Interleukin-17 and Immunity of Ocular infections

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Summary

The field of Interleukin-17 (IL-17) biology has received more attention during the last decade for evaluating the role of this cytokine to enhance the host defence against microbial infections. IL-17 is essential in controlling microbial colonization through the expeditious innate immune response to pathogens which involves the recruitment of neutrophils and the induction of antimicrobial peptides. IL-17 is synthesized by cell populations predominantly present within epithelial barriers, including specific subsets of Th17 cells and innate lymphoid cells. In

this review, we highlight both bacterial and fungal infections in human eyes and the role of IL-17 in host defence in addition to the benefit of using IL-17 for immunotherapy.

Key words
Il-17, bacteria, fungi, immune, innate immunity, adaptive immunity, ocular, eye, immunotherapy

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Introduction

The human eyes are valuable organs that are exposed to the external environment. For this reason, they are susceptible to ocular infections caused by various microorganisms worldwide. Infections can be by single or multiple pathogens that are associated with many factors including using contact lenses, immune system states, dry eye state, surgery, trauma, chronic nasolacrimal duct obstruction, age, and previous ocular infections.[1,2] Generally, bacteria, followed by viruses and fungi are involved in ocular infections. Bacteria are associated with many types of eye infections including keratitis, dacryocystitis, blepharitis, endophthalmitis, orbital cellulitis and conjunctivitis.[3] Fungi are widespread eukaryotic, unicellular or multicellular, and commonly associated with food spoilage. Many of these organisms are the primary source of carcinogenic mycotoxins, which can effect significantly human health.[4] There is a growing occurrence of opportunistic fungal infections among immunocompromised, including individuals with neutropenia, haematological malignancies, and those who have undergone bone marrow transplantation.[5,6] Eye infections caused by fungi are rare, but they can cause severe infections. Fungal infections can affect different parts of the human eye. Previous reports showed a direct association of opportunistic fungi with keratitis due to eye injury or using contaminated contact lenses.[7] Infected eyes if left untreated, can lead to a potentially blinding disease and in advance cases surgery for removing infected eyes as what happened in Singapore and the USA in 2006. Clinical symptoms of fungal eye infections can appear for several days to several weeks after fungal elements invasion. Generally, clinical symptoms of ocular infections by opportunistic fungi are similar to those of other microbial infections. For this reason, diagnosis and detection of the source of ocular infections are seriously critical without a precise and accurate identification test. The identification of clinical specimens can be achieved using conventional methods such as mycological culture and direct microscopic examination, as well as non-culture-based methods such as nucleic acid-based techniques and monoclonal antibodies. Treatment and management of emerging fungal infections are critical due to the spread of multidrug-resistant fungi. For this reason, despite developing new drugs, controlling fungal infections remain difficult in many cases. Meanwhile, compared to antibacterial antibiotics, antifungals have a lower efficacy due to their mechanism of action. Fungi are eukaryotes, so one has to take into account the side effects of antifungals on human tissues; therefore there is a limitation in considering fungal infections and treatment. Co-infections or poly-infections is a term used to describe the involvement of two or more than one microbial isolate including different species of bacteria or fungi or even bacteria and fungi at the same ocular site. This kind of infection can affect one or both eyes. Studies showed an increasing trend of co-infections. Eye co-infections are considered a serious challenge for ophthalmologists due to the difficulty to diagnose as bacterial eye infections mimic fungal infections.[8] Patients with ocular co-infections

present similar clinical symptoms such as ocular discharge, visual symptoms or a red or painful eye in case of bacterial and fungal infections. The immune system plays a key role in the human body's protection against microbial invasion. For this reason, the immune response within ocular sites protects eyes from infection and regulates healing processes following injuries. Within the eye microenvironment, the immune system expresses a response toward infections through immunosuppression and anti-inflammatory actions via ocular resident cells/tissues. Since the eye has limited regenerative properties, microbial infection and inflammation can lead to devastating health consequences. Thus, human eyes possess extraordinary features for immune-mediated inflammation reduction. This phenomenon is known as an immune privilege that has a pivotal role in ocular protection.[9] Interleukin-17A (IL-17A) is one of a family (IL-17B, C, D, E and F) that plays a central role in the control of microbial infections and mediate protective innate immunity to pathogens. IL-17A links T-cell activation to neutrophil mobilization and activation. For this reason, IL-17A is a pro-inflammatory cytokine, which was described fairly recently in 1995, that contributes to the pathogenesis of several inflammatory diseases.[10] The bioactivity of IL-17A has received immunological attention over the last few years due to their association with bacterial and fungal infections, psoriasis and other autoinflammatory disorders.[11,12] In addition, disorders in IL-17A regulation can lead to ocular diseases such as dry eye disease (DED) and infectious keratitis.

Microbial Eye Infections

The human eyes are very delicate and value sensory systems, serving as a primary source of information about the external environment. Humans heavily rely on vision as their predominant sense, making the eye the most delicate and perceptive organ within the human body.[13] Ocular infections can lead to impairments in visual which resulting in a major sight-threatening consequences such as keratitis and conjunctivitis.[14] Frequently, microorganisms involved in eye infections are bacteria, followed by viruses and fungi. Pathogenic bacteria are the primary agents responsible for conjunctivitis. Bacteria infect the ocular surface, specifically the mucous membrane of the conjunctiva. However, it is colonization population is regulated by the tears' lysosomes and humoral secretions such antibodies, as well as the protective mechanism of blinking.[15] Accurate and rapid diagnosis of microbial keratitis is needed for managing treatment and preventing a potentially vision-threatening risk.

Bacteria associated with eye infections

Bacteria typically target the external surface of the eye for colonization, while the internal parts of the ocular cavity remain sterile. In terms of immunology, the eye surface has multiple protective barriers that effectively prevent the occurrence of eye infections. Normally, the conjunctiva contains mostly antibodies, complement proteins, lysozyme, C-reactive protein, fibronectin, and transferrin that related to innate immunity. These components collectively contribute to the defence against bacterial pathogens. However, if any of the epithelium's ocular surface is compromised due to trauma or a decrease in local or systemic immune responses, eyes become more susceptible to microbial infections such as bacterial invasion.[16] Bacterial pathogens have been implicated in a spectrum of ocular surface infections, including conjunctivitis, scleritis, keratitis, blepharitis, canaliculitis, and dacryocystitis. Moreover, these bacteria can also cause more severe infections that extend to deeper ocular tissues, such as orbital cellulitis, preseptal cellulitis, necrotizing fasciitis, as well as intraocular infections like uveitis and endophthalmitis.[17]

Antibacterial treatment for eye infections

Bacterial infections of the eye are common, and ophthalmologists have a wide choice of antibiotic treatments comparing with other microbial infections. There are many ways of delivering antibiotics into the eye including subconjunctival injection, topical administration, subtenon injection, and intraocular injection. Ophthalmologists have a wide range of commercially eye antibiotics such in many different pharmaceutical formula including drops, cream and ointment that enables the achievement of elevated antibiotic concentrations for ocular tissues therapy.[18]

Fungal associated with eye infections

Ocular fungal infections are extremely rare. However, these kinds of infections can cause serious health consequences. Opportunistic fungi can affect different locations of the eyes. For example, keratitis is front layer of the eye, the cornea, that easily infected by fungal elements. These kind of infections occurs as a result of eye injury or bad usage of contact lenses.[19] Inflammation of eyes is called endophthalmitis that can be exogenous, when associated with direct fungal spores invasion,[20] and endogenous, when fungal elements spreads to one or both eyes from another primal body source.[21] Fungal infections are frequently associated with trauma as significant contributing agents. Fungal eye infection symptoms can occur after a few days to several weeks. These symptoms mimic bacterial eye infections including eye redness, eye pain, blurring in vi-

sion, tearing, and eye discharge.[22] Comparing with other pathogenic fungi, species related to the genus of *Fusarium, Aspergillus* and *Candida* are the most common opportunistic fungal agent causing ocular infections to human.[23] Routine laboratory techniques such as culturing and direct microscopic examination remain classical approaches for detection of fungal elements during ocular samples testing and permits a rapid presumptive diagnosis. Serological and molecular approaches have been widely used in recent years.[24]

Antifungal treatment for eye infections

Since the initial documentation of fungal keratitis, there has been an upward trend in the incidence of this condition. Compared to antibacterial drugs, antifungal agents have a lower efficacy due to lower tissue penetration.[25] Generally, amphotericin B, nystatin and natamycin are the most frequently used antifungals. There is a limited use of nystatin due to its toxicity and low rate of tissue penetration for treatment of opportunistic fungal keratitis compared to amphotericin B and natamycin.[26,27]

Antifungal resistance to eye infection

Resistance to common antifungal drugs by pathogenic fungi is a risky point. Fungal cells can develop mechanisms for resistance to antifungal drugs resulting in expanding fungal infections and complicating their treatment. Because of the genetic inherent resistance of some fungi, certain antifungal treatment might ineffective in treating fungal infections. For example, *Aspergillus* exhibited a notable fluconazole resistance.[28] Due to too low dosage of antifungal drugs or when treatment courses are not long enough, fungi have a chance to develop resistance to antifungal agents over time.[29-31]

Eye Coinfections

In developing countries, corneal blindness following cataracts is primarily attributed to ocular infections caused by bacteria, viruses, and fungi.[32] However, an escalating incidence of co-infections, wherein two or more pathogens coexist in the same ocular environment, affecting either one or both eyes, has been increasingly documented. In contrast to single-microorganism infections, which lack competitive dynamics in theory, co-infections have been demonstrated to engage multiple mechanisms that compete for host resources. This competitive interplay constitutes a pivotal factor that significantly influences the clinical trajectory and progression of the infection.[33] Clinical presentations of eye co-infections mimic different clinical cases resulting in a serious diagnostic challenge for ophthalmologists. This challenge affects directly patients through receiving multiple treatments instead of a specific treatment.[34] Among immunocompetent patients, eye infections are common particularly co-infection due to impaired the immune system.[35] Bacteria and fungi are the most frequent clinical entities causing eye co-infection.

Bacteria and Fungi of Eye Infections

Bacterial and fungal co-infections constitute the most prevalent type of ocular co-infection. *Staphylococcus* spp., followed by *Streptococcus* spp., *Pseudomonas* spp., *Klebsiella* spp., *Bacillus* spp., and species related to *Haemophilus* are main bacterial causative agents. Meanwhile, the species belong to *Aspergillus, Candida, Fusarium*, followed by *Curvularia, Alternaria, Cladosporium*, and *Bipolaris*, represent the genera of opportunistic fungal pathogens that are associated to ocular infections.[36] Co-infections of bacteria and fungus are more likely to be between the species related to the genus *Staphylococcus* and *Aspergillus* or *Fusarium* resulting in serious clinical symptoms.[35,37-40] To distinguish between bacterial and fungal keratitis based on clinical presentation is considered a serious challenge, as the characteristic symptoms of each infection may be overridden by mixed microbial infections.[41]

Immune System

Immune tissue, cells, and organs work together to form the immune system for protecting the body against harmful microbial pathogens, such as bacteria, viruses and fungi. Cellular defence mechanisms of the immune system involve various immune cells, such as specific killer T cells (T-cells), natural killer cells (NK), polymorphonuclear leukocytes, and macrophages that directly target pathogenic cells. Additionally, signalling networks via cytokines, humoral immunity affects cellular immunity through producing a range of immune mediators such as antibodies, cytokines, chemokines, and complement proteins to enhance immune protection against foreign invaders.[42] Altogether, the immune system parts help to recognize and eliminate the infectious agents causing the inflammation. Keratitis due to bacteria or fungi triggers the immune response to combat the invading microbial elements.

The Ocular Immune Response

The ocular surface is normally protected from mi-

crobes physically by a mucosal layer. The ocular immune response refers to the specialized immune mechanisms protecting the eyes from microbial infections. However, lymph vessels are missing in the interior of the ocular structure.[43] The eye components in nature have immunosuppressive and anti-inflammatory effects. The immunosuppressive activity exhibited by resident cells in the eye is commonly known as immune privilege, and it serves a critical function in preventing significant damage caused by infiltrating inflammatory cells, which can result in vision loss. The eye employs a wide range of mechanisms to regulate innate and adaptive immune cells, thus effectively mitigating the risk of blindness associated with intraocular inflammation.[44,45] Several immunosuppressive mechanisms have been identified thus far, which are attributed to the microenvironment within the eye. These mechanisms encompass ocular fluids, the blood-retina barriers, and resident parenchymal cells present in the eye. In order to safeguard the continuity of vision from two main domains: physical and immunological factors, intricate networks of neurons and immune components collaborate. It is worth noting that this complex interplay occurs within the context of the presence of microorganisms, whether they establish long-term residence in the ocular mucosa or are transient visitors introduced from the external environment, which have the potential to induce modifications in this delicate balance.[46]

The Eye and Immune Privilege

The immune privilege of the eyes is a unique state of anatomical, physiological, and immunoregulatory processes within the ocular tissues to protect eye and sight. This phenomenon allows eyes maintenance and immunological tolerance through restriction of the over-expression of inflammatory immune response.[9] The eyes' local immune components include macrophages and dendritic cells, as well as immunoglobulins, complement proteins. The immune privilege is a unique immune mechanism within eyes that prevents excessive immune responses and thus prevents the potentially eye-destroying consequences of unregulated inflammation.[42,47]

Interleukin-17 in Antifungal Immunity

In 1993, interleukin 17A (IL-17A), was first discovered.[48] From mouse EL4 thymoma cells, receptor of IL-17A was first cloned and identified in 1995.[49,50] IL-17 level increases in cases of inflammation and autoimmune diseases indicating to association with human immune disease[51,52] T helper 17 (Th17) cells is a subset of cluster differentiation 4^+ ($CD4^+$) which are the main IL-17 producers.[53] Later on, $CD8^+$ cells (Tc17), natural killer-T cells (NKT), γδ T cells, group 3 innate lymphoid cells (ILC3s), neutrophils and microglia were reported as sources of IL-17 production.[54,55] Meanwhile, IL-17 has an ability to stimulate the production of antimicrobial peptides (AMPs) such as cathelicidins and defensins, that exhibit direct antifungal bioactivity.[56] Also, IL-17 can induce secretion of pro-inflammatory cytokines, IL-1β, TNF-α and IL-6 which contribute to the elimination of fungal pathogens,[57] resulting in enhancing phagocytosis via macrophages and neutrophils to intracellular fungal elements.[58] Meanwhile, eye-colonizing by commensal induced the recruitment of IL-17-producing γδ T cells to the conjunctiva where they play a direct role in enhancing the neutrophil recruitment and the release of antimicrobials into the tears and protected the eye from pathogenic microbial infection.[59] Therefore, congenital defects in the IL-17 pathway induce opportunistic fungal pathogens such as *Candida albicans* for causing infections.[60] Studies indicated high production of L-17 by peripheral blood neutrophils in patients with fungal keratitis due to high levels of airborne *Aspergillus* and *Fusarium* conidia.[61] This also indicates the vital role of IL-17 in protection and fungal ocular infections.

IL-17 Immunity in Health and Disease

IL-17 plays a crucial role in protection against various pathogens including bacterial and fungal infections, in addition to diseases, inflammatory autoimmune disorders, and cancer.[62] Recently, over the last years, IL-17 has attracted attention in the context of immunology and as an immunotherapeutic agent.[63] IL-17 plays a vital role in maintaining the equilibrium between the host and the microbiota in barrier tissues under normal conditions. This cytokine coordinates an effective mechanism within the epithelium, preventing disruptions in microbial composition and uncontrolled microbial cell proliferation.[64,65] However, considering anti-IL-17 therapy is a critical, as it has the potential to disturb microbial cells and increase the risk of opportunistic infections.[66,67] Overexpression of IL-17 may lead to dry eye-induced corneal damage and goblet cell loss in this case anti-IL-17 treatment strongly recommended.[68] For example, monoclonal antibodies, are already available to inhibit the IL17 pathway (such as ixekizumab, brodalumab, or secukinumab).[69]

Conclusions

In general, ocular co-infections caused by bacterial and fungal pathogens are most common in immunocompromised individuals due to a weakened immune system. Eye immune privilege is a unique state of immunity against microbial invaders. IL-17 plays an important role in triggering the immune response against microbial pathogens and, in particular, pathogenic fungi.

Conflict of Interest
Authors declare that they have no conflict of interest.

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Περίληψη

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Το πεδίο έρευνας αναφορικά με τη βιολογία της Ιντερλευκίνης-17 (IL-17) έχει λάβει μεγάλη προσοχή κατά την τελευταία δεκαετία για την αξιολόγηση του ρόλου της στην ενίσχυση της άμυνας του ξενιστή έναντι μικροβιακών λοιμώξεων. Η IL-17 είναι απαραίτητη για τον έλεγχο του μικροβιακού αποικισμού μέσω της ταχείας φυσικής ανοσοαπόκρισης σε παθογόνα που περιλαμβάνει τη στρατολόγηση ουδετερόφιλων και την επαγωγή αντιμικροβιακών πεπτιδίων. Η IL-17 συντίθεται από πληθυσμούς κυττάρων που υπάρχουν κυρίως εντός επιθηλιακών φραγμών, συμπεριλαμβανομένων συγκεκριμένων υποομάδων κυττάρων Th17 και εγγενών λεμφοειδών κυττάρων. Στην παρούσα ανασκόπηση επισημαίνονται τόσο οι βακτηριακές όσο και οι μυκητιασικές λοιμώξεις των οφθαλμών και ο ρόλος της IL-17 στην άμυνα του ξενιστή, και επιπλέον τα οφέλη από τη χρήση της IL-17 ως ανοσοθεραπεία.

Λέξεις κλειδιά
Il-17, βακτήρια, μύκητες, ανοσοποιητικό, φυσική ανοσία, επίκτητη ανοσία, οφθαλμός, ανοσοθεραπεία

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