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Review

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Mechanobiology in the eye

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The eye presents a very dynamic biomechanical environment, and thus ocular cells must be highly mechanosensitive and mechanoresponsive. Moreover, defects in mechanobiological pathways contribute to a number of sight-threatening ocular diseases, highlighting the importance of ocular mechanobiology. We here give a concise overview of the mechanobiology of ocular cells in the lens and cornea (and how mechanobiology plays a role in associated pathologies in these tissues), before providing a detailed review of the mechanobiology of the common blinding disease, glaucoma. Mechanical stimuli are intimately linked with the pathology of glaucoma, both in terms of altered homeostasis of the eye's internal pressure control system and in the response of neural cells to elevated pressure in the eye. A complex array of mechanosensory elements (stretch-activated ion channels, integrins, G protein-coupled receptors) work together with intersecting networks of mechanotransducing pathways in cells of both the posterior and anterior eye in glaucoma. Despite intense research efforts over the past decades, much remains unknown about the mechanobiology of glaucoma. Continued investigation of glaucomatous mechanobiology is important, as it may reveal novel targets for treating this challenging disease.

The eye is a remarkably complex organ that permits sensing of visual information, an ability which is hugely advantageous for almost all higher organisms, including humans. Indeed, vision loss is consistently ranked as one of the most feared disabilities with significant impact on quality of life[1,2], and thus understanding the function of the eye has long been of great scientific and clinical interest.

Our goal in this work is to provide a concise survey of mechanobiology in vision. To those not familiar with the field, it may be initially surprising that mechanobiology is critically important in ocular physiology and pathology. However, the mammalian eye is a very biomechanically active environment: it is endowed with external (extraocular) and internal muscles, with a fluid circulatory system that internally pressurizes the eye globe, and with a rich vascular network. Further, the posterior eye is acted upon by cerebrospinal fluid pressure. It follows that ocular cells and tissues must be able to sense, transduce and respond to a variety of biomechanical stimuli.

Terminology

For the avoidance of doubt, we here explicitly define the terminology we will use throughout this review. We define mechanosensing as the ability of a cell to sense mechanical cues from its microenvironment[3], whereas we define mechanotransduction as the cellular processes that translate mechanical cues into biochemical signals[4]. Collectively, we refer to these processes, as well as any downstream signaling triggered by mechanotransduction, as mechanobiology.

Brief overview of two ocular pathologies involving mechanobiology

Mechanobiological processes often become particularly evident in pathological states. Here we touch on two such states in the eye to give readers a sense of the scope of ocular mechanobiology: posterior capsule opacification (PCO) and keratoconus. We note that the brief treatment of these two topics is not a reflection of them being unimportant; quite the contrary, they are very important, but are somewhat under-studied, and thus present excellent opportunities for novel research. We further recognize that there are other important ophthalmic diseases that likely involve abnormal biomechanics, including myopia[5,6], age-related macular degeneration[7], and diabetic retinopathy[8,9]. However, even though biomechanics and mechanobiology play roles in these conditions, the evidence for aberrant mechanobiological processes being critical initiators of pathology in these conditions is much less robust. Due to space constraints, we thus do not further discuss these conditions in this work, and note that further research in these areas is needed.

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The lens and posterior capsular opacification

The lens helps focus light on the retina and its form and function are complex. Accommodation is the process by which the eye changes its focal length, and involves the action of the ciliary muscles so as to change the shape of the lens[10]. Anatomically, moving from the center of the lens to its outer surface, the lens is formed by lens fibers; the lens epithelium whose apical surface is oriented towards the center of the lens; and the lens capsule, the basement membrane of the epithelium (Fig. 1)[11]. This capsule is rather thick (4–15 μm in humans, depending on age and location[12]) and demonstrates heterogeneous biomechanical properties that are predicted to lead to a spatially equibiaxial tensile stress field in the capsule[13,14], strongly suggesting the existence of a homeostatic mechano-feedback loop mediated by lens epithelial cells. This homeostatic environment is disrupted in patients receiving cataract surgery, in which a portion of the anterior lens capsule is removed; this disruption leads to PCO in c. 30% patients 5 years after surgery[15], with significant negative effects on vision. The pathophysiology of PCO is complex but in some forms is thought to involve aberrant migration and extracellular matrix (ECM) production by lens epithelial cells after capsular disruption[16]. It is thus thought that lens epithelial cell mechanobiology may be important in PCO[17], yet surprisingly little is known about relevant pathways. Cheng and colleagues have shown that Eph-ephrin signaling is important in lens biomechanical signaling[18,19], yet much more remains to be discovered about mechanobiology in this intriguing and clinically important area.

The cornea and keratoconus

The cornea is the clear tissue at the front of the eye which must transmit light efficiently for good visual acuity (Fig. 1). It also has an important structural role, which conflicts somewhat with the requirement for transparency. The cornea has therefore evolved to have a remarkable structure: a central stroma is located between anterior epithelial and posterior endothelial cells, each of which has a basement membrane, resulting in a five layer "sandwich".

Considering first the anterior-most aspect of the cornea, corneal epithelial cells are endowed with a number of known mechanosensors, including several TRPV-family stretch-activated ion channels[20–24], focal adhesion kinase (FAK) and paxillin[25], and integrins[26] including α6β4 and α3β1. Further, the corneal epithelium is exposed to a variety of external stresses, notably shear stresses including those due to tear film motion and blinking, as well as more complex stresses due to eye rubbing and contact lens wear[27]. These stresses, as well as the effects of substrate stiffness and topography, have been shown to affect a number of important aspects of corneal epithelial phenotype, including cytoskeletal architecture, junctional architecture, migration, apoptosis, and stemness, as reviewed in refs. 27,28.

We next consider the stroma, where stromal keratocytes are embedded in a dense connective tissue notable for its highly ordered collagen bundle structure and regular spacing, necessary for tissue optical clarity. Keratocytes are responsible for maintaining stromal ECM structure in the face of mechanical loading due to intraocular pressure (IOP), as well as for wound repair. Stromal keratocytes are sensitive to substrate stiffness and topography in a complex manner that depends on the local signaling environment, e.g., responses are modulated by levels of transforming growth factor-β1 (TGF-β1), interleukin-1β and tumor necrosis factor-α. Interested readers are referred to the excellent review by Thomasy et al. of this topic[28]. These cells are also sensitive to stretch[29–31], important in the development of the common pathology known as keratoconus, in which the cornea experiences significant abnormal deformation[32]. Mechanosensing and mechanotransduction in corneal keratocytes are intriguing: these cells form a syncytium and it has been shown that transient cell membrane disruptions (TPMDs; essentially transient micro-tears in the cell membrane) induced by ostensibly benign events such as eye rubbing, led to calcium increases in the affected cell, which in turn caused calcium waves in neighboring cells[33]. Focal adhesions have also been implicated as an important mechanosensory in corneal keratocytes[34], with downstream signaling involving YAP/TAZ[28].

Finally, we consider the corneal endothelium, which actively pumps ions, and hence fluid, to de-swell the cornea and thereby control stromal hydration and maintain optical clarity. These endothelial cells lay down a specialized basement membrane (Descemet's membrane; DM) and changes in the stiffness or topography of DM area strongly associated with corneal endothelial pathologies[35]. A number of studies have identified YAP and TAZ as key mechanotransducers in corneal endothelial cells (carefully reviewed in[28]), with changes in YAP/TAZ nuclear translocation being driven by changes in DM stiffness. YAP/TAZ mechanotransduction is modulated by TGF-β1, TGF-β2 and Wnt signaling, and these pathways are the subject of multiple studies in corneal tissue engineering as treatment for corneal dystrophies[28]. In brief, increased nuclear translocation of YAP led to more endothelial cell proliferation; conversely, several models in which YAP or TAZ nuclear translocation was reduced demonstrated reduced endothelial cell numbers, abnormal endothelial morphology and reduced endothelial regeneration after wounding, which are also features of corneal dystrophies. These data implicate YAP/TAZ signaling as being important in corneal dystrophies, although specific downstream signaling events from altered YAP/TAZ activation in these pathologies are currently unknown.

Glaucoma

Glaucoma is a complex family of pathologies of diverse etiology whose members share certain common clinical features, including structural change in the optic nerve head (ONH; Fig. 1) and progressive, irreversible damage to retinal ganglion cell (RGC) axons[36–38]. The RGCs are responsible for transmission of visual information from the retina to the brain, and damage to these cells is the sight-threatening event in glaucoma and cause of visual field deficits[39–42]. This disease affects nearly 80 million people worldwide, is the second leading cause of blindness in the modern world, costs $3+ billion annually in the US alone[43], and will increase in prevalence as the population ages[44].

Relevant to this article, the pathophysiology of glaucoma is closely intertwined with mechanics and mechanobiology. Many (although not all) glaucoma patients demonstrate elevated IOP; however, no matter the starting IOP, significant, sustained IOP reduction benefits patients[45–48]. Consequently, all current therapeutic approaches seek to reduce IOP, indicating a key role for mechanobiology in this disease[49,50]. Thus, and perhaps not surprisingly, glaucoma is the ophthalmic condition in which mechanobiology has been best studied, as will be seen below. Specifically, the study of why IOP is dysregulated in some glaucoma patients, and why elevated IOP causes RGC damage, are two topics of intense study that directly involve mechanobiology. We consider each of these in turn below.

Mechanobiology of the outflow pathway in glaucoma

IOP is determined and maintained by the constant secretion of aqueous humor, a clear fluid that fills the anterior eye, and by the resistance to its outflow from the anterior chamber. Outflow passes through the trabecular meshwork (TM) and Schlemm's canal (SC) inner wall endothelium with its basal lamina[51–53], the principal tissues of the conventional outflow pathway (Fig. 2A). Pathological alterations in the outflow tissues cause the characteristically increased outflow resistance in high-IOP glaucoma[52,54]. Strong evidence supports the existence of multiple mechanobiological homeostatic feedback loops regulating IOP[55]; generally, IOP elevation causes increased mechanical stimulation (stretch on TM cells and shear stress acting on SC cells), which in turn leads to phenotypic changes in outflow pathway tissues predicted to renormalize IOP, including matrix metalloproteinase secretion in response to TM stretch[56–58], increased nitric oxide production in response to shear stress on SC cells[59,60], and formation of pores in SC cells[61,62]. Thus, impairment of the ability of TM and/or SC cells to sense or transduce mechanobiological stimuli are expected to impair IOP homeostasis; as we will see below, there are a number of molecular players in these homeostatic pathways.

In addition to direct alterations in mechanosensing and/or mechanotransduction in outflow pathway tissues, there are important secondary effects in glaucomatous eyes. Notably, compelling evidence supports the

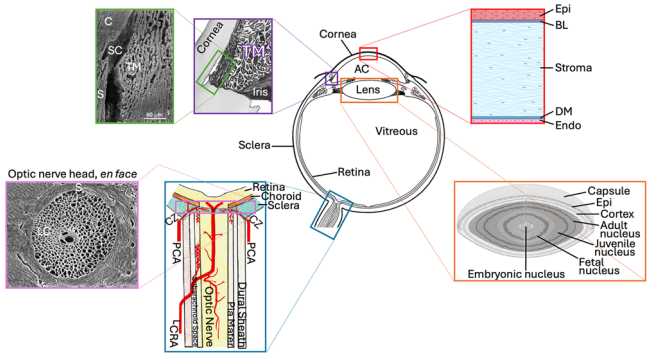

Fig. 1 | Schematic overview of human ocular anatomy, showing the cornea, anterior chamber (AC), lens, vitreous, retina and sclera . The inset at top right (red box) shows a magnified schematic view of the cornea, including (from anterior to posterior): the corneal epithelium (Epi), Bowman's Layer (BL), the corneal stroma with resident keratocytes (dark blue), Descemet's membrane (DM), and the corneal endothelium (Endo). The insets at top left show two magnified views of the conventional outflow pathway, located where the cornea, iris and sclera join. The purple boxed inset gives a schematic overview, while the green boxed image is a scanning electron micrograph from a human eye, in which Schlemm's canal (SC), the trabecular meshwork (TM), the cornea (C) and the sclera (S) are identified. At lower right (orange box), the lens is shown, with details of its internal structure. Finally, at lower left (blue box), a schematic view of the optic nerve and surrounding structures is shown, with blood vessels and other structures identified, including the posterior ciliary arteries (PCA), the retina, the sclera (S), the central retinal artery and vein (CRA), the subarachnoid space, the optic nerve, the pia mater, the dural sheath, and the circle of Zinn and Haller (CZ). Immediately to its left (purple box) is an *en face* view of the optic nerve head region, in which a digestion process has been carried out to leave only the major connective tissues, namely the sclera and lamina cribrosa (LC). The schematic image of the cornea was created in Biorender.com and is based on ref. 284, the image of the lens is taken from ref. 285, the overview of the conventional outflow pathway is modified from ref. 286, the scanning electron micrograph of the outflow pathway is modified from ref. 159, the overview of the optic nerve head is modified from ref. 287, and the *en face* view of the optic nerve head is modified from ref. 288.

observation that the TM from glaucoma eyes is markedly stiffer compared to that from ostensibly normal eyes[63–66], which in turn may negatively affect the tissue's response to mechanical stretch even from normal IOP fluctuations[67]. Consequently, TM and SC inner wall cells in the glaucomatous outflow tract are exposed to altered biomechanical stresses[61,66] that govern diverse mechanobiological adaptation processes involving cellular mechanosensing and mechanotransduction apparatuses. We discuss these separately in the following sections.

Mechanosensing

TM cells are equipped with several key mechanosensors such as mechanically-gated ion channels, integrin transmembrane receptors, and G protein-coupled receptors (GPCRs) (Fig. 2B).

Mechanosensitive ion channels. Mechanosensitive ion channels are directly and rapidly activated by stresses acting on the lipid bilayer or its associated non-membrane components[68]. Among the various types of channels found in the TM, TRPV4[69–77], Piezo1[78–81], and TREK-1[82–85] are the best understood. Interested readers are referred to recent reviews for further details on mechanosensitive ion channel biology[86–88]. TRPV4 channels in TM cells are activated by physiological pressure steps[80,85] and strains[69,70] to activate outflow-relevant downstream signaling components/mechanisms including Rho kinase, F-actin, paxillin and vinculin, reorganization of membrane lipids, and ECM release[69–71]. Recent evidence suggests that TRPV4 activity underpins increased outflow resistance under both physiological and pathological conditions[75]. The data that tonic TRPV4 activity is obligatory to maintain TM contractility and TGF-β2-induced ocular hypertension[75] may help resolve contradictory conclusions from previous studies, which implicated TRPV4 signaling in both ocular hypertension and hypotension[69–72,76,80,89]. For instance, TRPV4 has been proposed to lower IOP through phosphoinositide signaling in primary cilia[89], promote the release of polyunsaturated fatty acids[72], and activate downstream Piezo1 mechanosensing[90]. However, TRPV4-regulated Ca^{2+} influx in TM cells is unaffected by primary cilia ablation[69], polyunsaturated fatty acids stimulate rather than inhibit TRPV4[69], and TRPV4 signaling in TM cells is unaffected by pharmacological or genetic Piezo1 inhibition[80]. Furthermore, Piezo1 inhibition reduces outflow facility ex vivo and in vivo[80,81], suggesting opposing functions for Piezo1 vs. TRPV4 activation in the context of IOP homeostasis. Taken together, ion channel-mediated mechanosensing plays a clear role in modulating TM cell behavior, with only little published information available on SC cells. It is conceivable that small-molecule TRPV4 antagonists could be explored for clinical IOP lowering strategies to protect retinal neurons; yet, additional studies will be required to refine the involvement and cross-regulation of different mechanosensitive ion channels in outflow tissue physiology and glaucoma onset/progression.

Integrin transmembrane receptors. Integrin transmembrane receptors link the ECM to the actomyosin cytoskeleton via a complex of adapter proteins[91]. There are 12 different integrins in the outflow pathway[92]. While most of them are expressed in both the TM and SC (with some differences in the levels of α2β1, α3β1, α6β1, αvβ3, αvβ5 integrins[92]), their activity is likely to vary and subject to modulation. Consequently, the mechanosensing function of integrins is thought to change dynamically in tandem with alterations in the biophysical properties of the outflow tract. Interested readers are referred to recent reviews for more details on the plethora of biological processes in the TM controlled by integrin signaling[92–95]. Of all integrins in the outflow pathway, the αvβ3 integrin is most likely to be a key player in glaucoma pathophysiology. Unlike other integrins, αvβ3 integrin has several ligands implicated in outflow tissue and IOP homeostasis. For instance, connective tissue growth factor[96] and fluid shear stress[97] were shown to increase αvβ3 integrin activity in TM cells, with further implications for SC inner wall cells[97]. The glaucoma-associated glucocorticoid dexamethasone also increases the expression and activation of αvβ3 integrin through a secondary effect involving the transcription factor NFATc1[98,99]. By the same token, pro-fibrotic TGFβ2[100] was shown to increase TM cell αvβ3 integrin expression[101], with its activation further driving TGFβ2 expression via a potential feedback loop[102]. In addition, TGFβ2-induced thrombospondin-1 expression can activate αvβ3 integrin signaling[103].

Another important feature of αvβ3 integrin in mechanosensing is its spatial localization; αvβ3 integrins are found in podosomes/invadopodia-/filopodia-like structures (including tunneling nanotubes) in TM cells[104–106] and exhibit stable localization in focal adhesions driven by forces on the actomyosin network[107,108]. However, αvβ3 integrin has a weaker bond strength and faster binding/unbinding rates compared to other integrins such as α5β1 integrin within focal adhesions[109]. This makes αvβ3 integrin well suited to sense and modulate changes in the contractile properties of the TM/SC cytoskeleton (possibly acting as an on/off switch) involving force-induced changes in its interactions with ECM ligands[110]. Lastly, we consider known αvβ3 integrin crosstalk. Cooperative crosstalk between activated αvβ3 and β1 integrins in TM cells drives the formation of glaucoma-associated cross-linked actin networks[111] in a Rac1-dependent manner[99,103,112]. In another Rac-1-mediated signaling event, activated αvβ3 integrin was shown to decrease phagocytosis by inhibiting αvβ5 integrin activity[113,114] via transdominant crosstalk[115]. Cooperative signaling between αvβ3 and α5β1 integrins in focal adhesions facilitates RhoA-mediated fibronectin fibrillogenesis in TM cells; specifically, it increases the deposition of alternatively spliced fibronectin-EDA[116] that is associated with ECM changes observed in ocular hypertensive glaucoma[117]. Consistent with these critical functions in TM cellular processes, αvβ3 integrin activation was shown to decrease outflow facility and increase IOP in mice, while its knockdown had the opposite effect and decreased IOP[118]. In summary,

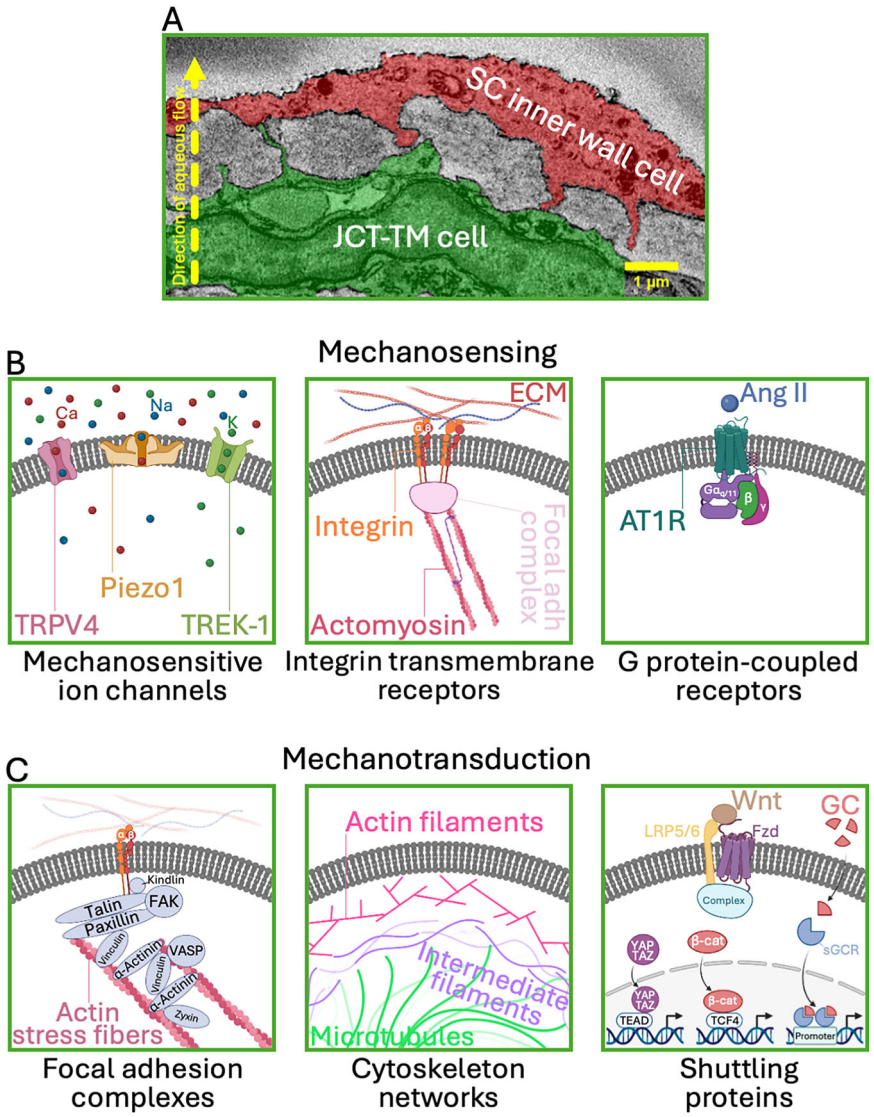

Fig. 2 | The principal tissues of the outflow pathway and key mechanosensing and mechanotransduction pathways. A Serial block-face scanning electron micrograph showing the interface between a Schlemm's canal (SC) inner wall cell and a juxtacanalicular-trabecular meshwork (JCT-TM) cell, with direction of aqueous humor flow indicated by the yellow arrow (reproduced and adapted from ref. 289 with permission from the authors under a Creative Commons license). **B** Schematic overview of relevant mechanosensing machineries including mechanosensitive ion channels (TRPV4, Piezo1, TREK-1), integrin transmembrane receptors, and G protein-coupled receptors (angiotensin II type 1 (AT1R) receptor). **C** Schematic overview of relevant mechanotransduction machineries including focal adhesion complexes (talin, paxillin, kindlin, vinculin, FAK, α-actinin, zyxin, VASP), cytoskeleton networks (actin filaments, intermediate filaments, microtubules), and shuttling proteins (YAP/TAZ, Wnt/β-catenin, glucocorticoid (GC)/soluble GC receptor). Schematics in (**B**, **C**) created using BioRender.com.

owing to their combined biochemical and mechanical properties, integrin receptor-mediated mechanosensing plays a central role in modulating outflow cell/tissue homeostasis and glaucoma pathophysiology. The wealth of data on αvβ3 integrin signaling highlights the importance of investigating mechanistic details of how integrins sense, respond to, and interact with ECM of varying properties with exquisite specificity. And while not without challenges, recent advances in other research fields[119] suggest that clinical development of new small-molecule inhibitors targeting αvβ1 integrins may be a viable strategy for treating ocular hypertensive glaucoma given the crosstalk with αvβ3 integrin in aberrant cross-linked actin network formation.

G protein-coupled receptors. GPCRs comprise the largest class of cell surface receptors[120]. Emerging evidence suggests that mechanosensitive 7-transmembrane GPCRs facilitate cellular responses to biophysical cues, such as mechanical stretch and fluid shear stress[121,122], in addition to light or chemical ligands[121]. This is thought to be a slower mechanism (seconds to minutes) compared to mechanically-gated ion channels (milliseconds)[121]. The angiotensin II type 1 (AT1R) receptor was among the first GPCRs for which ligand-independent activation by mechanical forces was shown[123], with clear implications in modulating outflow function and IOP homeostasis. Interested readers are referred to recent reviews for additional details on the role of the renin-angiotensin system in outflow (patho)physiology[124–126]. Upon binding to AT1R, angiotensin II has been shown to induce TM cell proliferation and increase mRNA and protein expression of glaucoma-associated fibrotic markers (e.g., collagen type I, fibronectin, phospho-myosin light chain (p-MLC), α-smooth muscle actin (αSMA)), possibly via a NOX4/ROS axis in cooperation with the SMAD3/TGFβ pathway[127–129]. Other studies showed that angiotensin II decreases outflow facility in rabbits[130] and monkeys[131,132], with additional evidence that AT1R activation may modulate uveoscleral outflow and elevate IOP[133–135]. By contrast, angiotensin (1–7)—the product of angiotensin II conversion by ACE2[136]—was shown to oppose the molecular and cellular effects of Ang II and lower IOP[130,137], with potential benefits for glaucoma therapy[138]. Taken together, GPCR-mediated mechanosensing contributes to modulating aqueous humor dynamics and IOP homeostasis. Of note, there are presently no studies that directly interrogated mechanosensitive GPCRs in SC cell/tissue function despite the known regulatory role of shear stress[139]. This opens the door for nuanced future investigations to refine the involvement and regulation (incl. crosstalk) of the renin-angiotensin system in outflow tissue physiology and pathophysiology in glaucoma.

We recognize that there are additional mechanosensing structures present throughout the outflow pathway that may mediate cellular responses to mechanical stretch and fluid shear stress. These include the somewhat lesser studied (yet no less important) putative mechanosensitive

GPCRs[140] as well as receptor tyrosine kinases, glycocalyx proteins, and junctional proteins[3]. Unfortunately, their inclusion is outside the scope of this work and readers are referred to the primary citations above.

Mechanotransduction

TM cells are endowed with key mechanotransduction machineries, including focal adhesion complexes, cytoskeleton networks, and shuttling proteins (Fig. 2C).

Focal adhesion complexes. Focal adhesion complexes transfer mechanical cues from the ECM to the actomyosin cytoskeleton. To execute this task, focal adhesions have two distinct compartments: an integrin transmembrane receptor[91] (discussed above) and an intracellular linkage complex composed of the large adapter protein talin[141] and numerous additional proteins such as kindlin, vinculin, paxillin, zyxin, and vasodilator-stimulated phosphoprotein (VASP)[91] that jointly form the interface with actin filaments. Another critical component of many cell-matrix junctions is FAK, serving important functions in downstream signaling[142]. The molecular composition of focal adhesions is highly variable, dynamic, and sensitive to ECM composition and mechanics[143]; this has direct implications for outflow tissue function and IOP regulation in health and disease. For example, ECM rigidity/stiffness has been shown to modulate focal adhesion size in TM cells. Vinculin puncta were larger and more frequent on stiff compared to soft matrix, independent of the culture substrate type (i.e., glass, synthetic polyacrylamide gel, natural ECM hydrogel)[144,145]. Of note, comparable observations were made in SC cells, showing more prominent vinculin-containing focal adhesions with increasing substrate stiffness[61]. In TM cells, FAK activation via phosphorylation increased with increased substrate rigidity[144]. By the same token, mechanical stretch was found to increase colocalization between vinculin and phospho-FAK, along with paxillin, in a TRPV4- and Rho-associated kinase (ROCK)-dependent manner[70]. As with other focal adhesion components, mechanical stretch augmented zyxin phosphorylation and translocation toward actin stress fibers in TM cells[70]. Lastly, as in indirect link to glaucoma pathophysiology, VASP was detected in the aqueous humor of glaucoma patients, suggesting that the outflow tissue endothelial barrier is altered in glaucoma[146]. Taken together, focal adhesion-mediated mechanotransduction processes play an integral role in TM/SC cell (patho)biology. Yet, there is no data on functional modulation of aqueous humor outflow facility and IOP homeostasis.

Cytoskeleton networks. The propagation of extracellular and cell-generated forces is mediated by the regulation of cytoskeleton tension[147]. The cytoskeleton networks are dynamic structures composed of filamentous and crosslinking proteins that provide mechanical support to cells and control their physiological functions[148]. There are three principal cytoskeleton networks that differ in composition: actin filaments, microtubules, and intermediate filaments—each displaying a highly organized structure. Filamentous (F)-actin and non-muscle myosin II form the contractile actomyosin system that is present in essentially all cells[149]. Multiple globular (G)-actin subunits polymerize to form linear F-actin, and several F-actin fibers arrange into actin bundles. The small Rho GTPase RhoA directly promotes the assembly of contractile actin stress fiber bundles by activating the downstream effectors ROCK and the formin mDia1/2[150,151]. The actomyosin network in TM cells, closely resembling that of smooth muscle cells, was first described in the late 1970s[152,153]. Since then, hundreds of research reports have focused on and refined the critical role of the actomyosin system in outflow tissue homeostasis as well as in the development of ocular hypertensive glaucoma. Interested readers are referred to recent reviews for further details[154–156].

The F-actin cytoskeletal arrangement differs significantly in healthy compared to glaucomatous TM cells in vitro and in vivo[157,158], with the former exhibiting an organized pattern with linear stress fibers and the latter exhibiting a disorganized network of tangled actin structures known as crosslinked actin networks. Actin fibers in both the TM and SC are affected by mechanical factors[159,160] and they have been associated with increased cell/tissue stiffness, outflow resistance and IOP[65,111], providing compelling evidence for the critical importance of the actomyosin cytoskeleton in aqueous humor outflow modulation[128,159]. Therefore, the outflow tissue actomyosin system has been the focus of several pharmacological approaches to improve outflow function and lower IOP in glaucoma. Strategies targeting the Rho-GTPase signaling pathway have proved most promising, given its crucial role in regulating aspects of cell shape, motility, proliferation, and apoptosis throughout the body[161]. Upon binding to GTP, Rho proteins stimulate the downstream effector ROCK. ROCK in turn promotes myosin II activity by activating/phosphorylating myosin light chain (MLC) and by inhibiting MLC phosphatase. In the conventional outflow pathway, ROCK regulates TM cell actomyosin contraction, adhesion, shape and stiffness, as well as ECM reorganization via this process—all involved in outflow resistance generation[162]. The specific ROCK inhibitor Y27632 was shown to induce potent but reversible changes in TM cell morphology and to decrease actin stress fibers, focal adhesions, and cell-cell junctions in vitro[163,164] in a substrate-independent manner[165]. In vivo administration of Y27632 resulted in increased outflow facility and decreased IOP in different animal models as well as in enucleated eyes[128,163,164,166,167]. Consequently, ROCK inhibitors were pursued for therapeutic development. Ripasudil entered the commercial market in Japan in 2014[167,168], while Netarsudil became available in the USA in 2018 followed by approval for use in Europe in 2019[169,170]. Taken together, cytoskeleton network-mediated mechanotransduction—and specifically the actomyosin system—contributes to modulating outflow cell/tissue homeostasis and glaucoma pathophysiology. The development of ROCK inhibitors for clinical management of ocular hypertensive glaucoma deserves to be considered a true "bench-to-bedside" success story that highlights the potential of targeted cytoskeleton-modulating therapies.

Shuttling proteins. The mechanical information arising from ECM modifications (perceived by focal adhesion complexes and propagated via cytoskeleton networks) impacts cytoplasmic proteins, inducing their structural modification and subsequent translocation to the nucleus[4]. Among the first proteins identified to shuttle between subcellular compartments was the focal adhesion adapter zyxin. Upon mechanical stretch, zyxin detaches from the membrane site and moves into the nucleus[171]. Several mechano-actuated shuttling proteins not physically connected to focal adhesions have also been described. The emerging picture is that bidirectional shuttling proteins are key factors in cellular mechanotransduction. Relevant to outflow tissue (patho)physiology are the YAP/TAZ[172], Wnt/β-catenin[173], and glucocorticoid[174] pathways—all governed by protein nuclear translocation. Of note, all of these signaling pathways crosstalk with YAP/TAZ mechanotransduction in TM cells. Interested readers are referred to a recent comprehensive review by Ghosh and Herberg of this complex topic[175].

YAP and its paralog TAZ[172] are transcriptional coactivators and master regulators of cellular mechanotransduction[176,177]. YAP/TAZ activity is modulated by a broad network of input cues, serving as a signaling nexus and integrator of multiple pathways[178]. YAP/TAZ proteins constantly shuttle between the cytoplasm and nucleus. Upon nuclear translocation, they bind to cognate transcription factors, such as TEAD family proteins, as YAP/TAZ lack DNA-binding domains. Via this principal regulatory mechanism, YAP/TAZ drive the expression of known downstream effectors and glaucoma-related putative effectors (e.g., transglutaminase-2, fibronectin, αSMA). In the Hippo-independent pathway, YAP/TAZ activity is primarily regulated by tension of the F-actin cytoskeleton that is contingent on the rigidity of the cellular substrate. For instance, increased ECM stiffness strongly promotes YAP/TAZ nuclear translocation to drive stiff-responsive gene expression involving increased ROCK activity and actomyosin contractile force generation[179,180]. Substantial evidence supports a clear role of YAP/TAZ mechanotransduction in ocular development, homeostasis, and disease[181,182]. For example, YAP/TAZ were found to be activated by

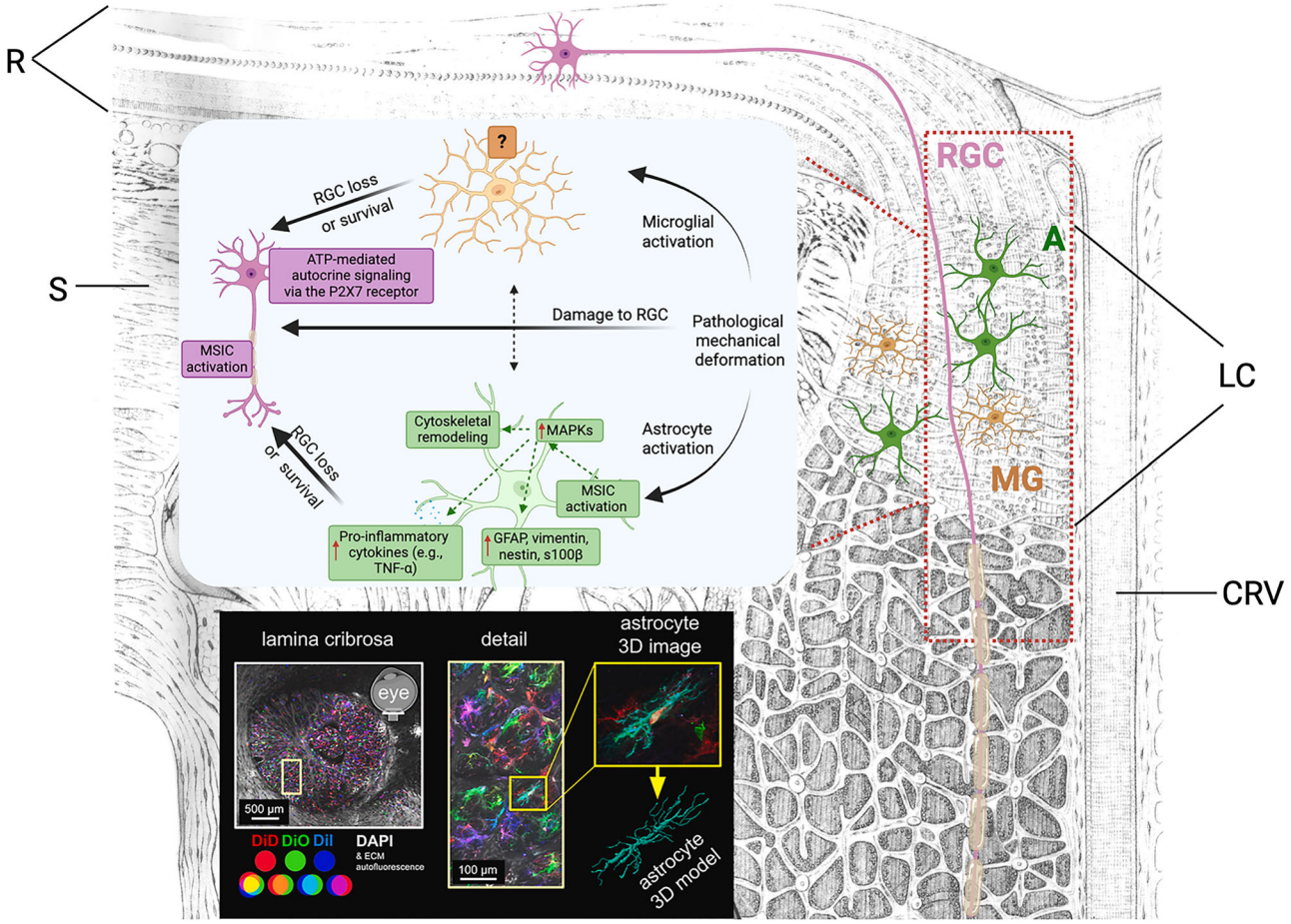

Fig. 3 | Overview of optic nerve head anatomy and relevant mechanobiologic components in glaucomatous optic neuropathy. Black and white background shows detailed anatomy in a human eye (R = retina; S = sclera; LC = lamina cribrosa; CRV = central retinal vessel). Lower left inset shows individually labeled optic nerve head astrocytes in a cross-sectional view through the optic nerve at the level of the lamina cribrosa. Individual cell types are overlain on the background image (RGC = retinal ganglion cell, including myelin sheath posterior to the lamina cribrosa; A = optic nerve head astrocytes; MG = optic nerve head microglial cells). Note that cells are not to scale. Inset at upper left show mechanobiologic machinery in these cell types. MSIC = mechanosensitive ion channel, including TRPV4 and Piezo1; MAPKs = mitogen-activated protein kinases, including ERK, c-JUN/JNK, p38 and p42/44. Background image from ref. 290 with permission; lower left inset from ref. 291, with permission. Cell overlays and mechanobiologic insets created using BioRender.com.

glaucoma-associated stressors in TM cells[145,183–195] and SC cells[196,197]. A recent genome-wide association study further identified the gene *YAP1* encoding for YAP—but not TAZ—among previously unknown glaucoma risk loci across different ancestries[198], suggesting a potential causal link between abnormal YAP/TAZ mechanotransduction and outflow dysfunction in ocular hypertensive glaucoma.

The evolutionarily conserved Wnt signaling pathway regulates critical aspects of embryonic development and tissue homeostasis[173]. Extracellular Wnt proteins stimulate diverse intracellular signal transduction cascades, including the canonical Wnt/β-catenin pathway and the alternative non-canonical pathway (i.e., Wnt/Ca^{2+} and Wnt planar cell polarity) that are subject to mutual regulation[173,199]. Without Wnt signaling, cytosolic β-catenin is recruited into the APC/Axin/GSK3/CK1 destruction complex, resulting in its phosphorylation followed by degradation. Binding of Wnt to its receptor complex composed of Frizzled and the low-density-lipoprotein-related protein5/6 triggers a series of events that disrupts the APC/Axin/GSK3 complex required for the targeted destruction of β-catenin. Via this mechanism, β-catenin triggers transcription by nuclear translocation and interaction with TCF/LEF transcription factors[200]. Wnt/β-catenin signaling has been studied extensively in numerous ocular diseases including glaucoma[201,202]. Wnt inhibitors such as sFRP1 and DKK1 are elevated in glaucoma, and their overexpression results in decreased aqueous humor outflow[203]. Furthermore, sFRP-1 levels are increased in TM cells cultured on stiff substrates[195], and Wnt inhibition has been shown to cause cell stiffening[204].

The pleiotropic actions of glucocorticoids are mediated by glucocorticoid signaling[174]. Glucocorticoids bind to intracellular glucocorticoid receptors, transcription factors of the nuclear receptor superfamily that are typically activated by ligands. These ligand-receptor complexes translocate into the nucleus where they interact with glucocorticoid response elements to modulate broad transcriptional activities (i.e., target genes comprise ~10–20% of the human genome) in what is considered the classical or "genomic" glucocorticoid pathway[205]. In contrast, glucocorticoids can also exert their actions in a more rapid "non-genomic" manner that affects several signaling pathways such as PKC, Ca^{2+}/calmodulin protein kinase II, nitric oxide, mitogen-activated protein kinase, caveolin-1, RhoA/ROCK[206]; this mechanism does not require nuclear glucocorticoid receptor-mediated transcription or translation[174]. Sustained use of widely prescribed glucocorticoids, such as prednisone/prednisolone or dexamethasone, has long been known to induce ocular hypertension in susceptible individuals causing glucocorticoid-induced glaucoma (a type of secondary open-angle glaucoma)[207–211]. Exposure of TM cells to dexamethasone induces ECM deposition (e.g., collagens, fibronectin, laminin, glycosaminoglycans, elastin) and cell/ECM stiffening[212,213]. Furthermore, dexamethasone drives the

formation of characteristic crosslinked actin networks[111,214], induces ER stress[215], and compromises TM cell phagocytic function[216]. Taken together, shuttling protein-mediated mechanotransduction plays a clear role in modulating TM cell behavior, with only little published information available on SC cells. The YAP/TAZ mechanotransduction pathway is by far the best understood. According to clinicaltrials.gov, there are several active clinical trials centered around blocking YAP/TAZ-TEAD interaction for the treatment of different cancers, with the potential to "cross-pollinate" and inform future glaucoma drug development approaches.

We recognize that there are additional cytoskeletal networks and shuttling protein-mediated mechanotransduction pathways relevant to the outflow pathway. These include the septin component of the cytoskeleton[217] and the TGFβ[218] and Notch[219] signaling pathways. Due to space constraints, we are not able to discuss them in this work.

Mechanobiology of RGC damage

RGC damage in glaucoma is an incompletely understood process, for which many mechanisms have been postulated. Here, we focus on mechanical insult at the level of the ONH, and more specifically the connective tissue region within the ONH known as the lamina cribrosa (LC; Figs. 1 and 3), since significant data supports this as an important mechanism[49,220]. For example, RGC damage occurs within the LC[221], where significant mechanical tissue deformation occurs[222]; patterns of vision loss in glaucoma are consistent with the heterogeneous physical structure of the LC[223]; and ONH cells are mechanoresponsive[224–227].

The ONH is an anatomically complex tissue containing multiple cell types, including astrocytes, RGCs, microglia, and vascular endothelia (Fig. 3); further, glaucoma is characterized by diverse cell and tissue-level changes, including impaired vascular function and changes in microglial activation and astrocyte reactivity, as elegantly reviewed in[228]. This complexity complicates understanding of the molecular and cellular pathways by which biomechanical insult culminates in RGC axonal dysfunction, and there are almost certainly multiple injury cascades[228].

Among the many causes of RGC loss in glaucoma, significant evidence points to an important role for the mechanobiology of ONH astrocytes[229–235]. Astrocytes are the major glial cell type in the ONH (Fig. 3), and have many functions[228,236,237]. In response to pathological mechanical deformation, astrocytes transition from a quiescent phenotype to a more reactive, proliferative one characterized by increased expression of intermediate filaments (e.g., glial fibrillary acidic protein, vimentin and nestin) and s100β, and elevated release of pro-inflammatory cytokines such as TNF-α, among other changes[229,238]. Astrocyte reactivity was originally thought to be solely deleterious; e.g., reactive astrocytes remodel the ONH via synthesis of ECM proteins and matrix metalloproteinases[229,239], which may contribute to RGC death by altering the normal biomechanical supportive functions of the ECM[234,235,240]. However, more nuanced recent work shows that astrocyte reactivity can also promote RGC survival[228], e.g., astrocyte-specific knock out of the transcription factor STAT3 increased RGC loss[241], and lipoxins secreted by reactive astrocytes are neuroprotective in experimental models of glaucoma[242]. More generally, it is now understood that astrocytes can exert both neurotoxic and neuroprotective effects after injury[243].

Multiple studies have shown that astrocytes respond to mechanical insult, such as that induced by elevated IOP[227,231,232,244–246], strongly suggesting that astrocyte mechanobiology is an important aspect of the pathogenesis of glaucoma. Which molecular pathway(s) are involved in ONH astrocyte mechanobiology, specifically in astrocytic response to stimuli such as those due to elevated IOP? Despite its importance, the answer to this question remains unknown, although evidence suggests that mechanosensitive ion channels are very important in this process[247]. Indeed, more than a dozen mechanosensitive ion channels have been reported to be expressed by astrocytes[248], although not all of these are "primarily" mechano-activated, i.e., directly respond to mechanical stretch, rather than e.g., modulating the effects of other channels. More specifically, channels present in mouse ONH astrocytes, as determined by several mRNA assays[248], include TRPC1-6, TRPM2, 4, 6 and 7, TRPV2 and 4, TRPP1 and 2, and Piezo1 and 2. However, which of these channels are most important in ONH astrocyte mechanosensation in vivo remains uncertain.

Downstream mechanotransduction likely involves several MAPKs, including ERK, c-JUN/JNK, p38[249] and p42/44[250]. In this context, p38 is particularly interesting: pharmacologic inhibition of p38 MAPK by small molecules was protective against optic nerve degeneration in a rat microbead model of ocular hypertension, but surprisingly was not protective at longer time points in the DBA/2J mouse model or the squirrel monkey microbead model[251,252]. However, these results are hard to interpret mechanistically, due to the multiple cell types expressing p38 in the ONH and the fact they target all four p38 MAPK isoforms, each of which have distinctive dell type-dependent functions. Nonetheless, much interest remains in the potential of modulating p38 activity as a neuroprotective treatment in glaucoma.

Downstream of mechanotransduction, mechanical strain causes many phenotypic changes in astrocytes consistent with glaucomatous pathophysiology, including migration and remodeling of the actin cytokeleton[231,232,245,246], changes in ECM turnover[100,227,233,244,253], and alterations in gap junctions[254]. There is also evidence of transient cell membrane damage when cells are exposed to pathological levels of strain, which can be repaired by Annexin4 in healthy ONH astrocytes[255].

Of course, astrocytes are not the only glial cell type in the ONH - microglia are also present. The mechanobiology of these cell types is somewhat less well-studied in the ONH. Microglia have been implicated as having an important role in neuroinflammatory processes involved in glaucoma[256–258]. However, their role is certainly complex: for example, microglial depletion in mice with ocular hypertension had no demonstrable effect on ONH pathology or RGC loss, suggesting that astrocytic changes may be more important in driving glaucomatous optic neuropathy than microglial changes[259]. The mechanobiology of the microglia within the ONH shares features with brain microglia[260], yet mechanobiological pathways in these cells are understudied.

Finally, it is now appreciated that RGCs are also mechanosensitive and may autonomously play a role in their own dysfunction in the glaucomatous eye[261]. Indeed, it has long been appreciated that macroscopic mechanical insult to RGC axons might play a role in RGC dysfunction, as RGC axons are "kinked" as they pass through the tortuous passages of the lamina cribrosa[36,262,263]. However, more recently we have learned that RGCs are directly mechanosensitive[256]; for example, they express TRPV4[264], the pannexin hemichannel Panx1[265] and the P2X7 receptor[266], and Piezo1 and Piezo2[267,268]. The distribution of these mechanosensory elements is spatially non-uniform in RGCs; for example, Piezo1 is reported to be expressed in soma and axons of RGCs, but not dendrites, which may be relevant to glaucoma since changes to RGCs occur at different times in different cell compartments (axons vs. soma, etc.)[269,270]. The Panx1/P2X7 system is particularly interesting: Mitchell and colleagues have shown, over a series of papers, that ATP release by Panx1 hemichannels acts as an autocrine signal via the P2X7 receptor that promotes neurodegeneration in RGCs[80–83] and ONH astrocytes[271,272]. However, there remains a major knowledge gap about how (and whether) direct mechanostimulation can cause RGC death, in part due to the many mechanisms that contribute to glaucomatous RGC death[273,274] and in part due to the complex interactions between RGCs and glial cells in the optic nerve head. We suggest that elucidating mechanistic pathways between astrocytic and RGC mechanosensation and RGC cell death is an important, understudied research area.

Conclusions and open questions

In this review, we have provided an overview of the mechanobiological landscape in the eye, with an initial focus on cornea and lens before diving deeper into anterior and posterior tissues involved in glaucoma. We define mechanosensation and mechanotransduction mechanisms, and unpack the respective key players that different ocular cells use to adapt to the complex and dynamically changing microenvironment within their tissue niches.

Unsurprisingly, many open questions remain, a few of which are listed below. We note that many of these questions, although framed in the context of the eye, are quite general and addressing these questions would have broad implications for our understanding of normal physiology and of pathophysiology.

- Do age-related changes in mechanosensing/mechanotransduction processes contribute to ocular pathologies? Age is a major risk factor for glaucoma and other ocular pathologies; yet, it is unclear how and to what extent the cellular programs and machineries in relevant tissues undergo pathological alterations over time.
- How do mechanobiological pathways adapt to varying biomechanical loads? Ocular tissues are subject to remarkably dynamic changes in their biophysical environment, with time scales ranging from seconds (ocular pulse) to many hours (diurnal variations)[275,276]. However, mechanistic details on how cells integrate this variable "mechanical dosing" in health and disease are scarce.
- What role does the nuclear envelope play in ocular mechanotransduction? Nuclear-cytoskeletal coupling is critical for force transmission to the nucleus and for the subsequent biological responses[277]. Studies in other fields have pointed to the nuclear envelope as a regulator of biochemical and biophysical interactions between the nucleus and cytoskeleton; yet, very little is known about the regulation of (epi) genome organization and gene expression by "nuclear mechanotransduction" in ocular cells.
- In glaucoma, how do inflammation, metabolic stress and immune function in both anterior and posterior tissues interact with aberrant mechanosensing/mechanotransduction to potentiate the effects of IOP in RGC loss? This has become a critical question in light of recent findings indicating an important, yet poorly understood, role for these systemic factors in glaucoma[278–282].
- How much RGC damage in glaucoma is directly attributable to RGC mechanosensation vs. indirect effects of ONH glial cell mechanobiology? It seems likely that both mechanisms are involved, but direct evidence about the relative importance of the two mechanisms is scarce and may be dependent on disease state. Relatedly, what mechanobiology-driven interaction(s) between astrocytes and microglia contribute to RGC loss; both cell types, which are the major glial cells of the optic nerve, have been implicated in RGC loss yet the cross-talk between the two glial cell types has not been extensively studied[259,283].

These are exciting areas for future mechanobiology research that hopefully will help identify the causal mechanism(s) underlying glaucoma and other sight-threatening pathologies, and to facilitate the screening and development of novel treatments.

Data availability

No datasets were generated or analyzed during the current study.

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Competing interests

The authors declare no competing interests.

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