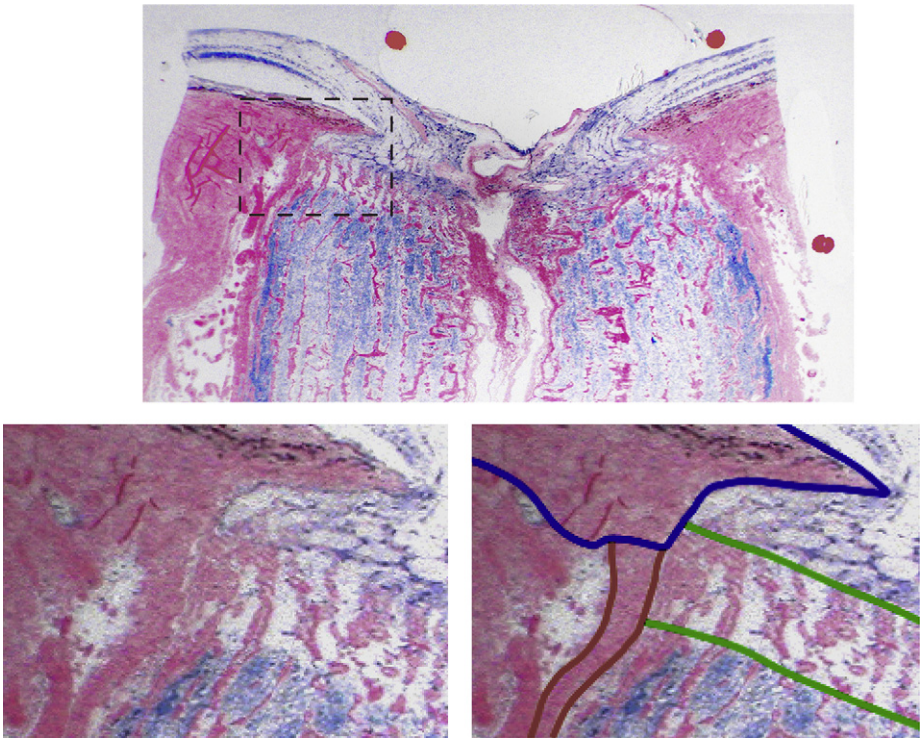

Fig. 5. Example of lamina cribrosa partially inserting into the pia mater (from Sigal et al., 2010a). Shown is a superior–inferior section of an ostensibly healthy (i.e. not glaucomatous) eye from a 79-year-old male donor fixed at 5 mmHg. The bottom panel is a zoomed view of the rectangle marked in the top panel. The bottom right panel shows outlines of the regions delineated as lamina cribrosa (green), sclera (blue) and pia mater (red). It has been traditionally thought that the lamina inserted solely into the sclera, but a laminar insertion into the pia has now been reported in humans (Sigal et al., 2010a) and monkeys (Yang et al., 2010).

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human eyes with a history of glaucoma, there was a significantly greater percentage of area occupied by elastin in the lamina cribrosa compared with age-matched control eyes (Pena et al., 1998). Hernandez and colleagues observed loss and fragmentation of elastin fibers at the bottom of the glaucomatous cup and disorganization in the peripheral walls of the cup. They described a thick dense collagenous matrix separating the remnant nerve bundles at the posterior laminar boundary (where the axons become myelinated) that was not present in normal eyes (Hernandez, 1992).

It has been proposed that ONH astrocytes and lamina cribrosa cells play a central role in mediating the laminar ECM remodeling response and the resulting axonal insult (Hernandez, 2000; Morgan, 2000). Cell activity associated with ECM remodeling has been observed in response to glaucoma in humans and exposure to chronically elevated IOP in animal models. Agapova and colleagues showed that matrix metalloproteinases (MMPs) are elevated in the lamina cribrosa of monkeys with experimental glaucoma, but not those with optic nerve transaction (Agapova et al., 2003). These compounds are known to break down the ECM and allow cells to migrate and rebuild the matrix (Hernandez, 2000). This result supports the hypothesis that elevated IOP, and presumably mechanical insult to the laminar cells and/or reduced blood flow in the laminar region, underlie the significant ECM remodeling observed in glaucomatous eyes. Interestingly, these potential mechanisms were both driven by exposure to chronically elevated IOP, a biomechanical insult, and are not simply a secondary effect of axonal damage and death.

4. Mechanotransduction in the lamina cribrosa

Several studies have investigated the mechanisms of cell mechanotransduction in astrocyte and LC cells in vitro (O'Brien et al., 1997; Kirwan et al., 2004, 2005; Rogers et al., 2010). Kirwan et al. (2004) have shown that cyclical mechanical stretch of the substrate on which cells were grown induced significant increases in TGF-β1 mRNA synthesis after 12 h and TGF-β1 protein secretion after 24 h. Both applied cyclical stretch and exogenously delivered TGF-β1 significantly increased MMP-2 activity in cell media.

Integrins are proteins that span the laminar astrocyte basement membranes and bind the cell cytoskeleton to the surrounding the ECM. Thus, integrins are particularly well-suited to act as mechanosensory elements in the lamina. Morrison has described the location and alteration of integrin subunits in normal and glaucomatous human and monkey eyes and proposed them as an important link between laminar deformation, IOP-induced cell stretch and damage, laminar connective tissue remodeling and laminar astrocyte mediated axonal insult in glaucoma (Morrison, 2006). In an in vitro study, O'Brien and colleagues have shown that hypotonic membrane stress activates stretch activated channels and Ca^{2+}-dependent maxi-K^{+} channels in LC cells (Irnaten

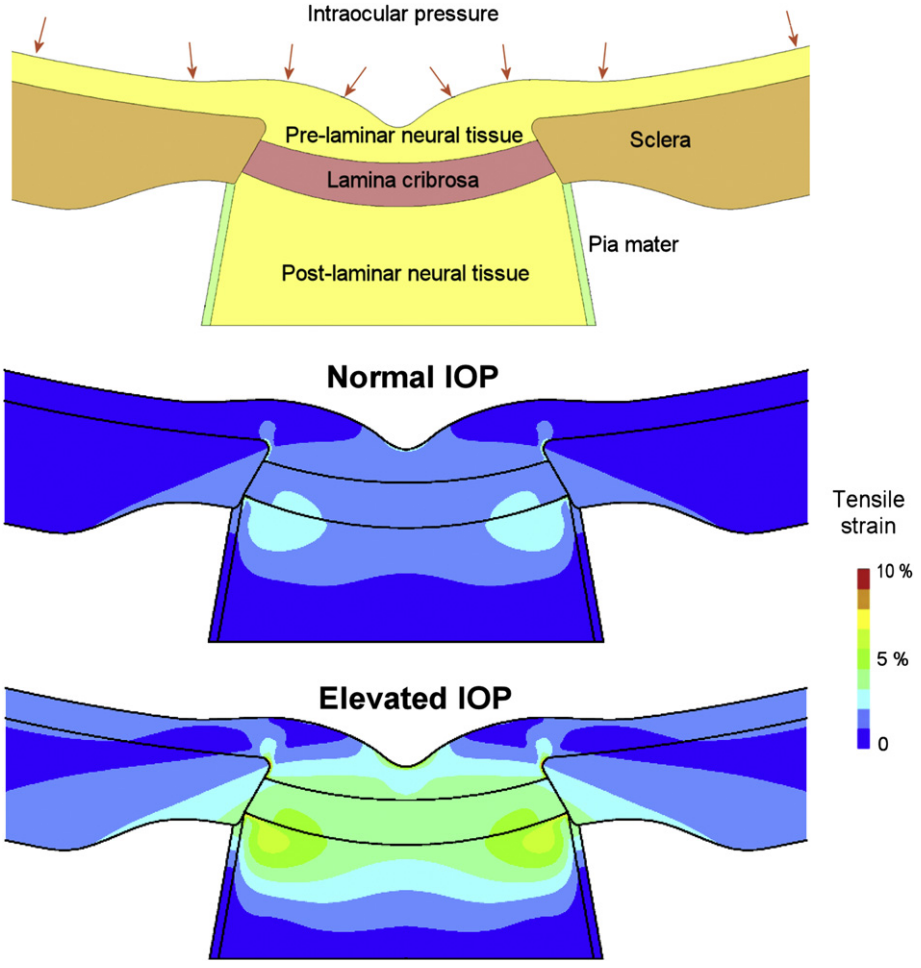

Fig. 6. Generic, axisymmetric finite element model of the ONH with five tissue regions: sclera, lamina cribrosa, pre- and retro-laminar neural tissues and the pia mater (top). The model was used to predict the IOP-related strains at normal (12.5 mmHg, middle) and elevated (25 mmHg, bottom) IOP. Note the regions of high strain in the retro-laminar neural tissues near the laminar insertion into the sclera, and in the pre-laminar neural tissues near the scleral canal opening.

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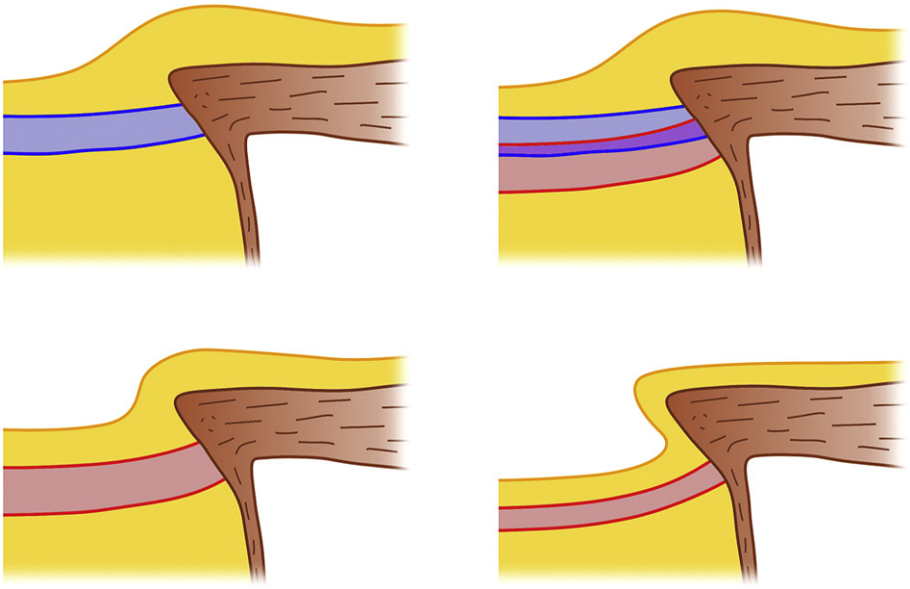

Fig. 7. Diagram illustrating our proposed progression of an ONH from a normal morphology, through early IOP-induced laminar remodeling, to end stage glaucomatous cupping and excavation. The top left pane shows a normal, healthy ONH (the lamina cribrosa is blue, pre- and retrolaminar tissues are yellow, and the sclera and pia mater are brown). Following chronic exposure to stress and/or strain that are beyond the physiologic tolerance of the resident cells, the lamina is remodeled to a thickened and cupped shape, and the laminar insertion begins to move posteriorly into the pia (top right; normal lamina in blue and remodeled lamina in red). As glaucomatous damage progresses with continued exposure to a biomechanically driven insult, the prelaminar neural tissues begin to thin (bottom left). Eventually, most of the RGC axons are lost and the lamina scars and thins to a classic cupped, excavated glaucomatous morphology (bottom right).

et al., 2009), which could act as another potential mechanotransduction mechanism in the lamina.

It has been established in other systems that the biologic response of tissues and cells depends strongly on the mode of the strain stimulus (tension, compression or shear), as well as on their magnitudes and temporal profiles (Edwards et al., 2001; LaPlaca et al., 2005; Pedersen and Swartz, 2005). It is therefore of interest to determine which modes of strain and stress the tissues of the ONH are exposed to as IOP is elevated. Note that strains are generally not homogenous (Sigal et al., 2007). When the LC deforms, some regions could be highly strained in different modes, while others remain largely unaffected. This is important because the biological effects on cells are likely to be more dependent on the local levels of strain or stress than on global levels (Tan et al., 2006; Wang and Thampatty, 2006).

Developing a comprehensive mechanistic understanding of the role of biomechanics in glaucoma using in vitro studies has been hampered by the lack of data on the true stresses and strains that the cells in the lamina experience. This is principally due to the technical challenges of measuring these quantities in vivo. Advances in imaging, such as second harmonic imaging (Brown et al., 2007), or deep-scanning SD-OCT (Kagemann et al., 2008; Agoumi et al., in press) may soon enable the reliable measurement of IOP-induced laminar deformation in vivo.

5. Modeling of laminar biomechanics

Numerical modeling has therefore become a common approach to study ONH biomechanics and evaluate hypothetical scenarios (Edwards and Good, 2001; Sigal et al., 2005, 2009a,b; Sander et al., 2006; Downs et al., 2009; Grytz and Meschke, 2009; Sigal, 2009; Roberts et al., 2010, in press). Fig. 6 shows an example of the predictions made with a finite element model of the ONH. Although the magnitude and distribution of the strains depends on the assumed shape and mechanical properties of the tissues, there has been remarkable consistency in the predictions made with generic (Bellezza et al., 2000; Sigal et al., 2005; Grytz and Meschke, 2009; Sigal, 2009), eye-specific (Sigal et al., 2007, 2009a,b; Roberts et al., 2010, in press), and analytic (Edwards and Good, 2001; Sander et al., 2006) models. All models consistently predict regions of relatively large strain in the peripheral lamina.

Models have also been used to study how ONH biomechanics are affected by the changes in the lamina and sclera associated with early experimental glaucoma. Eye-specific models created from 3D reconstructions of monkey ONHs show that for an identical IOP increase, laminar stresses were lower in the early experimental glaucoma eye than in the contralateral normal eye (Roberts et al., in press). The stress-lowering effects of laminar thickening and cupping have also been reported in sensitivity studies based on axisymmetric generic models of the human ONH (Sigal et al., 2005; Sigal, 2009) and in parameterized models of the monkey eye (Sigal et al., 2010c,d). When considered together, these studies suggest that connective tissue remodeling may be triggered within an ONH exposed to levels of stress and strain that exceed the physiologic tolerance of the resident cells. This suggests a biomechanical feedback mechanism through which cells modify their local environment in an attempt to return to a homeostatic mechanical environment. Note that this cascade of events could occur at IOPs in the normal range in eyes that are particularly susceptible to IOP-related stress, strain, ischemia, or cellular activation because of their individual geometric, material, vascular, and other properties.

6. Conclusion

When viewed in the context of ONH biomechanics and the glaucomatous changes in the laminar ECM at the anatomic, structural, cellular and subcellular levels, it seems plausible that connective tissue remodeling is a mechanism in the progression of laminar morphology from a normal state to that of a cupped, excavated glaucomatous state (Fig. 7). This remodeling is adaptive, at least for the load-bearing connective tissue, although it may not prevent irreparable harm to the retinal ganglion cells.

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