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FUNGAL GENOMICS AND PATHOGENESIS (S SHOHAM, SECTION EDITOR)

Host/Pathogen Interactions in Fungal Keratitis

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Abstract There are multiple overlapping mechanisms for protection against corneal fungal infections. The source of infection is nearly always exogenous and due to environmental molds (e.g., *Fusarium* and *Aspergillus*) or cutaneous yeasts (e.g., *Candida albicans*). Therefore, intact anatomical barriers and effective tear function are crucial first lines of defense. Antimicrobial substances such as lysozyme, lactoferrin, lipocalin, and defensins which are found in tears and/or produced by corneal cells constitute an additional line of defense. Finally, the presence of fungi or fungal products at the corneal surface triggers signaling pathways within resident corneal cells that then activate direct or indirect cellular responses. These include the recruitment of neutrophils and T cells to the site of infection and activation of antifungal mechanisms. Taken as a whole, host defenses at the ocular surface provide a multilayered and overwhelmingly effective shield against fungal keratitis.

Keywords Fungal · Keratitis · Cornea · *Aspergillus* · *Fusarium* · *Candida*

Introduction

Fungal infection of the cornea (mycotic keratitis) is a potentially devastating condition that is especially prevalent in the developing world and in patients with defects in corneal integrity. The ocular surface is frequently exposed to potentially pathogenic fungi. Under normal circumstances, the protection of the cornea from fungal infection is achieved through the coordinated activity of normal tear film physiology and intact anatomical barriers, which prevent effective binding and invasion, by fungi. When these lines of defense are breached, fungal pathogens are able to attach to the cornea, release toxic metabolites, and invade through tissue [1]. At this stage, cellular identification of fungal products followed by immune signaling and recruitment of inflammatory cells to the cornea plays a critical role in the host response. The ultimate outcome depends upon the clearance of infection prior to irreversible ocular tissue damage due to fungal-mediated and/or immune-mediated injury.

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Epidemiology and Microbiology

Fungal keratitis is an important cause of corneal infection and ulceration. Infection can occur with a wide variety of fungal pathogens, but the most commonly infecting organisms are species of *Fusarium*, *Aspergillus*, and *Candida*. Risk factors include the use of contact lenses, corneal surgery, steroid use, trauma, and history of herpetic eye disease [2]. The relative distribution of infecting fungi differs by geographical locale and environmental conditions [3•, 4]. A common cause of fungal keratitis is the inoculation of an environmental organism into the cornea in the context of traumatic injury to the eye. This is most likely to occur in tropical and agricultural regions. The most common filamentous fungal causes are *Fusarium* and *Aspergillus* species (e.g., *Aspergillus flavus* and *Aspergillus fumigatus*). Infections caused by dark molds (e.g., species of *Curvularia*, *Exerohilum*, and *Bipolaris*) and *Scedosporium* are less common but may also arise from the inoculation of environmental fungi into the cornea [5].

In temperate climates, the most common infecting pathogens are *Candida* species (especially *Candida albicans*). These organisms typically originate from the patients' own skin

and establish a foothold for infection in patients with impaired barriers for infection. As such, Candida keratitis often occurs as a complication of an invasive ocular procedure and in patients with underlying eye surface conditions [3•, 6]. Another mechanism for fungal keratitis is exposure to contaminated ophthalmic products. The epidemiology and microbiology for these infections depend on the specifics of the contaminated product. A dramatic example of this type of event is an outbreak of Fusarium keratitis in 2005–2006 that was linked to the use of a contact lens solution (ReNu with MoistureLoc) [7].

Clinical Considerations

The pathway to fungal infection requires exposure to potentially pathogenic fungi as described above, followed by their adherence to the corneal surface, and ultimately tissue invasion. In turn, the host response involves the identification of the fungal invader by immune and corneal epithelial cells followed by the recruitment and infiltration of inflammatory cells to the site of infection. The ultimate outcome then depends upon whether the infection can be cleared before irreparable tissue destruction has occurred due to the actions of the fungi and immune response. Once infection has developed, antifungal therapy is mandatory but may be insufficient. In a recent study from Denmark, visual outcomes after mycotic keratitis were generally poor, and 52 % of infected patients ultimately required corneal transplantation [3•].

Diagnosis may be difficult, and delays in the initiation of antifungal therapy are common. This is further complicated by differences in clinical presentation between various fungal pathogens. This is most striking for infections due to *Candida* in comparison to filamentous fungi. As described, Candida keratitis typically occurs in patients with pre-existing ocular conditions (e.g., corneal surface disorder, keratoplasty), and the clinical appearance is characterized by the ulceration of the corneal epithelium, necrosis, and inflammation of the stroma and suppuration [8]. It is often mistaken for bacterial keratitis [9]. Infection due to filamentous fungi is usually acquired from environmental sources following inoculation during trauma (which may be minor) or in association with contact lens use. The infection may present as an area of ulceration with firm elevated slough and serrated margins. There may be granular or feathery gray-white satellite stromal infiltrates, an immune ring (which may be caused by immune complexes), folds in Descemet's membrane, endothelial plaque, and mild iritis [10]. As the infection progresses, a hypopyon with cheesy and sometimes hemorrhagic appearance may develop and wax and wane [11]. However, these characteristics are not universal, and the clinical presentation of filamentous fungus keratitis can appear indistinguishable from infection due to other causes.

Corneal Anatomy and Tear Physiology as Host Defense Mechanisms

The first line of defense against fungal keratitis consists of an intact corneal surface with well-functioning tear mechanisms. Overall, the cornea is approximately 1.2 cm in horizontal diameter and 1.1 cm in vertical diameter. Superficially, it is composed of an epithelial layer made up of superficial, wing, and basal cells and the basement membrane [12]. Deep to the epithelial layer is the corneal stroma, which comprises about 85 % of the corneal thickness and provides structural integrity. Finally, underlying the stroma is the endothelial cell layer. The outermost superficial cell layer of the cornea contains multiple microvilli and ridges, which are covered by a layer of glycocalyx that is closely abutted by the tear film. Together with multiple tight junctions, these substances form a mechanical barrier to prevent microbial entry into the cornea. Conditions that alter this barrier such as traumatic ocular injury, corneal surgery, and underlying corneal surface abnormalities are all associated with enhanced risk for fungal keratitis [2, 3•].

The tear film plays a critically important and versatile protective role against fungal keratitis. Conversely, conditions associated with dry eyes or abnormal tear production may predispose to corneal damage and infection. Tears contain hundreds of distinct substances secreted by the lacrimal glands, the conjunctiva, and the cornea itself. Proper production and balance of these substances facilitates host defense at the ocular surface by three main modes of action: 1. Mechanical, i.e., blinking and reflexive tearing in response to a foreign object on the ocular surface. The combination of aqueous and lipid components facilitates the efficient removal of ocular debris thereby washing out potentially pathogenic fungi; 2. maintenance of ocular surface homeostasis and corneal integrity; by providing the necessary lubrication, oxygen, and nutrient support to the corneal surface, the tear film helps to prevent anatomical breaks that could be exploited by microbial invaders; and 3. direct and indirect antifungal activities of substances present within the tear film.

The volume and composition of the various tear components can change depending on the situation. For example, reflex tears are induced by neurological stimulation (as would occur with a foreign object) and play an important protective role by diluting, neutralizing, and washing out potential pathogenic fungal substances [13]. Reflex tears have high levels of lysozyme, lactoferrin, and lipocalin, all of which possess antifungal activity [13, 14]. Tears produced when the eyes are closed and to a lesser extent those produced when eyes are open have lower levels of these substances but display higher concentrations of secretory IgA and activated complement components, which also have antifungal properties [15].

Lysozyme, lactoferrin, and lipocalin exert their antimicrobial (and antifungal) activity via distinct mechanisms. Lysozyme cleaves chitin, an important component of fungal cell

walls. Lactoferrin acts as a detergent thereby breaking up the fungal cell membrane. Both lactoferrin and lipocalin can impair the acquisition of nutrients (e.g., iron) by potentially invasive fungi [16•, 17]. Lactoferrin scavenges divalent cations before the fungus can use them and lipocalin binds to fungal siderophores, thereby interfering with fungal iron acquisition [18].

Additional substances with potential antifungal activity that are found at the ocular surface include cystatin, secretory leukocyte protease inhibitor, surfactant proteins D, and the defensins [16•, 19•]. The important protective roles of beta-defensins 3 and 4 and cathelicidin cathelin-related antimicrobial peptide (CRAMP) was demonstrated in a murine model of *Fusarium solani* keratitis. The expression of beta-defensins and CRAMP was significantly increased during active disease and declined to baseline with the resolution of infection. Conversely, mice deficient in these antimicrobial peptides had delayed the elimination of pathogens [20•].

Sensing and Response Mechanisms at the Ocular Surface

The cornea contains multiple cell types that are able to sense and respond to fungal stimuli. These include macrophages and dendritic cells that are embedded within the epithelial and stromal layers of the cornea as well as corneal epithelial cell themselves [21]. Cell surface receptors, including toll-like receptors (TLRs), interleukin 1 receptor 1 (IL-1R1), and Dectin-1, have important roles in recognizing microbial pathogens and breakdown products at the corneal epithelium. The activation of TLRs and IL-1R1 leads to a series of intracellular events mediated by the adaptor protein MyD88 resulting in the translocation of NF-κB to the nucleus. This in turn leads to the release of inflammatory cytokines and chemokines and the recruitment of neutrophils to the corneal stroma [22]. In vitro, TLR2 and TLR4 in corneal epithelial have been shown to be involved in the response to *Fusarium* and *Aspergillus* [23, 24]. In mice with Fusarium and Aspergillus keratitis, TLR4, IL-1R1, and Dectin-1 have all been shown to be important in controlling fungal growth [25] [26]. The expression of TLR2, TLR4, Dectin-1, and the cytokines interleukin 1β (IL-1β), IL-8, IL-17, and tumor necrosis factor α have been found to be elevated in corneas from patients with Aspergillus and Fusarium keratitis [27•]. In a Chinese Han population, the presence of a specific TLR4 allele (rs10983755) was found to be associated with an increased risk of fungal keratitis (OR= 1.786, 95 % CI=1.207–2.642) [28].

The role of TLR2 in fungal keratitis host defenses is not completely clear. TLR2 appears to be protective in keratitis due to *Candida*, but not due to filamentous fungi [25, 29]. Some studies have shown it to contribute to tissue injury and further fungal invasion due to the exaggerated expression of inflammatory components. The inhibition of TLR2 expression in the corneas of rats with Aspergillus keratitis using silencing RNA was associated with the improved outcome of keratitis, which was characterized by decreased corneal opacity, less corneal perforation, suppressed neutrophil infiltration, reduced production of inflammatory cytokines and chemokines, and less fungal burden [30]. The role of TLR5 has been evaluated in experiments using flagellin, a TLR5 agonist. The use of flagellin as an immunostimulant in a *C. albicans* mouse fungal keratitis model resulted in the upregulation of corneal CXCL10 with the recruitment of CXCR3-expressing NK cells and the eradication of *C. albicans* within the corneas [31].

Corneal epithelial cells play an important role in detecting and responding to fungal invasion. The intracellular receptor NOD1 is upregulated and presumably activated by exposure to *Aspergillus* with the subsequent expression of the signaling molecules RIP2 and NF-κB p65 and ultimately the secretion of IL-6, IL-8, and TNF-α, and production of the antimicrobial peptides hBD2 and LL37 [32]. The cell surface receptor TREM-1 is also found in corneal epithelial cells and is upregulated by *Aspergillus*. This receptor may coordinate with TLR4 in the corneal response to fungal infection [33].

The evasion of host sensing and response mechanisms has been demonstrated as a fungal virulence factor in *Aspergillus* and *Fusarium* species infecting the cornea. Airborne conidia of these fungi express a surface protein (RodA hydrophobin), which covers beta-1, 3-glucan, and alpha-mannose on their cell walls, thereby impairing antifungal sensing by cell surface receptors and effective host responses. Treatment to remove this surface protein and the use of strains that lack a functional RodA protein restores effective antifungal responses within the cornea [34•].

The Role of Neutrophils and Th17 Cells

Once an infection is sensed, neutrophils are the predominant nonresident corneal cell types recruited to respond to fungal keratitis. Clinically, this may be observed in the hypopyon frequently encountered in fungal keratitis and the suppuration of the corneal structures, which is especially pronounced in Candida keratitis. The importance of neutrophils is underscored in cases where ocular corticosteroids are used. These agents, known for impairing neutrophil chemotaxis and function, are strongly associated with increased risk for fungal keratitis [35, 36].

Neutrophils participate in direct and indirect fungal killing and in the release of cytokines that direct further host responses to the infection [37–39]. The control of infection can be achieved via the neutrophil ingestion of fungi and by the release of antifungal metabolites [40, 41•]. These metabolites include NADPH, which leads to the oxidative killing of fungi and lipocalin-1, which sequesters fungal siderophores

[39, 41•]. Fungi, in turn, attempt to protect themselves by changing their structures (e.g., formation of double or triple cell walls or a hypha-in-hypha structure) to avoid ingestion or by the production of superoxide dismutases and thioredoxin to prevent oxidative killing [40, 41•].

CD4+ T lymphocytes play an important role in the host response to fungal keratitis. Following the activation of the host response, Th1 and Th17 are recruited to the cornea [27•, 42•]. Their importance has been demonstrated in mouse models of fungal keratitis due to *Aspergillus*, *Fusarium*, and *C. albicans*. In filamentous fungal models, protective immunity was associated with the temporal recruitment of IL-17-producing neutrophils and Th17 and Th1 cells to the cornea [42•]. In a *C. albicans* model, Th1-type adaptive immune response, immunologic memory, and enhanced resistance to infection were induced by previous exposure to *Candida* [43].

The role of IL-17-producing cells is increasingly recognized as an important aspect of ocular host defenses. It is speculated that collaboration between T cell, fibroblasts, epithelial cells, and neutrophils is mediated by IL-17 production in response to fungal elements at the cornea. The process involves the release of pro-inflammatory and chemotactic cytokines that activate effector cells (e.g., neutrophils) to participate in fungal killing [42•].

An over-exuberant inflammatory response, which is at least partially mediated by neutrophil activity, may also play a pathogenic role in fungal keratitis. The presence of neutrophils in fungal keratitis has been linked to elevated metalloproteinase levels, which in turn are associated with may mediate further tissue injury [44]. Likewise, IL-17-induced pro-inflammatory activity can act as a double-edged sword. In a mouse model of *C. albicans* keratitis, the inhibition of IL-17 production actually prevented the development of keratitis. It is possible that the production of that cytokine impairs corneal integrity and facilitates further fungal invasion and tissue damage [37].

Conclusion

In conclusion, antifungal host defenses at the ocular surface include a variety of overlapping mechanism for protection. Foremost, among these are mechanical factors in the form of tear flow and intact anatomical barriers and biologically active molecules within the tear layer and cornea. When these defense mechanisms are unable to repel pathogenic fungi, the identification of fungi via cellular receptors and cell signaling pathways are activated. This is then followed by the recruitment of inflammatory cells (predominantly neutrophils and CD4+ T lymphocytes) to the site of infection and the activation of effector mechanisms for fungal killing. The outcome of infection then depends upon whether host defenses in combination with effective antifungal therapy are able to clear infection prior to irreparable damage occurring due to the actions of the infection and the immune response.

Compliance with Ethics Guidelines

Conflict of Interest S Shoham has received research grants from Astellas, Merck, and Pfizer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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