• Review Article •

Potential immune involvement in cataract: from mechanisms to future scope of therapies

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Abstract

● The immune system is involved in many age-related pathological changes, also plays an important role in tissue regeneration after injury. But no immune involvement has been discussed regarding cataract since it is presumed that lens has no source of immune cells as an avascular zone. Latest research has challenged the longstanding view of the lens as an immune-privileged tissue, revealing the presence of resident immune cells and active immune responses within the lens. Thus, we summarized the immune involvement in maintaining lens homeostasis, which may be a deleterious role in the induction of lens opacification if inappropriately activated. Furthermore, bioengineer-based immunomodulatory therapies to fine-tune the micro immune environment within lens may be future strategies for *in situ* lens regeneration, as a novel treatment for cataract.

● **KEYWORDS:** lens; cataract; immune involvement; lens regeneration

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INTRODUCTION

Cataract, characterized by opacity of the lens, has been known as the leading cause of blindness worldwide[1]. Most cataracts develop due to aging or injury, in which proteins and fibers break down and clump together, clouding the lenses. But the precise pathogenesis remains elusive.

As an evolutionary adaptation, the eye is sheltered from sight-destroying inflammation, also known as immune privileged, achieved by local anatomical and physiological properties. Especially, as the key component of central light path, the lens has no direct access to vasculature, which was considered a guarantee for its transparency.

But inconsistent with former assumption, it has been reported in several studies that the lens is accessible to immune responses. Since immune system participates in both homeostasis and pathogenesis in many other sites, investigating its role in lens would be of vital importance in renewing understanding towards cataract.

Immunomodulation in Anterior Segment The leukocytes are responsible for continuously monitoring the immune system and signaling to the tissue when needed, directing them toward the site in regulated manner[2]. There are, however, areas of the body that are considered immune-privileged, including eyes. Initially, immune privilege was thought to result from physical barriers that restrict leukocyte entry, but it has evolved to be a more comprehensive understanding that encompasses active mechanisms promoting immune tolerance and ignorance. And recent literature suggests that immune quiescence is a more accurate description of how the brain and eye function in terms of immunity[3-4].

The anterior segment of the eye has been described as immune privileged for a long time, but recent discovery of immune responses in avascular zone made 'immune tolerant' a better description. Recently, ciliary body has been found to be the source of resident immune cells, with zonular fibers as the channel for the trafficking of immune cells to the lens, providing a potential structure basis of the immune surveillance[5-6].

Immunomodulation in the Aqueous Humor Continuously secreted by the ciliary body, aqueous humour fills the anterior and posterior chambers of the eye, and can be considered as an ultrafiltrate of plasma with the help of the blood-aqueous barrier (BAqB). The BAqB is formed by tight junction of non-pigmented epithelium and endothelial cells of iris/ciliary blood vessels, enabling cellular migration from blood to the aqueous

humour, and has been fully characterized as the vital part of immune deviation in ocular system[7].

Anterior chamber-associated immune deviation (ACAID) is a well-characterized phenomenon initiated within the aqueous humor, wherein antigens present in the anterior chamber are captured by antigen-presenting cells (APCs) that subsequently migrate to the spleen[7]. Additionally, the aqueous humor harbors immunosuppressive factors, which collectively shield intraocular tissues from immunogenic inflammation (Figure 1B)[8]. To promotes ACAID, aqueous humor facilitates the apoptosis of inflammatory cells such as lymphocytes, neutrophils, and monocytes[9]. Additionally, it convert primed T cells into transforming growth factor beta (TGF-β) -producing regulatory T cells[10]. And suppresses the lineage commitment and effector function acquisition of T helper 1 and T helper 17 cells[11-12]. This immunomodulatory environment can trigger both activated and regulatory phenotype in infiltrating leukocytes, thereby fostering immune regulation is critical for preserving this delicate ocular tissue[7].

Immunomodulation within the Lens Unlike most tissues, where resident immune cells are interspersed among endogenous cell populations, the avascular nature of the lens initially led to the assumption that it would be devoid of such immune cells. A key question that arises is the mechanism and timing by which immune cells might be delivered to this unique tissue, characterized by its lack of innervation, stroma, and vasculature.

A recent study has demonstrated that resident immune cells inhabit the lens epithelium in chickens, mice, and humans. These resident cells respond to sterile injury by swiftly migrating from both single and multicellular niches to the wound site. Notably, APCs expressing major histocompatibility complex (MHC) Class II were identified within the avascular lens, suggesting their capacity to initiate adaptive immune responses in this otherwise immune-privileged environment[6].

It is now recognized that the avascular lens can mount an immune response in contexts such as lens dysgenesis, corneal injury, and cataract surgery[5,13-14]. In N-cadherin lens-conditional knockout mice, dysgenic lenses develop opacities accompanied by the recruitment of immune cells—first macrophages, followed by B and T cells linked to adaptive immunity[5]. Furthermore, immunoproteasomes, specialized proteasome subunits regulated by the antiviral cytokine type I interferon γ, have been identified in the vertebrate lens. These subunits are traditionally associated with antigen presentation, and now some researchers suggest that the immunoproteasome may be involved in nonimmune functions as a role in the process of lens differentiation[15].

A number of studies have investigated about the possible routes for immune cells to enter the lens. Recent findings

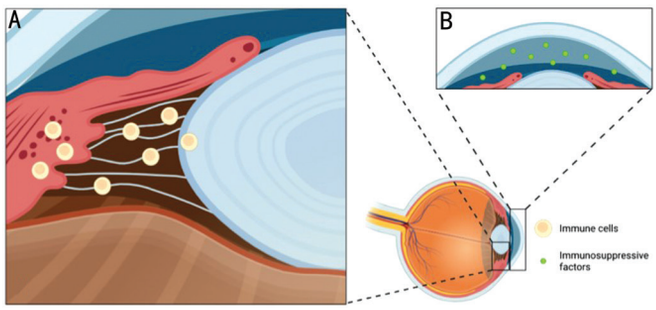

Figure 1 Immune involvement in anterior segment of the human eye A: Resident immune cells travel to the lens along the ciliary zonules from the adjacent ciliary body; B: Immunosuppressive factors in aqueous humor.

indicate that the vascularized ciliary body serves as a source of lens-resident immune cells, which migrate to the lens during development *via* the ciliary zonules (Figure 1A)[6]. These immune cells exhibit remarkable adaptability, altering their morphology to navigate narrow spaces and traverse basement membranes through both protease-dependent and independent mechanisms[16-17]. Another research group observed that macrophage-like cells may infiltrate breaches in the capsule of Trpm3-MM mutant lenses, particularly at the anterior pole[18]. Additionally, immune cells have been shown to transmigrate across epithelial basement membranes *in vivo*, with the recruitment of CD68+ cells—likely through the lens capsule—documented during severe lens dysgenesis resulting from N-cadherin deficiency[5,17,19]. Besides, immune invasion across the lens capsule has also been found in the absence of lens pathology[13].

Potential Immune Involvement in Cataract Formation

Cataracts are most commonly due to aging, which are so-called age-related cataracts (ARCs). Cataracts may also occur for other reasons, like after an eye injury or after surgery for another eye problem. Though the morphological changes in cataract lens are well-described as crystallin proteins aggregation, the detailed pathophysiological processes of cataracts formations, especially when taking immune system into account, require further investigation.

Senescence-Associated Immune Involvement in Cataract

ARCs are responsible for nearly 50% of world blindness[1]. Though numbers of studies have been made on the topic of ARCs, its pathological mechanism remains elusive, and thus effective medical treatments aside from surgery are lacking[20]. Cellular senescence is an important contributor to age-related pathologies, which would trigger immune involvements and also be influenced by immunosenescence[21].

Celluar Senescence and Immune Recruitment Cellular senescence represents a distinct form of irreversible growth arrest triggered by various stressors affecting proliferating cells[22]. The ocular lens is primarily composed of two cell

types: lens epithelial cells (LECs), which form a monolayer beneath the anterior capsule, and fiber cells, which make up the majority of the lens's mass. As a result of differentiation, mature fiber cells lose their nuclei and organelles and are incapable of de novo protein synthesis. Consequently, LECs are thought to be responsible for most of the functions of metabolism in lens[23]. Notably, cataract patients exhibit an age-related increase in senescent LECs[24]. Studies have reported that removal of senescent cells significantly reduced cataract incidence in aged mice[25].

The lens is constantly exposed to oxidative environments, with ultraviolet radiation (UVR) and H_2O_2 as leading sources[26]. Wherein, LECs are especially vulnerable to oxidative stress, which occurs stress-induced premature senescence (SIPS)[27-29]. Telomere erosion and shortening in LECs have been identified as key drivers of the lens senescence phenotype[30]. A common feature observed in most senescent cells is the activation of a hypersecretory state, known as the senescence-associated secretory phenotype (SASP)[31-32]. SASP composed of chemokines, cytokines, matrix-remodeling proteases, and extracellular vesicles (EVs), functionally connects senescence to a range of biological processes[32-33]. While immune cell recruitment supports proper tissue development and repair, their prolonged presence can lead to chronic inflammation, potentially contributing to aging-related diseases[34].

Immunosenescence and Cataractogenesis In contrast to younger individuals, the immune profile of older adults demonstrates a progressive decline in both innate and adaptive immune functions. This phenomenon, termed immunosenescence, significantly contributes to systemic aging[35]. Recent evidence underscores the close association between immunosenescence and various chronic age-related diseases, with cataracts emerging as a major cause of age-related vision impairment. Thus, given the plethora of evidence suggesting existence of resident immune cells within lens, we hypothesized immunosenescence as the underlying mechanism for ARCs.

With advancing age, individuals tend to develop a chronic condition of low-grade inflammation, known as inflammageing, which is crucially involved with the etiology and progression of many age-related diseases[36]. For example, excessive amount of pro-inflammatory cytokines in the central nervous system (CNS) leads to various brain function impairments, such as inhibition of hippocampal neurogenesis and cognitive decline[37]. Moreover, dysfunction in both innate and adaptive immune responses is the other result of immunosenescence, which compromises immunesurveillance, contributing to tumorigenesis and cancer progression[38]. It was newly found that in mouse model, oxidative stress promotes immune surveillance in lens, with upregulation of many cytokines and immune response genes[39]. Thus, immunosenescence in aging lens might contribute to the accumulation of oxidative damage, team with inflammageing in age-related cataractogenesis.

Immune Involvement in Lens Wounding and Links to Cataract Cataract can also be induced by ocular surgery and injury, which leave the lens with wounding and debris, breaking homeostatic balance. Maintaining tissue homeostasis is one of the primary functions of tissue resident immune cells[40]. In response to injury or degeneration, they would be quickly activated as the earliest responders to wounding[41]. But inappropriate immune responses have also been characterized as key components in leading tissue fibrosis, which might also contribute to cataractogenesis[42].

Among immune responses upon tissue injury, macrophages are one of the key cells that regulate the wound repair process, but also implicated as important participants in inducing fibrosis[42]. To facilitate wound healing, macrophage phenotype must transition from M1 (pro-inflammatory) to M2 (anti-inflammatory/pro-reparative) properly[43]. And the unbalanced M1/M2 ratio is responsible for tissue fibrosis[44]. For example, in murine Alport syndrome, progression of glomerulosclerosis and interstitial fibrosis is associated with significant M2 macrophage infiltrates[45]. After myocardial infarction, macrophages also orchestrate myocardial remodeling through fibrotic process[46]. Further, it was found that M2 macrophages induce epithelial-to-mesenchymal transition (EMT) through the TGF-β/Smad2 signaling pathway in bleomycin-induced lung fibrosis[47]. As one the newly confirmed resident immune cells for lens, macrophage infiltration was also found in degenerative lens, but its interaction with wounded lens tissue warrants further investigation[5].

Ocular trauma has been linked to cataractogenesis. For example, anterior subcapsular cataract (ASC), a common type of traumatic cataract, was found to be dramatically infiltrated by alpha-smooth muscle actin (α-SMA)+myofibroblasts, stimulating LECs to proliferate, undergo EMT, migrate to the wounding, which induced fibrosis beneath the anterior lens capsule[47]. Upon cataract surgeries, a rapid production of chemoattractant and pro-inflammatory cytokines, followed by recruitment of neutrophils and macrophages, was found in the wounding[14]. As a typical post-surgery cataract, posterior capsule opacification (PCO) was also well-recognized with EMT of LECs induced by TGF-β signaling, which resulted in increasing α-SMA+ myofibroblasts in post-cataract surgery wounding[14]. Moreover, a recent study indicated that the immune cells recruited to the post-cataract surgery wounded lens maybe another progenitors of the myofibroblasts, implicating a deeper immune involvement in this kind of cases[6].

Though up to 50% of patients undergo PCO within 2 to 5y after cataract surgery, it should be noted that transparent lens

regeneration after surgical extraction in rabbits, macaques and human infants with cataracts has been reported[48-49]. Thus, for surgery and trauma-induced cataracts, it would be important to reevaluate the potential relationship between immune response and cataractogenesis in wounded lenses. Furthermore, modulatory therapies targeting immune components during lens regeneration may be potential auxiliaries.

Immune Involvement in Steroids-Induced Cataract Another significant risk factor for cataract formation is prolonged use of steroids, known as a strong inhibitor on a broad range of immune responses. This kind of cataract exhibits distinctive opacification at central posterior location of lens, termed as steroid-induced posterior subcapsular cataracts (PSCs)[50]. Though, the role of steroids in the etiopathogenesis of steroid-induced PSCs is well known, the effect on the immune components within the eye, as well as the immune involvement in steroid-induced PSCs is lack of information.

Steroids exert their anti-inflammatory effects through the glucocorticoid receptor (GR)[51]. As a ligand-dependent transcription factor belonging to the nuclear receptor superfamily, GR is broadly expressed across various immune cells, which could reduce pro-inflammatory transcription factors and pro-inflammatory cytokine production[51]. In treating conditions of immune hyperreactivity, steroids use have been reported to induce various ophthalmic complications, especially cataracts[52]. But according to investigations of steroid-induced PSCs to date, none of these studies have explored how steroids influences critical lens cells functions, such as maintaining transparency or enabling proper refractive focusing[52].

Steroids plays key role in the regulation of macrophage homeostatic functions. Notably, steroids have been linked to the polarization of macrophages toward an M2-like phenotype, which is known to support processes such as wound healing and tissue regeneration[53-54]. Several studies have demonstrated that M2-polarized macrophages could promote EMT in different cells[55-56]. M2 macrophages would secrete high level of IL-10 and TGF-β, activating TGF-β/Smad2 signaling pathways, which induce EMT of epithelial cells[47]. EMT of LECs has been proposed as a major cause for the development of PCO after cataract surgery, mediated by TGF-β. Since recent studies have discovered the existence of macrophages in lens, long-term use of steroids may promote these macrophages towards M2 polarization, inducing EMT of LECs in the posterior region of lens, resulting in PSCs.

Potential Immunomodulatory Therapies To date, surgery is still the only effective treatment to permanently remove cataracts and restore vision, but the risks of complications are unignorable. And postoperative eye's ability to accommodate has generally been reduced or eliminated, depending on the kind of intraocular lens (IOLs) implanted. With the regenerative ability of LECs being unraveled, *in situ* lens regeneration is now becoming an attractive alternative which may be a potential therapy for cataract in the near future. It has been reported both in animals and humans that precisely preserving the integrity of the lens capsule and attached LECs during cataract surgery could regenerate a complete lens with refractive and accommodative abilities[49]. Since immune regulation in lens is involved both in the absence of lens pathology and after injury, as mentioned above[5,13-14]. Immunomodulatory therapies might facilitate the successful regeneration of functional lens.

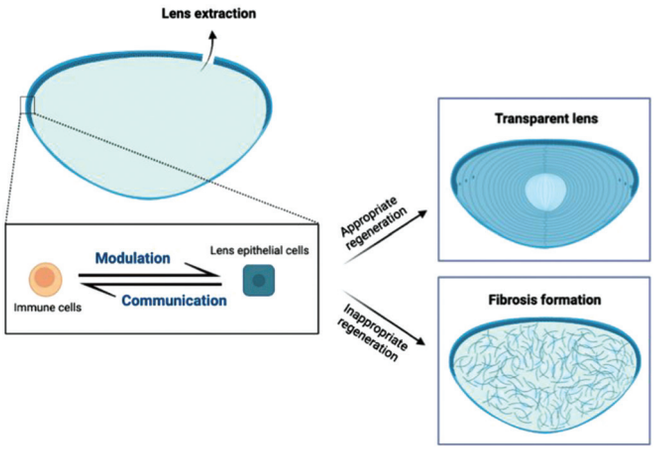

Figure 2 Possible immune involvement in lens regeneration After extraction of cataractous lens, residual LECs in the capsule undergo differentiation to fiber cells for lens regeneration. The interaction between immune cells and LECs affecting cell proliferation and differentiation procedures, is concerned to the transparency of regenerated lens. LECs: Lens epithelial cells.

Immune Regulation in Lens Regeneration: the Double-Edged Sword The immune system is pivotal in tissue regeneration following injury. Stem cells, crucial to this regenerative process, interact with the immune system in multiple ways to promote healing. After intracapsular lens extraction, the outcomes of lens repair—regeneration versus fibrosis of the residual capsule—are intricately linked to immune modulation (Figure 2)[57-58]. Understanding the role of immune regulation is essential for comprehending the microenvironment involved in lens regeneration.

Immune cells recruited to the wounded sites not only help to remove debris, but also contribute to appropriate cell proliferation and differentiation procedures by secreting signal molecules, without which the process of tissue regeneration would turn to be scar formation[59-60]. However, sustained inflammation can impede the regeneration process, and an aberrant immune response may result in fibrosis and scarring. Research has demonstrated that lens-resident immune cells can act as precursors to myofibroblasts, which are implicated in

PCO[6,61]. In the mouse cataract extraction model, up-regulation of the genes regulating the innate immune response and the intraocular infiltration of neutrophils and macrophages were confirmed after operation[14]. Immune system is linked to regeneration and fibrosis in many tissues, but whether there is link between the immune response after cataract extraction and lens regeneration still needs further examination.

In summary, immune regulation plays both supportive and inhibitory roles in lens regeneration. A finely tuned immune response is crucial for successful regeneration. Proteomic analyses have demonstrated that lens regeneration is closely linked to immune responses, revealing an enrichment in Fc-epsilon receptor signaling pathways and antigen processing and presentation of peptide antigens *via* MHC class I[62]. But detailed network between immune regulation and lens regeneration remains elusive.

Stem cells are distinguished by their capacity for self-renewal, proliferation, and differentiation into mature, lineage-specific cells. They are primarily categorized into two types: pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), which have the potential to differentiate into any cell type across all three embryonic germ layers, and multipotent or unipotent stem cells (commonly referred to as adult stem cells), which exhibit more restricted proliferation and differentiation abilities[63]. As a distinct subpopulation of LECs, lens stem cells (LSCs) unceasingly proliferate and differentiate into lens fiber cells, maintaining the physical and physiological features of lens. Comprehending how stem cells adapt and respond to different situations necessitates a detailed examination of their orchestration with local microenvironment, which is meticulously monitored by immune cells (Figure 2).

Recent research highlights the role of immune cells in modulating stem cell activity across various tissues. For example, T cells infiltrate neurogenic niches, inflammation influences alveolar regeneration, and macrophages establish transient niches for muscle stem cells. Growing evidence indicates that the interactions between immune cells and stem cells play as a driver factor in initiating regenerative processes. For example, muscle stem cells will be activated by damage-induced signals from macrophages, and regulatory T cells following injury, which are quiescent otherwise[64]. Advanced studies revealed more sophisticated immune-involved mechanisms which provide stem cells with appropriate signals to guide healing. Another study on later stage of muscle injury reveals that, immune-induced stem cell proliferation should be terminated at one point, followed by stimulating the differentiation of myoblasts from stem cells, so as to form the new muscle tissue. Thus, coordinated signals for stem cell activation and differentiation by immune cells is necessary for optimal regeneration *in situ*.

From a different perspective, stem cells are also integral to the immune system, modulating immune cell behavior. Some stem cells secrete molecules that attenuate hypercytokinemia and inflammation triggered by immune responses[65]. Additionally, certain adult stem cells exhibit immune memory; upon encountering wounding or inflammatory events, these stem cells leverage their prior exposure to modulate the immune response more effectively[66]. A more recent study found that stem cells within a damaged niche in the skin could communicate with immune systems by releasing cytokines and chemokines independently[67]. But whether and how LSCs and immune cells would interact with each other remains to be found.

Immunomodulatory Therapies in Lens Regeneration Since immune system plays an essential role in tissue regeneration, therapeutics targeting the immune regulation in lens should be future possibilities. But due to the double-edged effect of immune cells as both pro-regenerative and pro-fibrotic, the key is to maintain a balance within the microenvironment, which demands highly targeted medication.

The immune system significantly impacts tissue repair and regeneration, exerting both positive and negative effects. Consequently, modulating immune regulation in tissue healing has emerged as a promising strategy in regenerative medicine. This approach focuses on either enhancing pro-reparative processes to expedite healing or promoting the resolution phase to counteract fibrosis[68-71], but no immunomodulatory therapy applied specifically to lens regeneration has been reported. Translating these regenerative strategies into clinical practice requires deep understanding of the interactions between immune components and stem cells during tissue repairment.

Pharmaceutical administration for *in situ* tissue regeneration requires precise direction and stable concentration, which can be disrupted by surroundings. Hence, biomaterials that provide a structural framework to facilitate the attachment and migration of drugs are very desirable in regenerative medicine. For example, localized co-delivery of bone morphogenetic protein 2 (BMP2) and vascular endothelial growth factor receptor 1 (VEGFR1) to mouse joints by hydrogel could predispose skeletal stem cells to differentiate towards articular cartilage[72]. Exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells (iPSC-MSC-Exos) combined with thermosensitive chitosan/gelatin hydrogel significantly reduced rat corneal scar formation and accelerated epithelial and stromal *in situ* regeneration[73]. Thus, immunomodulatory factors delivery system boosting lens regeneration can be a potential axillary therapy for cataracts.

CONCLUSION

In this review, we present an overview of the findings supporting the potential immune involvement in ARCs and lens regeneration. Resident immune cells would not only promote immune surveillance of the lens, but also maintain lens homeostasis and potentiate lens regeneration after injury. But whether and how immune regulation join the occurrences of ARCs remain to be evaluated. Bioengineer-based immunomodulatory therapies to fine-tune the micro immune environment within lens may be future strategies for *in situ* regeneration.

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