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Immune responses to injury and their links to eye disease.

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REVIEW ARTICLE

Immune responses to injury and their links to eye disease

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The eye is regarded as an immune privileged site. Since the presence of a vasculature would impair vision, the vasculature of the eye is located outside of the central light path. As a result, many regions of the eye evolved mechanisms to deliver immune cells to sites of dysgenesis, injury, or in response to the many age-related pathologies. While the purpose of these immune responses is reparative or protective, cytokines released by immune cells compromise visual acuity by inducing inflammation and fibrosis. The response to traumatic or pathological injury is distinct in different regions of the eye. Age-related diseases impact both the anterior and posterior segment and lead to reduced quality of life and blindness. Here we focus attention on the role that inflammation and fibrosis play in the progression of age-related pathologies of the cornea and the lens as well as in glaucoma, the formation of epiretinal membranes, and in proliferative vitreoretinopathy. (Translational Research 2021; 000:1–20)

Abbreviations: 2ryERM = epiretinal membrane secondary to disease pathology; ACAID = anterior chamber immune deviation; APCs = Antigen Presenting Cells, this class includes dendritic cells and monocytes; ASC = anterior subcapsular cataracts; BALB/c = An albino mouse strain used for research and known to mount a primarily Th2 response to infection; BM = basement membrane; C57BL6 = A pigmented mouse strain used for research and known to mount a primarily Th1 response to infection; CCL2 = A cytokine expressed early during inflammation that attracts neutrophils, sometimes referred to as monocyte chemoattractant protein-1 (MCP-1)); CD45 = Cluster of differentiation 45 antigen; CNS = Central Nervous System; CXCL1 = A cytokine expressed early during inflammation that attracts neutrophils; DAMPs = damage-associated molecular patterns; DBA/2J = A strain of pigmented mice used in glaucoma research; EBM = Epithelial Basement Membrane; ECM = extracellular matrix; EMT = epithelial-mesenchymal transition; ERM = epiretinal membrane; F4/80 = A protein encoded by the ADGRE1 gene that, in mice, is expressed primarily on macrophages; FGF2 = fibroblast growth factor 2, also referred to as basic FGF; HA =hyaluronic acid; HSK = herpes stromal keratitis; HSP = heat shock protein; HSPGs = heparan sulfate proteoglycans; HSV = herpes simplex virus; ICN = intraepithelial corneal nerves; iERM = idiopathic epiretinal membrane; IL-20 = Interleukin-20;

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IL6 = Interleukin 6; ILM = Inner (or internal) limiting membrane; IOP = intraocular pressure; MAGP1 = Microfibril-associated glycoprotein 1; MHC-II = Major histocompatibility complex type II, a class of MHC proteins typically found only on APCs; mTOR = mechanistic target of rapamycin, a protein kinase encoded by the MTOR genes that regulates a variety of signal transduction events including cell growth, autophagy and actin cytoskeleton; N-cad = N-cadherin; NEI = National Eye Institute; NK = Natural killer T cells; PCO = Posterior capsular opacification; PDGF = Platelet derived growth factor; PDR = proliferative diabetic retinopathy; PVD = posterior vitreous detachment; PVR = proliferative vitreoretinopathy; Rag1-/- = A mouse model that lacks functional T and B cells and used to study the immune response; RGC = Retinal ganglion cells; RPE = Retinal pigment epithelial cells; RRD = rhegmatogenous (rupture, tear) retinal detachment; SMAD = Sons of Mothers Against Decapentaplegic, SMADs are a class of molecules that mediate TGF and bone morphogenetic protein signaling; TG = trigeminal ganglion; TGF1 = Transforming growth factor 1; Th1 = T-helper cell 1 response, proinflammatory adaptive response involving interferon gamma and associated with autoimmunity; Th17 = A T-helper cell that expresses high levels of IL-17 which can suppress T-regulatory cell function; Th2 = T-helper cell 2 response involving IgE and interleukins 4,5, and 13, also induces the anti-inflammatory interleukin 10 family cytokines; TM = trabecular meshwork; TNF = Tumor necrosis factor a cytokine produced during inflammation; Treg = T-regulatory cell; VEGF = Vascular endothelial growth factor; WHO = World Health Organization; SMA = Smooth muscle actin, a class of actin expressed in mesenchymal cells

INTRODUCTION

The eye is a unique site whose function relies on the transparency of several tissues and whose vasculature is limited to regions outside of the central light path. Inflammation, such as typically occurs in response to an injury, be it surgical or pathological, brings with it the danger of vision impairment (Fig 1). As immune responses are crucial elements of the repair response, the eye has developed distinct mechanisms to deliver

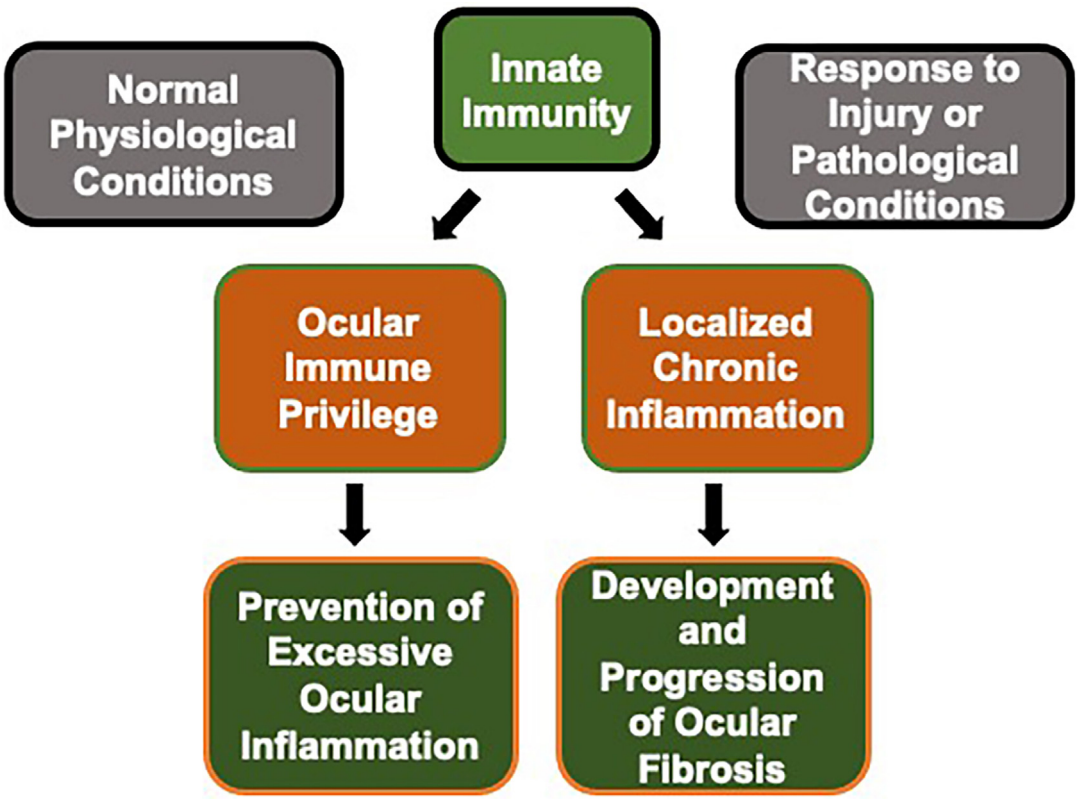

Fig 1. Inflammation-induced pathologies in the immune privileged eye. Diagram showing the importance of immune privilege in the eye to prevent\ocular inflammation and when that privilege is compromised, and innate immunity activated, inflammation of the eye results in fibrogenic pathologies. Diagram is modified from Murakami et al., Progress in Retinal and Eye Research (2019) 74:100778.[232] For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

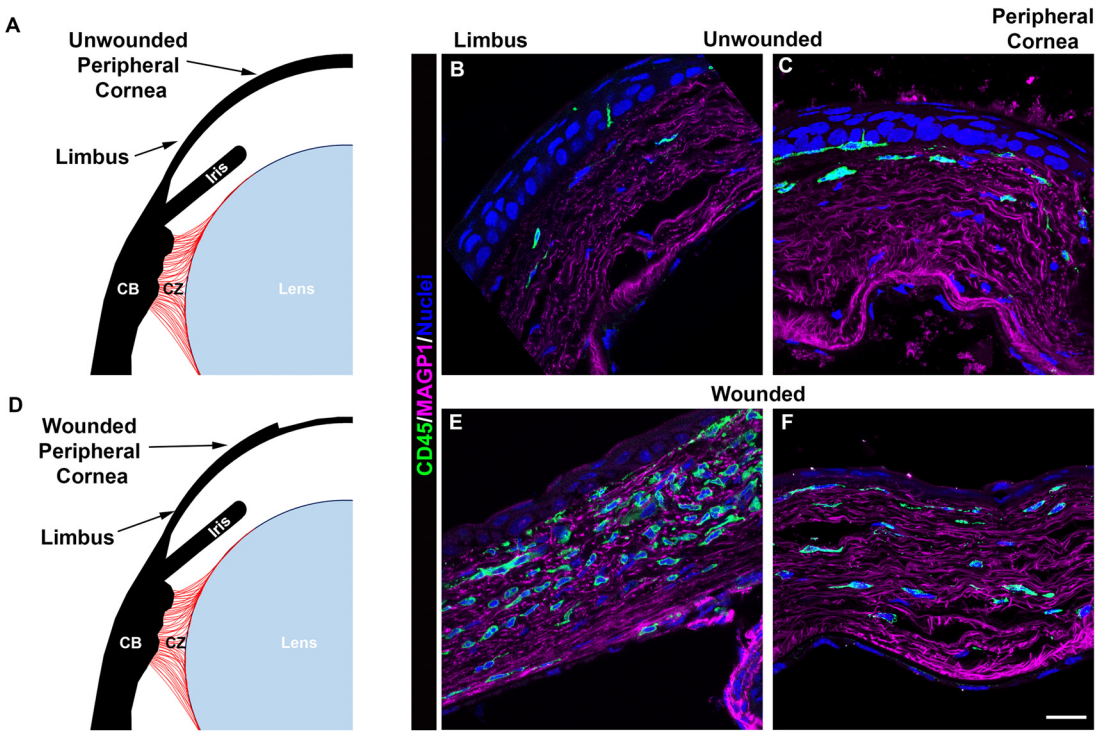

Fig 2. Following corneal debridement wounding immune cells are located along MAGP1-rich fibrils in the cornea stroma at the limbus and corneal periphery**.** A and D are cartoons showing the anatomical relationships between the limbus, peripheral cornea, iris, ciliary body and lens. Cryosections obtained from mouse eyes of unwounded (B,C) or one day post corneal debridement wounding (E, F) were imaged by confocal microscopy at the limbus (B,E) and the peripheral cornea (C, F). Sections were co-immunolabeled for Microfibril-associated glycoprotein 1 or MAGP1 (purple), the immune cell marker CD45 (green), and nuclei (blue). MAGP1 associates with fibrillin in the ciliary zonules. Magnification bars = 20μm. CB= ciliary body, CZ= ciliary zonules. This figure is adapted from DeDreu et al., FASEB J. (2020) 34:9316.[163] For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

immune responses to injury in avascular regions of the eye. In this review, we cover the common injuries and pathologies in these regions of the eye, how the immune system responds, and the link between inflammation and the negative outcomes of these immune responses, including fibrosis, that impair vision.

IMMUNE RESPONSES IN CORNEAL KERATITIS

Immune Mediated Wound Healing and Fibrosis: The cornea and the ocular surface. The term "ocular surface" embraces the corneal and conjunctival epithelia and the tear film[1-3] as well as a number of other ocular features including the lacrimal and Meibomian glands and the ocular microbiome. While the term had not originally included the intraepithelial corneal nerves (ICNs), the cells in the corneal stroma, or the corneal endothelial cells, homeostasis of the ocular surface requires contributions from all of these components. Resident and recruited immune cells maintain the ocular surface.[4-7] Recurrent erosions, corneal dystrophies, stem cell deficiency, infection by microorganisms, and autoimmune mediated diseases all disrupt the cornea and ocular surface and can lead to severe pathology and blindness. In the cornea, fibrosis presents as diffuse haze that can be transient or permanent or as focal opaque scars in the anterior or posterior stroma.[8-10] The terms fibrosis and scar are often used interchangeably in describing pathologies affecting the cornea. A common feature of corneal fibrosis is the increased expression of TGBβ1 by stromal cells.[8,11-13] If in the central cornea, fibrosis causes an increase in refractive error and/or astigmatism.

The immunology of the cornea has been extensively studied; yet its complexity has made understanding its role in homeostasis and disease progression challenging. While considered immune privileged, the cornea has a robust resident immune cell population that responds quickly to trauma and/or infection (Fig 2). The cornea's immune response is dominated by the process referred to as Anterior Chamber Immune

Deviation or ACAID.[14-16] ACAID was first described by Streilein and Niederkorn in 1981.[17] In the 40 years since then, ACAID has been shown to play roles in the induction of peripheral tolerance to eye-derived antigens, allowing corneal transplants to not be rejected. ACAID allows the anterior segment of the eye to regulate the activation of both innate and adaptive immune responses. ACAID begins when an antigen is detected in the anterior chamber. When antigen presenting cells (APCs) in the iris and ciliary body capture the antigen, the APCs enter the circulation and travel to either the thymus or spleen where they induce the generation of T regulatory cells.[18] In his Proctor Lecture for the Association for Research in Vision and Ophthalmology in 1996, J. Wayne Streilein referred to ACAID as an evolutionary "Faustian bargain".[19] ACAID suppresses the immune response to microorganisms and particulates in the air that get stuck in the tear film and enter the cornea by eye rubbing and blinking. It also limits the immune response to ocular tumors and certain viruses increasing the risk of blindness and death resulting from these severe, yet far less frequent, pathologies.[19]

While ACAID makes the ocular immune response unique, nonetheless, there are many aspects of the cornea immune response that are shared with the skin and other mucosal surfaces of the body. Keratitis is the term used to define the clinical outcome of numerous different corneal pathologies all of which involve inflammation.[20] Infectious keratitis is caused by invasion of the cornea by microorganisms; non-infectious keratitis can be caused by trauma and/or autoimmune conditions. If non-infectious keratitis does not resolve, the pathology can convert into the infectious form. To prevent scarring, keratitis must be treated early and aggressively to block progression of disease. As the population ages and the number of people with chronic autoimmune related conditions increase, the incidence of corneal pathology due to autoimmunity in the population is increasing. As the planet warms and temperatures rise, the numbers of infectious organisms present in the environment and in our water supply is increasing as well.[21] Research is currently being done to refine our understanding of corneal immunity and inflammation to allow us to develop treatments that halt pathology and permit restoration of function after keratitis resolves.

Non-infectious forms of keratitis and corneal pathology. Traumas to the cornea are the most common type of injury to the eye and the most frequent cause for a patient to be seen by an ophthalmologist in the emergency room setting.[22] Our understanding of how the cornea responds to sterile injuries like abrasions is largely based on the use of rodent models that have examined the response of the cornea to injury.[23-25] Superficial injuries to the corneal epithelium typically heal well and do not lead to scars but they do predispose the cornea to recurrent epithelial erosions.[26] Deeper traumas involving the corneal stroma as well as the corneal epithelium disrupt the organization of the lamellae of collagen fibers in the stroma required for corneal transparency.[27,28] Restoring tissue integrity requires synthesis and deposition of extracellular matrix.

Debridement injury activates dendritic cells in the basal layer of the epithelium and leads to the influx of neutrophils and platelets into the corneal stroma and of $\gamma\delta$ T cells into the corneal epithelium.[5,29-33] Dendritic cells are antigen presenting; after activation they migrate to the draining lymph nodes and induce the adaptive immune response. Depleting mice of neutrophils or $\gamma\delta$ T cells impairs reepithelialization of the cornea.[30,32] Wildtype mice express both IL-20 and its receptor on corneal epithelial cells, as well as on dendritic cells and monocytes. Treating neutrophil or $\gamma\delta$ T cell depleted mice which have delayed wound healing with IL-20 restores corneal reepithelialization.[32] In the neutrophil depleted mice, IL-20 promoted recruitment and activation of $\gamma\delta$ T cells in the wounded cornea. In $\gamma\delta$ T cell depleted mice, IL-20 restores corneal reepithelialization without increasing neutrophil influx. Thus, IL-20 signaling plays an anti-inflammatory role by limiting neutrophil influx. Yet, in other tissues, IL-20 can enhance fibrosis and has been linked to development of autoimmunity.[34]

Deeper traumas involving both the corneal epithelium and the corneal stroma disrupt the epithelial basement membrane (EBM) and the organization of the lamellae of collagen fibers in the stroma that generate corneal transparency.[27,28] Once reepithelialization is complete and the epithelial barrier restored, stromal immune cells begin removing collagen and elastin debris from the stroma, as well as the dead immune cells that were recruited into the stroma during the acute response to injury.

The EBM is known to play roles in restricting cytokine access to the stroma.[10,27,41] Once the EBM is injured or removed, cytokines from epithelial cells and tears diffuse into the stroma and activate target cells. Debridement injuries leave the EBM intact but deeper wounds do not.[42] EBM reassembly begins during reepithelialization but restoring the barrier to cytokines can take several weeks.[25] Stromal repair can also take weeks or months.[41] The de novo synthesis of collagen, elastin, and proteoglycans in the cornea stroma is mediated by α smooth muscle actin+ (αSMA+) myofibroblasts. Myofibroblasts differentiate from both corneal stromal keratocytes and fibrocytes during the response to ocular trauma.[43-45] Fibrocytes differentiate from recruited monocytes and/or resident tissue

macrophages. Transforming growth factor β (TGF β) is a cytokine which functions in both immunity and extracellular matrix regulation.[35] TGF β has three isoforms (TGF β1, TGF β2, and TGF β3) and all three are expressed by numerous types of immune cells. TGF β1 null mice develop systemic immune cell infiltration into tissues [36-38] due, in part, to the requirement for TGF β1 for the formation of T regulatory cells.[35] In the cornea, TGF β1 and TGF β2 are expressed by corneal epithelial and stromal cells[39]; they can also be present in the tears.[40] While both isoforms play roles in regulating scar formation after injuries to the stroma, TGF β1 plays a more important role. While myofibroblast formation is dependent on TGF β1 signaling, in vitro studies have shown that TGF β3 reduces the generation of αSMA+ myofibroblasts and their ability to deposit collagen into extracellular matrices.[46,47] These studies highlight the complexity involved in TGF β mediated scar formation in response to deeper keratectomy wounds.

A single topical application of Mitomycin C at the time of surgery has been shown to minimize scar formation after refractive and glaucoma surgery.[45] The mechanism underlying MMC-induced reduced cornea scarring has been shown to be due to reduced conversion of keratocytes to myofibroblasts.[44] However, recent studies have shown that MMC treatment also alters gene expression in wounded corneal epithelial cells and enhances reinnervation of the corneal epithelial sensory nerves.[26,48] For scars that form secondary to non-surgical trauma, treatments are limited. One of the most promising treatments is the use of autologous plasma, rich in growth factors, as an eye drop.[49,50] It is safe, and has been shown to improve healing by improving keratocyte migration, reducing TGF β1-induced myofibroblast differentiation, and stimulating scarless regeneration after corneal injury.

Matrix deposition within the stroma after trauma reestablishes structural integrity but it does so at the cost of generating haze, caused by disorganization of the collagen lamellae, and focal scars. Repair mechanisms that evolved to restore corneal strength after injury often cannot restore the original morphology to the corneal stroma since collagen fibers often extend from limbus to limbus across the center of the corneal stroma.[51,52] Studies in the cornea and skin indicate that delays in apoptosis of the myofibroblasts that appear during wound-healing is a hallmark of fibrosis.[53,54] While the cornea presents challenges to resolving haze and scars, research on treatments to reduce fibrosis is one worth investing in going forward. An even slight decrease in the extent of haze or the size of a centrally placed corneal scar would make a huge difference to a patient's quality of life and avoid the need for a corneal transplant.

$\gamma\delta$ T cells express and secrete the cytokine IL17.[55] Another T cell lineage, T-helper (Th17) cells, also secrete IL17.[56] Th17 cells have been studied extensively with respect to dry eye disease and other autoimmune conditions impacting the cornea including Sjogren's Syndrome.[6,57,58] Th17 cells have the ability to suppress the functions of regulatory T cells (Tregs) .[59,60] Loss of Treg function within tissues and can lead to chronic inflammation,[61,62] whereas excess numbers or activation of Tregs increases the risk of infection by microorganisms[6] and to a wide spectrum of ocular pathologies ranging from dry eye disease and chronic pain to recurrent erosions. These conditions can lead to cornea scarring and thinning.[63-65] Increased Treg activity increases the risk of infection by suppressing the activation of cytotoxic T cells.[60] Treatments for dry eye disease include artificial tears, autologous serum eye drops and topical treatments that suppress the immune response including cyclosporine A, corticosteroids, tacrolimus, and low dose tetracycline.[66]

Infectious keratitis. Infectious keratitis is more likely to lead to corneal pathology than non-infectious keratitis. The cornea's immune response to infection is greater to prevent the CNS (retina and brain) from getting infected. Following diagnosis and identification of the microorganism involved, drug treatment is initiated. Treatment includes eyedrops and/or direct delivery of drugs by intrastromal or intravitreal injection.[67,68] When fibrosis occurs in the central visual axis from infectious keratitis it reduces visual acuity; in severe cases a corneal transplant is recommended. The microorganisms that most commonly infect the cornea are bacteria (Staphylococcus aureus and Pseudomonas aeruginosa), viruses (Herpes simplex and Herpes zoster), and fungi (Fusarium, Aspergillus, and Candida).

Bacterial keratitis. Bacterial keratitis is the most common form of infectious keratitis and is more frequent in contact lens wearers. In both C57BL6 and BALB/c mouse strains, infection results in rapid recruitment of neutrophils which activate cytotoxic T cells and macrophages.[59] C57BL6 mice mount a Th1 immune response to bacterial infection whereas BALB/c mice mount a Th2 response.[69,70] The Th1 response is pro-inflammatory; Th1 mice clear bacteria more quickly than Th2 mice but, in doing so, the immune response causes more corneal damage. Thus, the immune response in the Th2 mice is anti-inflammatory when compared to that seen in Th1 mice. The World Health Organization (WHO) has found that the world's leading cause of corneal blindness results from trachoma,[71] a bacterial infection endemic to developing countries that causes permanent corneal scarring. In a 2010 study, WHO

estimated that corneal blindness from all causes, including trachoma, accounted for 7% of the world's blind population making it the 3rd most common cause of blindness.[72] Since trachoma can be treated by antibiotics, it is the leading cause of preventable blindness in the world. Corneal scars are the leading cause of corneal transplants in the US.

Viral keratitis. In viral keratitis resulting from Herpes simplex virus (HSV) infection, the virus infects the corneal epithelial cells and the intraepithelial corneal nerves (ICNs). Retrograde transport in the ICN axons delivers the virus to the trigeminal ganglion (TG) where the nerve cell bodies are located.[73-75] Acute HSV infection attracts and activates dendritic cells, neutrophils, monocytes, and macrophages leading to a so called "cytokine storm" at the TG and the ocular surface.[75-77] Within 3 days, Natural killer (NK) T cells that specialize in eliminating viruses begin accumulating in the cornea.[78,79] In mice, between 6 and 8 days after acute infection, the virus enters a latent state within trigeminal neurons and causes no symptoms. Herpes stromal keratitis (HSK) results from reactivation of latent HSV. Cytotoxic T cells are key to the immune response in HSK[79]; viral reactivation also induces neutrophil accumulation within the trigeminal ganglion. If HSK is not controlled, viral particles replicating in the TG can travel to the brainstem and cause lethal encephalitis. HSK causes corneal fibrosis and focal loss of sensory innervation to the cornea due to death of TG neurons.[80] Neurotrophic keratitis due to a complete loss of sensory innervation will result from repeated bouts of HSK reactivation.[81] Herpes Zoster infections are less frequent and believed to be controlled by the cornea's immune system similarly to HSV.[82]

Fungal Keratitis. Fungal keratitis has historically been associated with trauma to the cornea that involves plant matter and/or objects contaminated with soil. In the United States, Candida and Aspergillus are the most common causes; however, in South Florida, Fusarium is more common. Diagnosis is often made only after a corneal ulcer develops with fungi penetrating far into the corneal stroma. The immune response of the cornea to a fungal infection is robust[83]; the damage done to the tissue by immune cell recruitment is significant.[84,85] Modulating the immune response has become a major target of research efforts to reduce the damage seen in corneas with fungal keratitis. IL6 is one of several cytokines increased after fungal infection of the cornea; IL6 plays roles in macrophage activation and T cell differentiation. In a mouse model of fungal keratitis,[85] mice treated with a neutralizing antibody against IL6 had fewer immune cells infiltrating the cornea and in the draining lymph nodes. Additional studies are underway that may result in new treatments to reduce the damage done to the cornea by fungal keratitis.

GLAUCOMA: AN EYE DISEASE INVOLVING INFLAMMATION AND FIBROSIS IN BOTH THE ANTERIOR AND POSTERIOR CHAMBERS OF THE EYE

Glaucoma encompasses a number of age-related degenerative eye diseases, the most common form being open-angle glaucoma (OAG), with other types including angle-closure glaucoma and uveitic glaucoma.[86,87] Glaucoma is defined as an optic neuropathy, most typically associated with high intraocular pressure (IOP) resulting from a block of aqueous humor outflow from the anterior chamber of the eye.[86,87] In both open-angle and closed-angle glaucoma, inflammatory cytokines are elevated in the aqueous humor.[88-91] However, the biggest threat to vision from this increased IOP is the death of retinal ganglion cells (RGCs), whose axons exit the retina through the optic disc where they are bundled together to form the optic nerve. As a result of RGC death, glaucoma patients experience loss of vision, beginning with their peripheral vision. Without treatment, glaucoma will lead to blindness.[87] Most therapeutic approaches are aimed at lowering pressure by increasing aqueous humor outflow using either topical pharmaceuticals, or surgical approaches including laser treatments as well as more invasive surgical techniques.[92] Glaucoma drugs that increase fluid drainage from the eye include the commonly used prostaglandin analogs, Rho kinase inhibitors, nitric oxides, and miotic or cholinergic agents.[93] Another pharmaceutical approach is to lower the amount of fluid made by the eye. Examples of the drugs that target fluid production include alpha-adrenergic agonists, beta blockers, and carbonic anhydrase inhibitors.[93] While a machine learning approach has been able to accurately predict glaucoma based on the profile of immune mediators in the aqueous humor,[94] no current drug treatments of OAG are targeted at suppressing inflammation in the anterior or posterior chambers, and some therapeutics including the prostaglandin analogs have the potential to induce an inflammatory response. Glaucoma filtration surgery can be highly effective at lowering IOP.[95] The primary reason that this approach fails is scarring at the incision site in the region of the conjunctiva/Tenon's capsule. An interesting new approach being investigated to prevent scarring at this site involves a clinically relevant biomimetic of this subconjunctival tissue that includes an immune component.[96] Importantly, as the primary goal of all glaucoma therapies is to prevent damage to the retina and the optic nerve, there is much focus on

developing effective neurotherapeutics for glaucoma that would prevent RGC death.[97-100] When such neuroprotective treatments are widely available, the outcomes of glaucoma will be greatly improved.

The aqueous humor is a nutrient source for several avascular regions in the anterior segment including the cornea, lens and trabecular meshwork (TM).[101] It is produced by the ciliary epithelial cells that line the ciliary body and occupies the space between the cornea and the iris/lens. Normal pressure is maintained in the eye by outflow of the aqueous humor through the TM, a spongy tissue at the intersection of the posterior cornea and the iris consisting of stromal cells, fibroblasts and immune cells within a loose connective tissue.[102] From the TM, the drainage pathway leads to Schlemm's canal, a blind-ended vessel with lymphatic properties that transports aqueous humor and antigen presenting cells (APCs)[103-105] into episcleral veins via the aqueous veins.[106]

Outflow blockage in glaucoma correlates with an increase in the stiffness of the TM and the lymphatic endothelial cells that line Schlemm's canal. These features have been linked to changes in the biomechanics of the constituent cells,[107] and the activation of profibrogenic pathways.[108] In open angle glaucoma, stiffness of the TM is also associated with increased deposition of matricellular proteins including tenascin-C and thrombospondin,[109] both associated with wound-repair and fibrosis. The alterations to the matrix microenvironment in glaucoma are accompanied by changes to the cytoskeleton of TM stromal cells that contribute to a fibrotic outcome.[110,111] The increased stiffness of Schlemm's canal in glaucoma is also linked to increased presence of actin stress fibers as well as assembly of vinculin-rich focal adhesions in its endothelial cells.[107]

The stiffening of the TM is a feature shared among most types of glaucoma and is linked to the induction of both TGF β /SMAD[111-114] and Rho/Rock signaling pathways,[115,116] the increased production of matricellular proteins,[109] and fibrosis[117]. Resident stromal cells, fibrocytes (mesenchymal cells that form from monocyte precursors[118]), and other mesenchymal cell populations are all potential myofibroblast progenitors in the TM, and contributors to fibrosis. In other tissues, the appearance of myofibroblasts and the production of a pro-fibrogenic microenvironment is often linked to an inflammatory response.[119-121] It will be important to establish whether there is a direct link between inflammation, fibrosis, and the stiffening of the trabecular meshwork associated with the onset of open angle glaucoma with evidence-based studies. However, the likelihood of a significant immune component in glaucoma, including as a potential cause of the stiffness of the trabecular meshwork, can be drawn from studies showing the presence of proinflammatory molecules in the aqueous humor proteome of patients with POAG.[91,122] Studies of uveitic glaucoma, a rarer form of the disease, provide more direct evidence of a causative link between immune cells and the induction of glaucoma in the anterior chamber.[123] Uveitis is inflammation of the middle layer of the eye, the uvea, which functions to provide the vascular support required for phototransduction. As seen in other types of glaucoma, this inflammatory condition causes glaucoma by blocking aqueous humor outflow through the trabecular meshwork.[124] Inflammation and fibrosis are also outcomes of the repair response to surgical treatments for glaucoma.[125]

In contrast to the limited evidence regarding the causative role of inflammation in stiffening of the trabecular meshwork, the damaging effects of glaucoma on the retina and optic nerve are closely tied to inflammatory responses. Neuroinflammation, defined as inflammation of nervous tissue, is considered a major factor in the death of RGCs and their axons in the optic nerve.[126,127] The features associated with neuroinflammation in glaucoma are typical of classical neurodegenerative pathologies.[128] Muller glia, astrocytes, and microglia are resident to the retina and astrocytes are present at the optic nerve head. These glial cells have innate immune-like functions, performing immune surveillance and functioning as rapid responders to retina damage or injury.[126] Both astrocytes and Muller glia cells are activated in glaucoma and linked to its pathogenesis.[129,130] Following RGC cell death as a result of elevated IOP, the pro-inflammatory pathways that activate astrocytes and microglia are likely to be induced by DAMPs (damage-associated molecular patterns) released by damaged RGC cells.[131] This pathway has been proposed to mediate early stages of glaucoma. Following their migration to sites of injury in the retina, these activated astrocytes have the potential of forming glial scars.[132,133]

The microglia in the retina, like all CNS microglia, express antigens common to macrophages and monocytes,[134] and are the progeny of monocytes that populate the retina during development. Importantly, in addition to astrocytes and microglia, the neuroinflammatory response in glaucoma also involves blood-derived immune cells, including circulating monocytes.[126] In fact, the infiltration of proinflammatory monocytes into the retina and optic nerve head has been linked to the onset of glaucoma in animal models of the disease.[126,135] Gene ontology analytics have shown that genes associated with the immune response, including leukocyte activation and

chemotaxis, are among the earliest genes upregulated in the DBA/2J mouse model of glaucoma.[126] These genes are induced at a time when IOP is elevated, but prior to a detectable loss of axons, suggesting that these immune cells may have a causative role in the retinal damage that occurs in glaucoma.

There is additional evidence that the impact of glaucoma on RGCs may involve inflammatory responses early in the disease process.[126] Studies with DBA/2J. Wld^s mice suggest that early immune responses in glaucoma are linked directly to high IOP and are independent of RGC dysfunction.[136] Progressive degeneration of RGCs and axons associated with neuroinflammation also occurs in patients with a normal IOP (normal tension glaucoma),[137] suggesting yet another mechanism that can lead to inflammation and retinal damage in glaucoma. Importantly, the risk of both glaucoma and neuroinflammation increases with age.

In experimental models of glaucoma, the activated glial cells of the retina express MHC-II proteins and produce proinflammatory cytokines and chemokines including TNF α .[138,139] The expression of these molecules is associated with infiltration by blood-derived immune cells.[140,141] In addition to activation of microglia, acute elevation of IOP induces accumulation of hyalocytes from the vitreous and macrophages into the subretinal space.[142] These immune cells provide another source of pro-inflammatory cytokines .[143] In human glaucoma, proinflammatory cytokines, particularly TNF α, are increased in the vitreous, retina and optic nerve.[127,144-147]

As research continues to advance our understanding of the immune response and its regulation, it has become clear that immune privileged sites like the eye possess immune competence.[148] In addition, in degenerative eye diseases of the retina, it has been shown that the blood-retinal barrier is compromised.[149] Evidence that this occurs in glaucoma include the detection of autoantibodies in the retina[150] and the infiltration by inflammatory leukocytes and macrophages[139] that have been detected even before glaucoma symptoms are evident.[151] There is both clinical and experimental evidence that neurodegeneration occurring as a result of high IOP in glaucoma is associated with a Heat Shock Protein (HSP)-dependent T cell response.[152,153] And the protection from glaucomatous RGC loss provided in Rag1-/- (T- and B-cell-deficient) knockout mice in which IOP elevation has been induced provides further evidence of a role for the immune response in glaucoma.[154] In a mouse model of glaucoma, neuronal damage is minimized or prevented when monocyte entry into the optic nerve head is blocked pharmacologically, genetically, or through radiation treatments.[135,155,156]

PROTECTIVE AND REPARATIVE IMMUNE RESPONSES TO WOUNDING IN THE LENS AND THEIR LINKS TO FIBROSIS

The lens is suspended in the center of the eye by tendon-like ciliary zonule fibers. These zonules link the lens to the ciliary body, which is located behind the iris and in front of the retina along the periphery of the eye. The zonules are made of fibrillin that is produced by the nonpigmented ciliary epithelial cells.[157] Accommodation, the process by which lens shape is constantly altered to focus images on the retina,[158,159] is transmitted through the ciliary zonules and regulated by contraction of the smooth muscle cells of the ciliary body. Together, the lens and ciliary zonules define a border between the aqueous humor in the anterior chamber of the eye, and the vitreous humor in the posterior eye chamber, both of which are in direct contact with the superficial surface of the matrix capsule that surrounds the lens.

While the ciliary body has a rich vasculature, the adult lens is a transparent, avascular tissue. A vasculature is associated with the embryonic lens during its development in mammalian (not avian) species that is removed around the time of birth. The fact that the eye is considered an immune privileged site, and that the lens is avascular[160] and surrounded by a thick matrix capsule,[161] had led investigators to presume that immune cells would not be associated with or recruited to wounded or dysgenic lenses, even though non-canonical mechanisms of immune cell recruitment had been discovered for other avascular regions of the eye.[65,162] It is only recently that it has been shown that there is surveillance of the lens by immune cells in response to eye injury, an adaptive immune response to lens degeneration, and a repair response by immune cells activated upon lens wounding.[163-165] These studies also provided evidence that the association of immune cells with the lens has negative outcomes, including a role for immune cells in lens fibrosis.[164,165] As a relatively new area of study, there still remains much to learn about the innate and adaptive immune responses to lens wounding, the mechanisms regulating surveillance of the lens by immune cells, and how inflammation can lead to impairment of lens function. Here we review the significant progress that has been made in the early stages of investigating lens immune responses to wounding.

Evidence of an adaptive immune response to lens degeneration. One of the earliest pieces of evidence that the lens has the ability to mount an adaptive immune response came from studies with an N-cadherin lens-conditional knockout ($N\text{-}cad^{\Delta lens}$) mouse.[164] The absence of N-cadherin causes a progressive

degeneration in the region of the lens occupied by the lens fiber cells.[166] The morphogenetic defects and subsequent apoptotic death of these lens fiber cells leads to the recruitment of macrophages followed by B and T cells, in the presence of an intact lens capsule.[164] The immune cells recruited to these dysgenic lenses are induced to express the myofibroblast protein αSMA prior to the development of cataract-like opacities in adult N-cad$^{\Delta lens}$ mice.[164] The appearance of myofibroblasts was correlated with the presence of a collagen I-rich matrix in the dysgenic regions of these lenses, a microenvironment that has been associated with various lens cataract phenotypes.

Lens resident immune cells. Consistent with the discovery that immune cells are recruited to regions of lens degeneration, the normal lens was found to harbor a population of resident immune cells.[165] While not previously described in the lens, resident immune cells have been characterized in almost all tissues,[167,168] including other immune privileged sites in the body such as the cornea and the hair follicles of the skin.[169,170] Resident immune cells are activated upon injury to function as the earliest responders to a wound site and have been called sentinels of the immune system. They play essential roles in maintaining tissue homeostasis including functions in guarding against infection, clearing cellular debris, and immune surveillance.[168] Resident immune cells also have an active role in directing wound closure, an innate immune response that has evolved over time. While resident macrophages with a hemangioblastic lineage had been identified amongst the cells of the lens primordium,[171,172] it was initially believed that they disappeared early in lens development, following lens vesicle closure.[172] It is now known that a population of lens resident immune cells is established during embryonic development and maintained in the adult.[165] Analogous to resident immune cells in the cornea, the resident immune cells of the lens are located interspersed between the cells that make up the lens epithelium in all species examined thus far, including humans.[165] They are activated upon cataract surgery wounding to rapidly populate sites of lens epithelial cell injury. Among them are immune cells with dendritic morphologies that express MHC type II antigen, identifying them as antigen presenting cells (APCs).[165] This finding suggests that lens APCs play a role in the adaptive immune response activated in response to lens dysgenesis.

Post-cataract surgery fibrosis – Posterior capsule opacification (PCO). Cataract surgery removes the differentiated lens fiber cells that comprise the bulk of the lens, leaving behind the matrix capsule surrounding the lens and the closely associated wounded lens epithelial cells amongst which the resident immune cells reside. An intraocular lens is implanted within this capsular bag that replaces the function of focusing images on the retina. While generally a highly successful procedure, a large number of post-cataract surgery patients develop a fibrotic vision-impairing condition called posterior capsule opacification (PCO) along the fiber cell-denuded region of posterior lens capsule.[173] At the cellular and molecular level, PCO is linked to the appearance of Collagen I-producing, αSMA+ myofibroblasts, of which one well-characterized source is the epithelial-mesenchymal transition (EMT) of lens epithelial cells.[174-188] The resident immune cells of the lens also have been identified as a progenitor source of αSMA+ myofibroblasts post-cataract surgery.[165,189] These immune cells are highly susceptible to being signaled to transition to a myofibroblast phenotype, an outcome promoted by factors in their microenvironment. In addition, the identification of a population of resident APCs in the lens[165] is consistent with their recruitment of neutrophils and monocytes to the post-cataract surgery lens. These immune cell types have been demonstrated to convert to αSMA+ myofibroblasts that are associated with the development of fibrosis.[119,121] A direct link between the inflammatory response to cataract surgery and post-cataract surgery fibrosis was shown in clinical studies which demonstrated that the use of anti-inflammatory steroid medications in cataract patients reduced PCO to levels that did not require surgical treatment to restore vision.[190]

Cytokine and immune responses to cataract surgery. Studies with a mouse cataract surgery model have shown that circulating innate immune cells are recruited to the lens post-wounding.[191] The recruitment of these immune cells to wounded lens tissue occurred subsequent to the rapid induction of chemoattractant and pro-inflammatory cytokines by the injured lens tissue.[191] These studies demonstrated that the lens inflammatory response to wounding includes the induction of pro-inflammatory proteins like S100a9 and chemoattractants for neutrophils, macrophages, and monocytes, including the chemokines CXCL1, CCL2 (monocyte chemoattractant protein-1 (MCP-1)). The induction of each induced cytokine and chemokine was shown to have a distinct profile for how quickly and how long it was elevated post-cataract surgery.[191]. This mouse cataract surgery model also showed that cells expressing αM integrin, a receptor expressed by both neutrophils and macrophages, are among the earliest innate immune cells to become associated with the post-surgery lens capsular bag, and were followed by immune cells expressing F4/80, an antibody that identifies a subset of macrophages.[192] Interestingly, F4/80 is the immune cell marker used to identify the presence of

tissue resident macrophages within the lens primordium.[172] The results of these post-cataract surgery wounding studies also suggest a link between the inflammatory response to lens wounding and the mechanisms responsible for TGF β -activation and the induction of fibrosis.[191]

Surveillance of the Lens by Immune Cells in Response to Eye Injury. Immune surveillance protects tissues, with a primary role in maintaining tissue homeostasis. This phenomenon is best studied in cancer research in the context of the activation of both innate and adaptive immunity to eliminate cancer cells, as well as the mechanisms used by cancer to evade surveillance by immune cells.[193]. Interestingly, studies with the N-cad$^{\Delta lens}$ mouse revealed that lens degeneration activated an immune surveillance response in other regions of the eye, including the central cornea and retina.[164] In a mouse model of optic nerve injury, it was discovered that injuring the lens induced the secretion of factors by macrophages that stimulated axon regeneration by the injured retinal ganglion cells.[194]

Evidence of cooperative immune responses in the eye was also provided by studies revealing that surveillance of the lens by immune cells is induced in response to debridement wounding of the cornea.[163] In these studies, it was discovered that within one day of cornea wounding, immune cells sourced in the ciliary body are induced to travel along the ciliary zonules and populate the lens anterior surface from where they migrate across the lens capsule (Fig 3).[163] While these studies identified the ciliary body as a source of immune cells that both surveille and become associated with the lens, the hyalocytes located in the vitreous humor just posterior to the lens[195] are also a potential source of the immune cells that surveille the adult lens. The finding that there is active surveillance of the lens by immune cells that can migrate across the lens capsule to populate this avascular tissue suggests that the high level of cataractogenesis in autoimmune diseases such as diabetes and uveitis[196,197] may be linked to the high concentration of immune cells in the aqueous and vitreous humors in these diseases. Similarly, since anterior subcapsular cataracts (ASC) result from ocular trauma, and this trauma also induces the accumulation of cytokines and inflammatory cells in the aqueous humor,[198] it should be considered that the αSMA+ myofibroblasts and a collagen I-rich matrix that characterize ASC opacities may be linked to immune cells that become associated with the lens.

The impact of uveitis on cataract surgery outcomes. Uveitis is a multifactorial inflammatory disease that has destructive effects in both anterior and posterior segments of the eye.[148,199-201] It is characterized by inflammation within the uvea, the middle layer of the eye that contains most of its vasculature. The uvea is located between the sclera and the retina, and includes the iris, the ciliary body, and the choroid. While uveitis is linked to diseases, injuries and/or infections of the eye, it can also be a component of autoimmune or inflammatory disorders that occur in other parts of the body, such as sarcoidosis. The most common type of uveitis occurs in the front of the eye, anterior uveitis, in the region between the cornea and lens. Other forms of uveitis are intermediate (occurring primarily in the vitreous), posterior (retina and choroid) and panuveitis. When untreated, uveitis can lead to scarring, swelling or

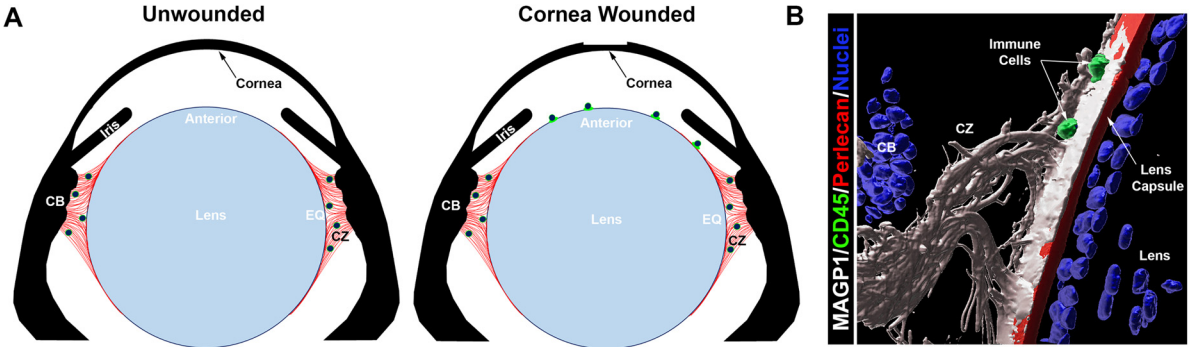

Fig 3. Surveillance of the lens by immune cells in response to wounding of the cornea. (A) Model of immune cells (green) traveling between the ciliary body (CB) and the lens along ciliary zonules (CZ, red) that link to the equatorial (EQ) lens capsule and extend along the capsule surface under physiological conditions (left panel), and migrating to the anterior surface of the lens to surveille this tissue in response to corneal debridement wounding (right panel); (B) 3D surface structure rendering of a confocal Z-stack imaged at one day post-corneal wounding showing immune cells (CD45+, green) migrating along within ciliary zonule (CZ) fibrils (MAGP1, white) that extend along the surface of the matrix capsule that surrounds the lens (perlecan, red). Also seen are the ciliary zonules (white) that link the lens to the ciliary body (CB). Nuclei in both the lens and ciliary body are labeled blue. This figure is adapted from DeDreu et al., FASEB J. (2020) 34:9316.[163] For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

detachment of the retina, optic nerve damage, glaucoma, and lens cataract, all of which are associated with vision loss. While this inflammatory disease has been linked to cataract formation,[202] the exact mechanism is not yet known. In contrast, there is a significant literature showing post-cataract surgery complications in patients with uveitis, particularly if inflammation is not controlled prior to surgery. The complications of cataract surgery in patients with uveitis include PCO, glaucoma, macular edema, and retinal detachments,[173,203-205] evidence that many regions of the eye are impacted by ocular inflammation after cataract surgery. Together with the discovery that immune surveillance of the lens is induced when the cornea is wounded[163] and the surveillance of the cornea and retina by immune cells in induced in response to lens degeneration,[164] these findings demonstrate that immune responses across the eye are highly interactive.

INFLAMMATION AND FIBROSIS IN THE RETINA: EPIRETINAL MEMBRANES (ERMS) AND PROLIFERATIVE VITREORETINOPATHY (PVR)

Idiopathic and secondary epiretinal membranes. Fibrotic deposits on the inner retinal surface are often described in the clinical literature using the word "membrane".[206] When retinal surgeons remove the fibrotic tissue from the retina, it peels off as an intact sheet. While not a membrane in the cell biological sense of a lipid bilayer, these structures are consistent with the dictionary definition of membrane which is "a thin soft pliable sheet or layer especially of animal or plant origin." (https://www.merriam-webster.com/dictionary/membrane). The term epiretinal membrane (ERM) describes the layer of cells and extracellular matrix deposited onto the inner surface of the retina as a result of aging and pathology (https://www.asrs.org/patients/retinal-diseases/19/epiretinal-membranes).

Numerous different ways to classify and describe retinal membranes have been proposed, adopted, and revised making the literature on this subject challenging. Idiopathic ERMs (iERMs) are typically diagnosed by a clinician looking at the patient's fundus, the region that they see when looking through the cornea and lens to the back of the eye and that encompasses the retina, optic disc, macula, and fovea. Patients may not have any symptoms but clinicians looking at the fundus often see wrinkles near the macula in what are called macular puckers.[206] ERMs can also form due to ocular pathology; these ERMs are referred to as secondary ERMs (2^{ry} ERMs). Pathologies that lead to 2^{ry} ERMs include proliferative diabetic retinopathy, central vein occlusion, uveitis, proliferative vitreoretinopathy, retinal detachment, surgery, trauma, macular hole, and retinitis

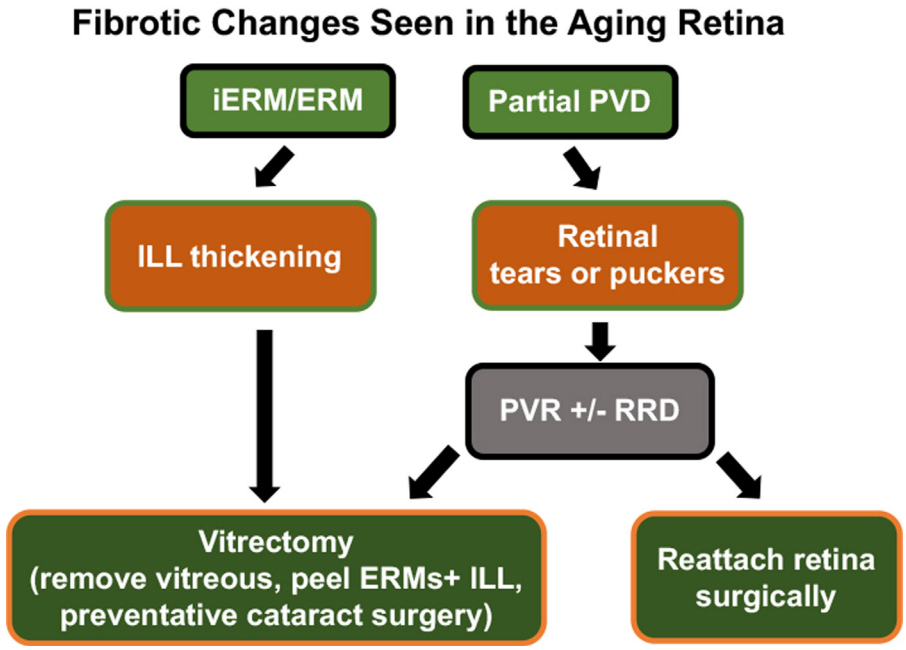

Fig 4. Fibrotic changes seen in the aging retina. When chronic inflammation occurs in association with age-related idiopathic epiretinal membranes (iERMs) and posterior vitreous detachment (PVD) retinal pathologies involving fibrosis are promoted. ILL= inner limiting membrane, PVR= proliferative vitreoretinopathy, RRD= Rhegmatogenous (rupture, tear) Retinal Detachment. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

pigmentosa.[207] 2^{ry} ERMs are more visually impairing due to their size, cellularity, pigmentation, and vascularization. However, iERMs along with posterior vitreous detachments (PVDs), which are described below, also can lead to serious visual impairment due to the traction they exert around the macula which can lead to formation of macular holes, inflammation, and retinal detachment (Fig 4).

The adhesion of the retina to the retinal pigment epithelial (RPE) cells is unique in that it does not involve cell:cell or cell:substrate adhesion molecules. Instead, their interaction depends on the close relationship established in the interdigitation of the outer segments of the retina's rods and cones with the apical microvilli extended from RPE cells.[208] The tips of the rod outer segments are ensheathed by RPE microvilli.[209,210] The intraocular pressure inside the large posterior chamber between the lens and the retina provides the force that stabilizes retinal:RPE adhesion. This chamber is filled with the vitreous humor, a gel-like substance consisting of water, collagens, glycoproteins, proteoglycans, as well as a number of hyalocytes. Transcriptional profiling has shown that hyalocytes are a unique innate immune cell type similar to resident macrophages that express genes for antigen processing and presentation.[207] Type II collagen makes up 60%−75% of the collagens in the vitreous with the remaining collagens being types V, IX, and XI.[211] Hyaluronic acid (HA) makes up 96% of the total glycosaminoglycans in the vitreous and associates with type II collagen fibrils covalently and non-covalently.[212] Because their sugars bind and organize water molecules, this proteoglycan:collagen interaction results in gel formation. Type II collagen allows the vitreous to adhere to the lens capsule anteriorly and the Inner Limiting Membrane (ILM) posteriorly. The ILM is a basement membrane structure that mediates vitreoretinal adhesion and plays an important role in pathological traction on the retina.[213]

As the vitreous ages, it undergoes changes in its composition which leads to its contraction and to a condition called Posterior Vitreous Detachment (PVD). The National Eye Institute (NEI) states that detachment of the vitreous from the retina typically occurs after the age of 50; by 80 years of age, most people have undergone PVD in both eyes (https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/vitreous-detachment). PVD can occur slowly over time or acutely with or without symptoms. PVD symptoms are a sudden increase in the number or sizes of floaters or an increase in spontaneous flashes of light.[214] PVD can be confirmed clinically using optical coherence tomography. Although the vitreous detaches from the ILM, it remains attached to the lens. As it shrinks, the collagen fibers in the vitreous pull on the ILM. Because adhesion of the vitreous collagens to the ILM is stronger at some sites than others, PVD is sometimes incomplete. The forces exerted on the retina during progression of PVD can lead to retinal tears and detachment.[215] When this takes place near or within the macula significant damage to vision can result. Such damage to or traction on the retina from PVD can be detected by an ophthalmologist.

The vitreous shrinks with age due to reduction in its proteoglycan content, which can be visualized by staining with cupromeronic blue, a dye that binds to the sugar residues on proteoglycans.[216,217] Chondroitin sulfate side chains on type IX collagen, a proteoglycan, are reduced or lost completely in the aging vitreous. Deglycanation of proteoglycans renders their core proteins more susceptible to proteolysis. As proteoglycans are deglycanated and degraded, water within the gel diffuses into the posterior chamber in a process referred to as vitreous liquefaction.[216]

The composition of the ILM resembles that of a typical basement membrane (BM), consisting of type IV collagen, laminins, nidogen-1, and the heparan sulfate proteoglycans (HSPGs) perlecan and collagen XVIII.[213] The ILM is produced by the Muller glial cells.[218] After the first 2 years of life, retinal Muller cells decrease production of ILM proteins. Muller cells are less abundant and change their morphology within the macular region of the eye. The thickness of the ILM is thinner at the foveola (center of the fovea) in human and primate eyes (30- 40 nm) than outside the foveola (0.9−1.0 μm at the parafovea)[219]. Where it is thinner, the retina is more susceptible to traction forces exerted by the vitreous during PVD or by ERMs. The ILM, like several other basement membranes in the body, thickens with age[220]; while the exact cause for age related ILM thickening is not known, the mechanical forces exerted on the Muller cells by age-related contraction of the vitreous have been hypothesized to increase Muller cell synthesis of ECM contributing to development of age related ERMs and to retinal pathology.

Damage to the ILM caused by incomplete detachment of the vitreous exposes the inner retina to fluid which leads to the most common type of retinal detachment, referred to as a rhegmatogenous (secondary to a rupture or tear) retinal detachment (RRD). RRDs can spontaneously reattach but, unfortunately, they often result in permanent loss of vision.[221] After detachment, fluid from the vitreous enters the hole created. Immune cells are recruited to the site from both the vitreous and the vasculature under the RPE cells which disrupts the blood:retinal barrier. RPE and glial cells become activated, and together migrate onto the surface of the ILM, proliferate, and differentiate into myofibroblasts forming a 2^{ry} ERM.

A recent study by Coltrini and colleagues looked at RNA isolated from the cells present in iERMs obtained by "membrane peeling" from 56 patients.[222] The iERMs were staged clinically and assigned scores of A or B, with a score of B given to iERMs that were thicker and more easily visualized due to vascularization and pigmentation from de-differentiated RPE cells. The authors surveyed the literature and selected 20 genes frequently associated with iERM, which fell into 4 different categories (cell proliferation genes, biological markers, ECM proteins, and cytokines/chemokines). Quantitative (q)PCR on the isolated RNA showed that progression of iERMs from stage A to B was associated with increased RNA expression of genes associated with fibrosis and cell proliferation and, surprisingly, a reduction in expression of Muller cell specific genes.

In diabetics, and when retinal holes and tears are large, 2^{ry} ERMs grow into the posterior chamber, often along fragments of partially detached vitreous. Patients with retinal membranes partially attached to the ILM and floating within the vitreous are said to have Proliferative Diabetic Retinopathy (PDR) or Proliferative Vitreoretinopathy (PVR). PVR is defined as a pro-fibrotic syndrome that occurs after any retinal tear, retinal detachment, or following the repair of a retinal detachment. Treatment for iERMs, PDR, and PVR involves removing the vitreous surgically (vitrectomy) along with the membranes and the ILM.[223] If a retinal detachment is also present, it will be reattached using one of several different procedures. Removing the vitreous eliminates tractional forces on the retina and can allow retinal holes and tears to resolve. Cataract surgery is often performed along with vitrectomy because removal of the vitreous from the posterior aspect of the lens accelerates cataract progression.

Numerous different types of cells are present in ERM membranes; the most abundant are those that express αSMA and called myofibroblasts.[224] Unlike the myofibroblasts present in the trabecular meshwork after glaucoma surgery and those present in the cornea after trauma or refractive surgery, the myofibroblasts in ERMs are often derived from cell types present only in the retina including activated Muller glial and RPE cells as well as immune cells recruited from the retinal vasculature and from the vitreous.[225] TGF β1 is known to promote the growth of ERMs and PVR and is expressed by several of these activated cell types.[226,227]

Researchers have attempted to identify factors that could predict development of new ERMs and their progression after vitrectomy.[228] After RRD occurs, ERMs develop in 4 stages: (1) ischemia and inflammation, (2) apoptosis, (3) cell proliferation, migration, and myofibroblast formation, and (4) contraction of membrane scars which leads to re-detachment of the retina These stages correlate only loosely to the 4 stages of ERM formation diagnosed clinically, which are mild (A), moderate (B), marked (C1, C2, and C3), and massive (D). The early ischemic phase initiates when the ILM and retinal vessels break, and fluid separates the inner retina from the RPE cells. This deprives the inner retina (photoreceptors, bipolar cells, and retinal ganglion cells) of oxygen and nutrients but does not induce ischemia in the outer retina and the RPE cells which continue to be perfused by the choroidal vasculature.

Studies have shown that within 3 days of detachment, approximately 20% of photoreceptors die by a combination of necrosis, apoptosis, and necroptosis. By 28 days, more than 50% of the photoreceptors have died. Cell death leads to release of angiogenic and inflammatory growth factors that recruit more immune cells from the choroidal vasculature. Following apoptosis of photoreceptors, the proliferation and differentiation of Muller glial and RPE cells into αSMA expressing myofibroblasts occurs and extracellular matrix accumulates forming membranes both on top of the ILM and under the retina between the degenerating photoreceptors and the RPE.[226] Serum factors from damaged and leaky blood vessels are also released into the vitreous. Injecting peritoneal macrophages into the vitreous of young rabbits induces ERM formation, highlighting the critical role that immune cells play in the development of ERMs.[229] These macrophages secrete FGF2 and TGF β1. T-helper cells are also recruited. Their role is more complicated because they can secrete both anti-inflammatory (IL10 and IFNγ) and proinflammatory (FGF2, PDGF, TGF β1, and VEGF) cytokines and chemokines. Yet, mice lacking T and B cells develop PVR in at similar rates in animal models of the disease[230] making it unlikely that PVR is initiated by autoimmunity. Autoantibodies against type II collagen do appear in the vitreous as PVR progresses but are not thought to be causal.

A recent proteomic study aimed at understanding the progression of PRV compared expression of 200 cytokines and chemokines in the vitreous of patients with ERMs (the control group) to the vitreous of patients with early (A, B) and advanced (C, D) stages of PVR.[231] There were more cytokines in the vitreous in early PVR than late PVR. Pathway analysis shows that the cytokines elevated in early PVR mediate T-cell recruitment and mTOR signaling, while in late PVR the predominant cytokines are involved in monocyte responses and stem-cell recruitment. The authors conclude that early PVR membranes are dependent on T-cell mediated cell signaling. Based on this proteomic data, several potential new therapeutics for treating PVR in its early stages are suggested: mTOR inhibitors

(sirolimus and metformin), the PI3K inhibitor (Idelalisib), and an IL13 inhibitor (Lebrikizumab).

Vitrectomy and membrane peeling remain treatments of choice for PVR to quickly release all tractional forces on the retina and to encourage tears to repair themselves. Success rates for closing idiopathic macular holes by vitrectomy in non-diabetics ranges from 85%−100%.[206] Large tears or holes are less likely to completely resolve after surgery. Developing therapeutics that could be administered at the time of vitrectomy to stop or delay further progression of PVR should be a goal to help preserve the remaining visual acuity of these patients.

CONCLUSIONS

It is becoming increasingly evident that understanding immune responses in the avascular regions of the eye holds the key to developing therapeutics that can effectively protect the eye, promote repair and block fibrotic outcomes that are particularly prevalent as the eye ages. In this review, we highlight the cooperative immune surveillance responses that are activated when one region of the eye is injured or experiences a degenerative pathology. While pathology in the posterior segment has long been known to accelerate cataract formation in the anterior segment, how it impacts the rest of the anterior segment is underappreciated. Because of age-related PVD and vitreous liquification, cytokines induced by retinal pathology can diffuse into the aqueous. There they can induce recruitment of immune cells into the anterior segment inducing and/or accelerating fibrosis and basement membrane thickening in the cornea, lacrimal and Meibomian glands, and in the TM. Likewise, chronic non-infectious keratitis and repeated reactivation of viral keratitis induce immune cell activation, recruitment, and cytokine secretion into the aqueous. Because of vitreous liquification, these cytokines diffuse into the vitreous where they activate hyalocytes and accelerate the progression of age related ERM formation, retinal traction, and progression to PVRs. Since cells and tissues in both the anterior and posterior segments of the eye can cause fibrosis secondary to inflammation, treatments to prevent fibrosis need to consider their impact on the entire eye and not just one region.

AUTHOR CONTRIBUTIONS

A. Sue Menko and Mary Ann Stepp have researched the literature for and co-written this review.

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