·Review·

Ocular diseases: immunological and molecular mechanisms

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Abstract

• **Many factors, such as environmental, microbial and endogenous stress, antigen localization, can trigger the immunological events that affect the ending of the diverse spectrum of ocular disorders. Significant advances in understanding of immunological and molecular mechanisms have been researched to improve the diagnosis and therapy for patients with ocular inflammatory diseases. Some kinds of ocular diseases are inadequately responsive to current medications; therefore, immunotherapy may be a potential choice as an alternative or adjunctive treatment, even in the prophylactic setting. This article first provides an overview of the immunological and molecular mechanisms concerning several typical and common ocular diseases; second, the functions of immunological roles in some of systemic autoimmunity will be discussed; third, we will provide a summary of the mechanisms that dictate immune cell trafficking to ocular local microenvironment in response to inflammation.**

• **KEYWORDS:** immunological mechanism; ocular diseases; systemic autoimmunity; immune response; chemokines

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INTRODUCTION

Immunological and molecular mechanisms of ocular tissues prevent or resolve inflammation and maintain homeostasis. Indeed, the immune system protect host by response efficiently to environmental and pathogenic insults, maintaining tolerance to self-antigens and commensal microbial flora. Activation is exactly regulated, and immunological reaction requires the coordinated effort both the innate and adaptive immune responses. The innate immune system is the first-line of defense to control initial infection and coordinate the adaptive immune response, which culminates in inducement of antigen-specific T and B cells, decreases microbial destroy and generation of immunological molecular to defense foreign invaders. Sometimes, aberrant activation of the immune system could result in autoimmunity, which in turn destroy the ocular and associated tissues. In fact, ocular diseases consist of a diverse stage of pathologies and specific mechanisms. After ocular tissue destroyed by pathogenic factors, it will incite and express immunological response through its own anatomical and physiological features. It has improved local or systemic immunomodulation with anti-inflammatory agents have successfully improved these conditions or bringing these conditions under control. Thus, it is important for a more rational clinical approach to treat ocular diseases if we can understand the immunological and molecular mechanisms by which the ocular diseases participate in immune-inflammatory disorders. The aim is to first provide an overview of the immunological and molecular mechanisms of several typical and common ocular diseases. Second, the functions of immunological roles in some of systemic autoimmunity diseases will be discussed. Third, we will provide a summary of the mechanisms that dictate immune cell trafficking to ocular local microenvironment in response to inflammation.

CORNEA AND OCULAR SURFACE DISEASE

The cornea and ocular surface contacted with the external world constantly and directly, are required a optimum and native immune protection system to defense damage *in vivo* or *in vitro* The ocular surface consists of three distinct anatomical regions: the cornea, limbus, and the conjunctiva, which function both in concert and independently fight against microbial, immunogenic and traumatic attack.

For many years, the belief that essential absence of corneal antigen presented cells (APCs) was assumed to be a critical role of corneal immune privilege. However, this paradigm has now shifted with the demonstration of a diverse population of resident APCs for recent research [1]. Dendritic cells (DCs) were recently found to reside both in the peripheral cornea and in the central cornea [2]. While a large

number of DCs are express major histocompatibility complex (MHC) class II in the periphery, a large population of MHC class II-negative immature/precursor DCs are present both in the central epithelium and stroma. Immature DCs do neither express MHC-II nor costimulatory molecules unless they are incited by cytokines. It is improved that a large number of DCs in the cornea remain with an undifferentiated state. That is to say, immune cells settled in the cornea present constitutively as a participant in immune and inflammatory responses, rather than a collagenous tissue that simply responds to the activity of infiltrating cells.

Microbiotic Keratitis

Herpes simplex virus type-1 Ocular herpes simplex virus type-1 (HSV-1) infections, contributing to blindness in large measure secondary to recurrent infection, include both epithelial keratitis and immune stromal keratitis. Herpes stromal keratitis is a recurrent disease initiated after mucosal infection with HSV-1 through attachment to cognate receptors of epithelial cornea by its surface glycoproteins, in order to destroy the integrity of the corneal epithelium [3-4]. The virion envelope, attach to and melt the host cell plasma membrane. Upon HSV-1 infection and spread, apoptosis induction was observed. HSV-1 can hide from host defenses and lead to recurrent infections and potentially irreversible damage to the corneal tissue [5]. The virion can be spread cell-to-cell by cell lysis and shed viral progeny. HSV also can replicate in the corneal epithelial cells which layers are triggered. After the host was infected, whether vial latency or resolution, it simply depend on the initial viral quantity[6].

Data from researches show that the resulting clinical disease is not associated with this viral replication in the cornea, but rather is due to the host immune response to be restimulated by the latency of the virus. Secreted factors from infected and uninfected epithelial cells recruit a variety of leukocytes into the adjacent stromal tissue [*e.g.* neutrophils, polymorphonuclear leukocytes (PMN), macrophages, NK cells, dendritic cells, and γδ T cells][7]. Cytokines IL-2 can be induced by various resident corneal cells, and APCs can incur destructive effects by HSK on the stroma. IL-2 knockout mice can be ameliorated by treat with recombinant IL-2. Facing a conceivably blinding inflammatory attack, the cornea present many immunosuppressive factors to reduce inflammation and neovascularization, such as TGF-β, IL-1 receptor antagonists. However, the roles of Th1 T cell and IFN-γ in the immunology response have two paradoxical sides [8-9]. It has been improved that IL-1 has an intimate relathionship with corneal melting through induction of Langerhans cells (LCs) migration into the cornea, which result the tissue into further destruction.

Corneal epithelium and stroma whichmaintain corneal immune privilege through constitutively express IL-1 receptor antagonist (IL-1 RA) to neutralize IL-1 [10]. Polymorphonuclear cells secrete Vascular endothelial growth factor (VEGF) due to corneal neovascularization [11]. LCs, settling near the limbus, can be induced into the site of inflammation quickely following HSV-1 infection [12]. The quantity of LCs in the cornea is pertinent with the extent of stromal damage in HSK.

In the mouse models of HSK, $CD4^+$ Th1 cells have been suggested to be key mediators in the immunopathogenesis of HSV-1 infection [13]. As far as other local tissue factors are concerned, a perfect balance between cytokines IL-12 and IFN-α, IL-4 and IL-10, which mature Th0 cells into Th1 or Th2 respectively, orchestrates the kind of T-helper response generated. An increasing expression of cytokines IL-2 and IFN-α in HSK further confirm the role of $CD4^+$ Th1 immune response in HSK pathogenesis [14]. Verjans *et al* [15] have a hypothesis that diverse clinical spectrum of disease with recurrent HSK may either basis on a heterogeneous immune response to the HSV epitopes, or, heterogeneity in the expression of corneal autoantigens in the host[16].

Pseudomonas keratitis Pseudomonas keratitis is a painful and potentially blinding corneal infection caused by the Gram-negative bacterium *Pseudomonas aeruginosa* (*P. aeruginosa*). Severe sight-threatening ulceration and necrosis destroy of the cornea are predominant in Pseudomonal infections; which is a common contaminant of contact lens wash solutions due to its innate and acquired resistance to biocides. *P.aeruginosa* can adhere to the surface of the contact lens and colonize; then adaptive and innate immune response are actively involved in bacterial clearance of PA-induced keratitis. Pathological process of Pseudomonal infections includes epithelial edema, mucopurulent exudate, coagulative necrosis, suppurative stromal infiltrate, in addition to a hypopyon[17]. A Th1-dominant response is severe corneal disease and perforation, whereas Th2-dominant response refers resistance to infection and a milder process of disease without corneal perforation. Polymorphonuclear neutrophils cells into the site of inflammation are the predominant infiltrating cells through upregulating the expression intercellular adhesion molecule-1 (ICAM-1). PMN and macrophages are recruited to engulf bacteria, release lysosomal enzymes and oxidative compounds to kill *P.aeruginosa* Macrophage also produce various pro-inflammatory cytokines enhanced the antibacterial immune response, such as interleukin 6 (IL-6), IL-1β, tumor necrosis factor α (TNF-α) and macrophage inflammatory protein 2 (MIP-2). IL-6 can express within 24h of *P. aeruginosa* invasion, and take part in recruitment of PMN cells into the site of inflammation.

Sun *et al* [18] have reported that *P.aeruginosa* activates expression of Toll like receptors (TLR)-4/5 on resident corneal macrophages, inducing transcription of chemokines and cytokines such as KC/CXCL1, as well as IL-1α and IL-1β. In corneal ulcers, there is elevated expression of TLR2, TLR4, TLR5 and TLR9, the NLRP3 and NLRC4

inflammasomes [19]. These inflammatory mediators can promote bacterial clearance, however, out of control, it may result in excessively immunology response which can make a destroy. Therefore, a fast and efficient role of immune response is critical in shortening the spread and reducing severity of pseudomonas keratitis.

Fungal keratitis Fungal keratitis secondary to *Aspergillus* and *Candida* species is an infection of the cornea by fungal pathogens. Since its diagnosis is difficult, the availability of antifungal agents is limited and its clinical outcome is poor, fungal keratitis is still a great challenge in ophthalmologic clinic. Although received an accurate diagnosis and efficient treatment, 20% of fungal keratitis patients may suffer from corneal perforation [20], which may be attributed to secondary corneal damage induced by excessive inflammatory responses. Fungal infection can be induced by using two strains of fungi: *aspergillus fumigatus* and *candida albicans*. Once fungi attack the corneal stroma, innate immune cells recognize pathogens with pattern-recognition receptors (PRRs), especially C-type lectin receptors (CLRs). It is recently reported that Dectin-1 is clearly expressed in the cornea and functions to detect invading fungi. The clinical prognosis mainly depend on not only pathogenic virulence but also host immune response. PRRs-mediated inflammatory response enhances clearance of fungi and promote tissue repair. *Aspergillus* and *Candida* are also be detected by human corneal TLRs 2 and 4 for hosting an immune response. TLRs 2 and 4 recognize fungal zymosan and mannan, induce production of IL-6 and IL-1β when fronted with *Aspergillus*, which is diminished by knocking down these innate receptors [21]. In a recent study showed that suppressing TLR2 expression in the cornea results in a decrease in neutrophil infiltration, allowing the cornea to preserve its morphological integrity. Suppressing TLR2 expression also caused a decrease in TNF-α, IL-1β, IL-6, IL-12, monocyte chemoattractant protein (MCP-1)/CCL2 and MIP-2/CXCL2 expression [22]. It seems if out of control, prolonged over-reactive host immune response may amplify the inflammation, and lead to tissue injury, even corneal perforation. Therefore, precise regulatory mechanisms are required to modulate the inflammatory response in fungal keratitis.

***Acanthamoeba* keratitis** Amphizoic amoebae became a threat due to their pathogenic potential as facultative parasites, causative agents of vision-threatening *Acanthamoeba* keratitis (AK). Recently, AK incidences have been reported worldwide, particularly in contact lens wearers with a predominance of soft contact lens use[23]. *Acanthamoeba spp.* is free-living organisms existing as vegetative mononuclear trophozoites with characteristic acanthopodia and as double-walled dormant cysts. They can intrude into human bodies from different sources, colonize some organs, multiply, and exist as opportunistic parasites causing pathogenic effects. The appropriate diagnosis needs laboratory identification of the specific pathogen for confirmation. AK is a sight-threatening corneal disease that manifests as severe eye pain, photophobia, blurred vision, and neuritis. *Acanthamoeba* genotypes related to keratitis are mainly T3 and T4. In the research on the host immune mechanism of AK, it is found that patients with severity of infection and incidence of disease have lower tear levels of IgA compared with healthy controls, which implicate the role of mucosa-mediated immunity in AK [24]. The innate immune response begins with migration of neutrophils and macrophages, which are believed to play important role in resolution of AK. Macrophages have a chemotactic ability to the pathogen, and an inherent response to kill the trophozoites *in vivo*. Neutrophils, like macrophages, also as the first-line defense against both *Acanthamoeba* cysts and trophozoites. Meanwhile, secretion of IgA antibody has been improved as adaptive immune system to defense AK through promoting neutrophil-mediated killing of trophozoites and preventing adhesion of the trophozoites to the corneal epithelium. Furthermore, it keeps from the corneal meltdown plant of trophozoites by inhibiting mannose-induced cytopathic protein (MIP-133)-induced digestion of the corneal epithelium and stroma. Most of the published literature suggests that earlier detection of visualization of cysts in the cornea based on *in vivo* confocal microscopy (IVCM) may be beneficial in treatment of AK [25]. It is also suggested combination anti-inflammatory therapy seems to be effective for treatment of AK.

Corneal Transplantation Serves as a simple surgical disease to study mechanisms regulating immunity and angiogenesis. Cornea is an avascular tissue and neovascularization of the corneal graft will increase the chance of rejection. According to Collaborative Corneal Transplantation Studies, the recipient cornea is considered "high-risk" once neovascularization in stroma exists in two or more quadrants before operation. Another factor, which leads to graft rejection, include growth of lymphatic vessels into the cornea [26]. Aberrant growth of these vessels in the cornea breaks its immune privilege. The relationship between angiogenesis and immune system in the cornea is related because resident immune cells play a crucial role in initiating and promoting angiogenesis. Inflamed and neovascularized host beds carry a higher risk of graft rejection. Angiogenesis can induce migration of LCs into the cornea; maturation of resident LCs and DCs of the cornea, which can then serve as APCs [27]. Cytokines IL-1 and TNF- α have a high expression by APCs, which lead to recruitment of neutrophils, suppression of anterior chamber-associated immune deviation (ACAID), maturation of corneal APCs, upregulation of vascular adhesion molecules, and recruitment of leukocytes[28]. An increasing expression of IL-6, MCP-1 and IP-10 were found in aqueous humor during rejection of corneal transplantation.

Many laboratories research has demonstrated the presence of specific chemokines during the progression of allograft rejection. In the cornea, there is a high expression of specific species, including CCL2/MCP-1, CCL3/MIP-1α, CCL4/MIP-1β, CXCL10/IP-10, and CCL5/RANTES after corneal transplantation. These chemokines associate with particular receptors: CCR1 with CCL3/MIP-1α and CCL5/RANTES; CCR5 with CCL3/MIP-1α, CCL4/MIP-1β, and CCL5/RANTES; CCR2 with CCL2/MCP-1; and CXCR3 with CXCL10/IP-10[29]. However, there have been no studies to be showed which the relationship between chemokine or chemokine receptor deficiency and corneal transplant rejection has been examined. In addition, recipients of high-risk transplants express very high levels of the IP-10/CXCL10 chemokine. Chemokines function together with other molecular mediators including integrins and adhesion molecules to direct the immune response toward the graft.

Dry Eye Disease Dry eye disease (DED) is a chronic condition that is characterized by tear-film instability, tear hyperosmolarity, ocular surface inflammation, and damage resulting from reduced tear quality and/or quantity. It has a feature as increased osmolarity of the tear film and inflammation of the ocular surface. The composition of the tears can reflect the state of inflammation, and proteins such as inflammatory mediators are thought to modulate DED and relate with disease severity. ocular surface inflammation was associated with excessive tear evaporation, which leads to tear film instability. Recent report has shown an important role for chemokines in the pathogenesis of dry eye syndromes (*e.g.* IL-1, IL-6, IL-8, TNF-α). Corneal epithelial cells respond to stress signals by producing cytokine mediators of inflammation such as TNF- α, IL-1β, IL- 8 and MMPs[30-31]. The increase of these cytokines can lead to proliferation of epithelial cell, keratinization, and angiogenesis, even more could link ocular surface disease with a number of lid margin disorders, such as rosacea. More recently, Th-17 associated cytokines and IL-17 have been found in the ocular surface epithelium of DED. It has been hypothesized that epithelial cells subjected to desiccation conditions promote DCs to secrete IL-6, IL-23 and TGF-β, which in turn induce Th-17 cells [32]. The better understanding for the role of chemokines and its receptors in DED could provide new methods for development of molecular treatment for immune modulation in this ocular surface disorder.

Allergic Conjunctives Allergic conjunctive (AC) are inflammation of the conjunctiva secondary to an immune response to external antigens, usually called allergens. Allergic disorders are primarily characterized as IgE- and/or T-lymphocyte- mediated disorders that affect the cornea, conjunctiva, eyelids, and tear film. Therefore, AC seems to be a syndrome affecting the entire ocular surface rather than a single disease. It consists of diverse spectrum of ocular diseases, *e.g.* seasonal allergic conjunctives (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), which are its chronic forms. In recently research, giant papillary conjunctivitis (GPC), and contact or drug-induced dermatoconjunctivitis (CDC) are seemed to be subtypes of AC, because of their mechanism of allergy [33]. This pathological process of allergic reaction consists of IgE-mediated and non-IgE mediated, atopy could affect clinical evolution [34]. Many factors can affected signs and symptoms of AC, such as genetics, environment, and immune regulation mechanisms, all of which work together in a complex immunological response. This unbalance of immune homeostasis can result into a variety of allergic ocular diseases (AOD).

The conjunctiva has an abundance of Langerhans' cells that initiate allergen-induced immune response when these antigen-presenting cells encounter an allergen on the conjunctiva [35]. The immune cells, such as lymphocytes, distributed over the conjunctiva form a mucosal immune system known as the conjunctiva-associated lymphoid tissue. IgE could be detected in human tears of AC patients [36]. $CD23^+$ $CD21^+$ $CD40^+$, subtype of B cells, located in the conjunctival lymphoid, it infer that they might be precursors of IgE-producing B cells and contribute to local IgE synthesis [37]. Activated mast cells can release several cytokines (TNF-**α**, IL-4, IL-6, and IL-13) contributing to increase local inflammatory Th2 response [38-39], it also can increase Fcε RI density in chronic keratoconjunctivits[40-41].

Recent research suggested that macrophages could be the aim for study in AC, since it seemed to be act as APCs and affcet ocular allergy [42-44]; nevertheless, further research will be paid more attention on the real role of macrophages in AC.

Thymic stromal lymphopoietin (TSLP), an epithelium-derived cytokine, is regarded as a novel pro-allergic molecule and can strongly activate dendritic cells through interaction with the TSLP receptor (TSLPR) to induce an inflammatory Th2-type response that is essential for initiating allergic inflammation [45].

UVEITIS

Uveitis is defined as an inflammation of the uveal tract or middle coat of the eye (iris, ciliary body, and choroid). The inflammatory pathways of autoimmune posterior uveitis are complex and have been reviewed in detail in previous publications[46-48]. After immunization, Th1 and Th17 cells are activated by APCs in the periphery, migrate to the ocular site, and overcome the local immune privilege. The expression of pro-inflammatory cytokines and chemokines by immune cells and resident cells attracts monocytes, macrophages, neutrophils, natural killer (NK) cells, natural killer T cells, and γδ-T cells and supports the development of a local nonspecific immune response, which results in tissue damage. The uveitogenic effector responses involve different cytokine expression patterns (Th-1: IL-1, IL-15, IL-2, IL-6,

IFN-γ, TNF-α; Th-17: IL-17A, IL-17F, IL-21, IL-22, IL-6). Whereas IL-2 and IL-15 are important factors for the activation and survival of T cells and NK cells, IFN-γ and TNF-α represent important activators of cells in the innate immune system. IL-1 and IL-6 are essential for the induction of Th-17 cells[49]. Sauer *et al* [50] presented an overview of the levels of the various intraocular ILs that can be found in different forms of uveitis in humans, revealing elevated levels of IL-1β, IL-2, IL-6, IFN-γ and TNF-α in most cases of uveitis.

Although B cells and autoantibodies currently appear to play only a minor role in autoimmune uveitis (EAU) inducement, levels of Th2 cytokines (*e.g.* IL-4, IL-5, and IL-10), which are necessary for the activation, proliferation, and differentiation of B cells to antibody-producing plasma cells, are elevated [51-52]. In juvenile idiopathic arthritis (JIA), the presence of anti-nuclear antibodies represents an important risk factor for the development of uveitis. However, the role of B cells in the pathogenesis of uveitis in humans is far not known.

In experimental animal models, increased levels of IL-1β can break down the blood-retinal barrier and attract polymorphonuclear cells and monocytes [53-56]. Furthermore, the importance of IL-1 has been shown for the Th17 cell generation and for the development of autoimmune responses [57]. IL-1R-deficient mice demonstrated less inflammation in an immune complex-induced uveitis model than compare with the control one [58]. In murine model, suppression of uveitis was achieved with IL-1R antagonists[59-62]. Increased levels of IL-1β have also been found in the serum or aqueous humor from patients with chronic uveitis [63-64]. IL-2, which is expressed by activated Th1 effector cells, is one of the cytokines predominantly secreted in uveitis [65-66]. Increased intraocular levels of IL-6 have been observed in idiopathic uveitis and in uveitis associated with Behçet's disease, sarcoidosis, Vogt-Koyanagi-Harada, ankylosing spondylitis, and Fuchs cyclitis [67]. IL-6 is a key player in generating Th-17 cells, while it inhibits the generation of regulatory T cells [68-69]. Thereby, IL-6 enhances acute inflammation and, furthermore, triggers the progression to chronic inflammation. Th-17 cells, which are specialized cells of the adaptive immune system in initiating an inflammatory response, have also been found to be involved in the pathogenesis of uveitis in humans [70] and in a mouse model of EAU [71]. The use of an anti-IL-17 antibody significantly reduced ocular inflammation in the murine model of EAU[71].

UVEAL MELANOMA

Uveal melanoma is the most common cancer of the eye and it metastasizes in up to 50% of patients with large tumors. Strategies have been developed to control metastatic disease; however, success is limited and metastatic uveal melanoma remains universally fatal. Immunotherapy is being explored to be a potential option to prevent metastatic disease. Since uveal melanomas develop in the immune-privileged environment of the eye, these tumors may express novel and immunogenic tumor antigens to which the patient's endogenous T cells are not tolerated.

The immune system interacts with tumor cells *via* the innate and adaptive arms of the immune response. Similar to cutaneous melanomas, tumor-infiltrating lymphocytes (TIL) have been found in uveal melanomas [72-78]. $CD8^+$ T cells from the peripheral blood of uveal melanoma patients, or TIL isolated from primary uveal melanomas are capable of lysing human uveal melanoma cells *in vitro*[79-80].

The loss or downregulation of HLA-I is an important immune escape mechanism that is exploited by tumor cells to avoid T cell recognition and promote tumor progression. In contrast to the majority of tumors, in uveal melanoma HLA-I expression is upregulated during progression to metastatic disease and correlates with a poor prognosis[81-82].

A number of directly immunosuppressive properties of uveal melanomas have been identified and include local secretion of TGF-β [83], and IFN-γ-mediated induction of the enzyme indoleamine 2, 3 dioxygenase that depletes the local environment of tryptophan necessary for T cell clonal expansion, proliferation and survival [84]. IFN-γ-induced expression of programmed death ligand-1 by primary uveal melanomas and its metastases inhibits T cell activation *via* binding to program death-1 on the T cell[85]. Uveal melanoma cells are resistant to Fas ligand-induced apoptosis by CTL, despite their expression of both Fas and Fas ligand [86]. Furthermore, IFN-γ-stimulated uveal melanoma cells become resistant to perforin-mediated cytolysis by MHC-class-I-restricted, cytolytic $CD8^+$ T cells [87]. Of note, although IFN-γ is an important cytokine that supports T cell activation, it seems to have two faces in immunomodulation of uveal melanoma.

Uveal melanoma cells can indirectly inhibit antitumor immune responses *via* induction of immunosuppressive lymphoid and myeloid cell populations in the tumor microenvironment. Tumor-infiltrating T regulatory cells, which are predominantly $CD4^+$ $FOXP3^+$ T lymphocytes that produce TGF-β, have been observed in primary uveal melanoma tissue[88-89].

The clinical and genetic differences between cutaneous and uveal melanomas can be found, therefore, somatic mutations in the heterotrimeric G-protein α-subunit *GNAQ*, and its related gene *GNA11*, were recently reported to be frequently found in uveal and absent in cutaneous melanoma[90-91].

Zhou *et al* [92] reported that uveal melanoma cells as agents for $CD8^+$ T cells inhibited the activation of $CD8^+$ T cells, and attributed the inhibition to the lack of costimulation and HLA-II expression. Two other studies reported the activation of $CD8^+$ T cells; however, most of these responses were not restricted to HLA-I, and it was unclear if the activated $CD8^+$

T cells were responding to uveal melanoma tumor antigens or to alloantigens[93].

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD), a degenerative disease of the outer retina, take a considerable challenge for doctors because its etiology has not yet been clearly stated and treatment options are limited. Many scientific literatures on AMD has pay more attention to markers of inflammatory cytokines as well as the complement system, such as macrophages, inflammatory cytokins of the innate immune system. The research of up-regulation, overexpression, and ectopic expression of inflammatory cytokines, complement, macrophages and microglia that are closely related to the innate immune system [94]. Increased levels of IL-17-both protein and mRNA-within AMD maculae and that the ultrastructure of some IL-17 stimulated ARPE-19 cells clearly displays autophagy and mitochondrial damage[95].

AMD represent an age-related susceptibility to aberrant innate immune activation based on acquisition of foreign-like structural motifs. In this way, AMD may be viewed as a disease of the innate immune system [96]. Meanwhile, during the last few years, numerous trials have been started to verify the therapeutic effects of various drugs aimed to directly downgrade the retinochoroidal immune response in AMD patients [97]. In the next future, the outcomes of these clinical studies will be able to provide a more exact explanation of the role of the agents directed against the immune response in therapeutic recommendations for AMD patients.

IMMUNOLOGICAL MECHANISM

Inducement of immune response finely controls the movement of distinct subsets of immune cells into and out of specific tissues. Leukocyte, such as APCs and T cell, recruitment from blood to tissue, usually exists in the multistep process. Because the accumulation of leukocytes in tissues contributes to a wide variety of diseases, these "molecular codes" provide new targets for inhibiting tissue-specific inflammation. However, immune cell migration is also a critical stage for protective immune responses to tissues. Therefore, the reaction basis on identifying trafficking molecules that will specifically inhibit key cell subsets that drive disease processes without affecting the migration of leukocytes required for protective immunity.

Chemokine receptors regulate leukocyte retention in tissues. The migration of leukocytes to inflammatory sites depends on a cascade of discrete events mediated by chemokines and their receptors. Evidence of these immunological changes include altered levels of cytokines and chemokines, changes in the numbers and activation states of various leukocyte populations. Little is known about the constantly recruitment of DCs and macrophage precursors into peripheral tissues in the absence of inflammation. The behaviors of APCs are related to switching in chemokine receptor expression by these cells. During inflammation, CCL2, CCL5, and CXCL8 are produced to attract immature DCs that express CXCR4 and CCR4 respectively. In addition, these DCs are suited for migration into inflammatory sites by their expression of functional receptors.

Inflammatory signals induce resident DCs to undergo maturation. Upon maturation, DCs downregulate pattern recognition receptors necessary for surveillance of antigens and upregulate CCR7, a receptor important in the homing of DCs to the lymph nodes. Maturing $CCR7^+$ DCs then enter CCL21-expressing lymphatic vessels and travel to the draining lymph nodes where CCR7 ligands are produced. DCs migration into and along afferent lymphatics occurs including: 1) mobilization; 2) detachment; 3) interstitial migration; 4) entry into the afferent lymphatics; 5) transit *via* lymph. Recent data have shown that lymphatic endothelial cells upregulate E-selectin, chemokines (CCL5, CCL20, and CXCL5), and adhesion molecules (ICAM-1 and VCAM-1) after cytokine stimulation *in vitro* or *in vivo*. Once in the draining lymph nodes, antigen-loaded mature DCs activate naive T cells, which then proliferate and enter the blood and migrate back to the site of inflammation.

The importance of this observation relates to a general principle that sequences of peptides of some ocular tissues may be important for the preservation of self-tolerance and autoimmunity. Future studies should be focused on understanding the mechanism of tolerance induction and how to use this information to create new immunologically based pharmaceuticals to treat ocular injuries. Structural analysis of receptors required for microbial pathogenesis, immunity, and cell-cell contact are all likely to lead to new therapies.

CONCLUSION

The ocular tissues have developed many immunological mechanisms to protect themselves against the potential harm from these noxious agents (environmental pollutants and irritants, microbes, and other potential agents), and regulate their response avoiding unwanted damage. A clearer picture of immunological mechanism about ocular disease is being painted from recent discoveries to explain the diverse features and severity of clinical diseases. The role of immuno-inflammatory responses in ocular tissues has continuously been and has been becoming the focus for therapeutic approaches, therefore, identification of the critical pathways of immunological will provide new molecular targets for pharmacological intervention in inflammatory, infectious, alloimmune and autoimmune diseases and may lead to novel highly specific strategies for immunotherapy. Data from immunotherapy of ocular diseases have shown some drugs to be beneficial and have a satisfactory safety profile. However, a large number of problems should be considered in future and urgent need to solve, as many ocular diseases are inadequately responsive to current medications. For example, how the levels of immunological molecules are regulated and whether they can be pharmacologically

manipulated and offer novel therapeutic approaches. Unique features of the accessible surfaces of the ocular tissues offer opportunities for development of small molecules that disrupt immunological or inflammatory processes. Therefore, it is crucial to understand the immunological mechanism for handle with diverse ocular diseases.

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