

IMMUNOLOGY OF ALLERGIC EYE DISEASE

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ABSTRACT

Ocular allergy results from the exposure of the conjunctiva to an allergen and includes a spectrum of clinical disorders that involve different levels of immune activity at the conjunctival and/or corneal interface. Each of these clinical entities is caused by an IgE-mediated sensitisation to the antigen and the activation of mast cells and eosinophils. In the more chronic entities, there is also an interaction of the allergen with T-cells and a T-helper 2 pattern of cytokine release.

The spectrum of ocular allergy is variable and notably seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most basic and least severe of the allergic inflammatory disorders. In SAC and PAC, a type I hypersensitivity reaction appears to be responsible for the signs and symptoms. In SAC, there are minimal pathological changes and only the early signs of cellular activation at the molecular level occur. In PAC, the inflammatory markers become more pronounced with the increased duration of allergenic stimulation.

In the more chronic forms of allergic conjunctivitis, namely vernal keratoconjunctivitis (VKC) in childhood and atopic keratoconjunctivitis (AKC) in adulthood, there is a mixed type I and type IV hypersensitivity reaction. There is a persistent state of mast cell, eosinophil and lymphocyte activation and this may result in the serious corneal complications that can occur with these diseases. Giant papillary conjunctivitis (GPC) that manifests in contact lens wearers also tends to be chronic with a mixed hypersensitivity reaction but has no significant corneal involvement.

As our understanding of the underlying immunological mechanisms in allergic eye disease continues to grow, future avenues for pharmacological targeting of different categories of allergic eye disease will become available. Appropriate treatment may be based on the specific immunopathology, and directed at the activated cell types primarily responsible for the disease process.

INTRODUCTION

Approximately 15-20% of the world population is affected by some form of allergic disease.¹ Numerous recent reports indicate that the incidence and prevalence of allergic conditions have increased dramatically during the past 40 years and continue to rise.²⁻⁴

The ocular allergic response results from the exposure of the conjunctiva to an allergen. It is estimated that ocular/conjunctival symptomatology is present in 40-

60% of allergic individuals,⁵ and occasionally the ocular component may be the most prominent and disabling feature of their allergy. In a large study of 5 000 allergic children, 32% had ocular disease as the **single** manifestation of their allergies.⁶

Allergic conjunctivitis is encountered on a daily basis in general practice and its diagnosis and management are the responsibility not only of ophthalmologists, but also general practitioners, paediatricians, allergists and pharmacists. Conjunctivitis can vary from being seasonal, where some individuals are affected for only a few weeks to months, to perennial with symptoms that last throughout the year.

The tremendous progress made in understanding allergic mechanisms and inflammation has brought new insights into the pathophysiology of allergic eye diseases. This review aims to provide an overview of the immunology and histopathology of allergic eye diseases with reference to the recent advances in our understanding of the pathogenesis of allergic eye diseases.

The eye presents unique immunological features since it is relatively isolated from the systemic immune system, and has an efficient **local protection system** in the structures of the external eye. The eye is constantly exposed to foreign substances, and the ocular tissues have a complete array of immune cells to interact with these offending antigens. This represents an ideal site for hypersensitivity reactions because of the large number of mast cells in the conjunctiva and the potential for local synthesis of IgE.⁷

Allergic diseases of the eye are the most common conditions affecting the external ocular adnexa.⁸ Ocular allergy is not confined to the conjunctiva but affects the entire ocular surface including conjunctiva, lids, cornea, lacrimal gland and tear film.

Ocular allergic conditions represent a spectrum of diseases that affect the ocular surface, from the acute, self-limited, mild form of seasonal allergic conjunctivitis to the chronic, severe, sight-threatening atopic keratoconjunctivitis. Two acute disorders, seasonal allergic conjunctivitis and perennial allergic conjunctivitis, and three chronic diseases, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis, are described.⁹ This spectrum, with their similarities and differences, can be better appreciated through immunopathologic evaluation.

ACUTE ALLERGIC DISORDERS

Seasonal and perennial allergic conjunctivitis

Seasonal allergic conjunctivitis (SAC) is without doubt the most common form of ocular allergy and is associated with sensitisation and exposure of the ocular surface to allergens in the environment, particularly pollen.¹⁰ It is also invariably associated with hay fever. The perennial form (perennial allergic conjunctivitis (PAC)) appears to be an extension of SAC based on the similarity of clinical symptoms and the immune mechanism involved.¹¹ PAC usually involves sensitisation to mites or to multiple antigens.

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SAC and PAC are examples of a type I hypersensitivity allergic response. The offending environmental allergens dissolve in the tear film and traverse the conjunctival epithelium. The allergen or allergens react with specific IgE antibodies bound to the surface of conjunctival mast cells. This activation of mast cells and the release of mediators, particularly histamine, are central to the pathogenesis.⁵

It has been demonstrated that there are two separate allergic responses in SAC and PAC, namely an early-phase response and a late-phase response.¹¹

Early-phase response

In the early-phase reaction, an allergen binds to allergen-specific IgE on the mast cell. The mast cell Fc receptors are cross-linked by the allergens, sending signals via the cell membrane into the cytoplasm, activating the mast cells and resulting in the release of allergic mediators.¹¹ This early-phase reaction is immediate.

There are two components of the allergic mediator release from the mast cells.

The first is the degranulation of mast cells due to an influx of calcium and a change in membrane permeability of the cell. This results in the release of **pre-formed** mediators including histamine, proteoglycans (heparin) and proteases (tryptase). Eosinophil chemotactic factor is also released.

The released histamine binds to the H₁ and H₂ receptors on the cell surfaces of the conjunctival tissue. Binding to the H₁ receptors results in vasodilation and increased vascular permeability and this is responsible for the primary allergic symptoms of ocular itching, burning and tearing. Binding to the H₂ receptors results in increased mucus production at the ocular surface.¹²

The second component of mast cell activation is the release of **newly synthesised** mediators formed via the arachidonic acid cascade.

This *de novo* synthesis of inflammatory mediators occurs when calcium influx into the cell activates phospholipase A₂. This liberates arachidonic acid from membrane-bound phospholipids. This in turn leads to the formation of eicosanoids such as prostaglandins via the cyclo-oxygenase pathway and leukotrienes via the lipo-oxygenase pathway (Fig. 1).

PGD₂ is the major prostaglandin produced by the mast cell and is considered to be 10 times more potent than histamine.¹³ It increases conjunctival microvascular permeability, together with the other newly synthesised mediators. These are responsible for the redness, pruritus, chemosis and mucus production associated with allergic eye disease.

Late-phase reaction

More severe allergic reactions may demonstrate a late-phase reaction. These may be either sustained early-phase reactions or more discrete second peaks of response. The second-peak late-phase conjunctival reaction occurs from 2 to 9 hours after antigen exposure.¹⁴ This occurs at a cellular level and does not correlate with a separate clinical late-phase response of allergic conjunctivitis.

Usually about 4-6 hours after allergen exposure, an influx occurs into conjunctival tissue of non-specific cells of the inflammatory response, including neutrophils, basophils, eosinophils and T-lymphocytes.¹⁵ The eosinophils and T-helper type 2 (TH₂) lymphocytes and cytokines are primarily responsible for the late-phase reaction.

The infiltration of eosinophils is paramount to the allergic response. Chemotactic factors released during mast-cell degranulation aid in eosinophil attraction and activation. The eosinophils release toxic proteins such as eosinophil major basic protein (MBP) and eosinophil cationic protein (ECP). These proteins have profound cytotoxic effects and stimulate further degranulation of the mast cells, initiating a cascade of allergic events.¹⁷

The TH₂ lymphocytes commonly release cytokines, i.e. interleukin 4 (IL-4), IL-5, IL-6 and IL-13, during the late-phase allergic inflammatory response. A recent study now indicates that mast cells may also be a source of TH₂-type cytokines.¹⁸ This study also shows that the phenotype of the conjunctival mast cell may further delineate which cytokines are released. For example, tryptase-positive mast cells secrete IL-5 and IL-6 whereas tryptase and chymase-positive mast cells preferentially secrete IL-4 and IL-13.¹⁸ The tryptase and chymase-positive mast cells tend to be the more prevalent phenotype in conjunctival tissue.

The function of mast cells in SAC and PAC is clearly an important one, and ongoing research continues to demonstrate their multi-functional role. The other factors that appear to play a crucial role in the inflammatory process in SAC and PAC include the above-mentioned TH₂-type cytokines, an increase in the ratio of TH₁/TH₂ cytokines,¹⁹ and an increased statement of adhesion molecules.²⁰

However, not all exposed persons are affected by the various allergens, and it is believed that genetic and local factors may also play a role. Local factors such as increased mucosal permeability or local defence mechanisms, e.g. opsonisation and phagocytosis, may allow for increased penetration of allergens.

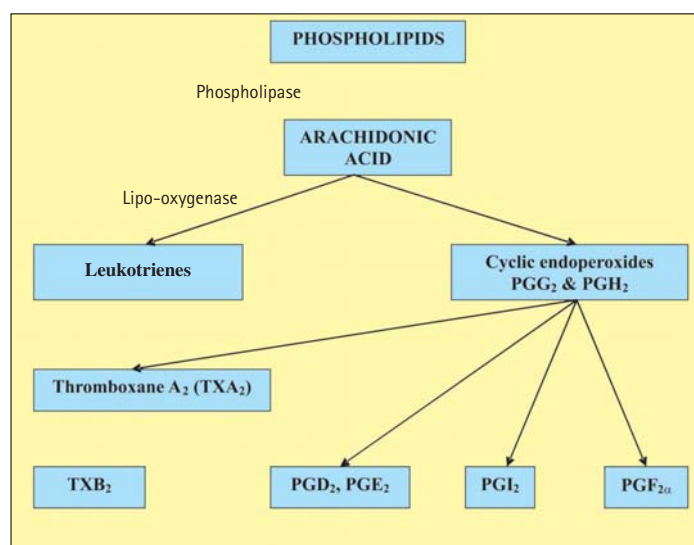


Fig. 1. Arachidonic acid pathway.

CHRONIC ALLERGIC DISORDERS

Vernal keratoconjunctivitis and atopic keratoconjunctivitis

These are complex diseases that partially carry a similar pathophysiological profile to SAC and PAC, yet important differences exist. In addition to a type I hypersensitivity reaction characterised by the early- and late-phase allergic responses, a type IV hypersensitivity reaction plays a pivotal role. The inflammation in the conjunctiva is chronic and tends to be more severe, and in the presence of corneal involvement may be sight-threatening.

Vernal keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a severe ocular allergic disease that occurs predominantly in children.²¹ VKC is characterised by intense ocular symptomatology including persistent itching, chronic conjunctival hyperaemia, and a recurrent mucoid discharge. These symptoms are typically accompanied by giant papillae on the upper tarsal conjunctiva and/or limbal infiltrates or nodules. Corneal involvement is common and is characterised by punctate keratitis or sterile corneal ulcers.

The clinical and histopathological changes associated with VKC have been demonstrated to be both an IgE- (type I hypersensitivity) and TH2-mediated disease (type IV hypersensitivity).⁷

Biopsy of a tarsal conjunctival papilla in VKC reveals very distinct histopathological findings. The conjunctival epithelium is thickened and contains a combination of various cellular types that include mast cells, eosinophils, basophils and abundant activated lymphocytes, none of which is seen in normal individuals.²² These findings support the concept that VKC is a mixed type I and IV reaction.

In the type IV hypersensitivity reaction of VKC, the role of the activated T-lymphocytes and their release of cytokines have been extensively explored.²³ It has been demonstrated that cytokines such as IL-8 serve as a chemo-attractant and activator of polymorphonuclear cells and play a crucial role in inflammatory cell migration.²⁴ It has also been shown that the association of VKC with co-stimulatory molecules on antigen-presenting cells, such as Langerhan's cells, represents an important mechanism for TH2 cell activation and further cytokine release.²⁵

The presence of cytokines and their receptors represent a common feature of allergic disease. These, in conjunction with increased numbers of eosinophils, macrophages and fibroblasts (when compared with SAC and PAC), may contribute to the serious corneal complications sometimes seen in VKC.

The toxic enzymes of degranulated eosinophils such as ECP and MBP have been found in the tears, conjunctival epithelium, and the periphery of corneal ulcers in VKC patients, suggesting their aetiopathogenic role in many of the associated problems.²⁶ MBP has been shown to possess epitheliotoxic capabilities and prevents epithelial healing,²⁷ and ECP levels (in tears) have been found to be directly correlated with patients' symptoms in VKC. In fact tear ECP level has been used in clinical trials as a marker for eosinophil activation and to evaluate the efficacy of drug therapy in VKC.²⁸

The measurement of tear tryptase levels may also serve as a clinical marker of allergic disease as it is increased in VKC (and in SAC).²⁹

Atopic keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is similar to VKC but usually occurs in adult patients with a history of atopic dermatitis. AKC can be a very severe disease because of its protracted clinical course and the frequent exacerbations that occur, especially during the winter months. The cornea is frequently involved, with diffuse superficial epitheliopathy or corneal ulcers, ultimately resulting in scarring and reduced visual acuity.³⁰

AKC is thought to result from a complex immunological mechanism that, similar to VKC, involves both type I and type IV hypersensitivity reactions.¹¹ The TH2 cells play a crucial role in the inflammatory response in AKC as evidenced by the elevated systemic levels of the cytokines IL-4 and IL-5.³¹ These cytokines are usually present in higher concentrations in the more severe forms of ocular disease, and hence tear levels of IL-5 may be used as a marker to signify the more aggressive and proliferative forms of ocular allergy. Langerhans' cells bearing IgE on their surfaces have also been shown to be involved in the ocular inflammatory response in AKC.³³

The histopathological findings of AKC are diagnostically specific and include a mixture of mast cell, eosinophil and lymphocyte infiltration into the conjunctival epithelium. Large numbers of mononuclear cells have also been found. They also demonstrate goblet cell proliferation, epithelial pseudobulbar formation, occasional frank granuloma formation and perivasculitis.³⁴ This supports the theory that the **local ocular** environment is important in the development of the more chronic forms of ocular allergy such as AKC.

Impairment of the ocular surface epithelium over the conjunctiva and cornea in AKC patients appears to be caused by a variety of factors. These include the direct effects of eosinophil-based mediators, decreased secretory IgA, pseudotubule formation, and the exotoxin effects of *Staphylococcus aureus* colonisation of eyelids,³⁴ considered to be due to deficient immunoregulation in AKC patients. This renders them more susceptible to developing herpes simplex virus and staphylococcal infections.

Giant papillary conjunctivitis

Giant papillary conjunctivitis (GPC) is an allergic, non-IgE-mediated inflammation, usually of the upper tarsal conjunctiva. It is most frequently induced by the use of contact lenses, but may also be triggered by the use of ocular prostheses, the presence of corneo-conjunctival sutures or a protruding scleral buckling. Corneal involvement is seldom seen and therefore GPC does not manifest the serious symptoms of VKC and AKC.

Several factors may be involved in the pathogenesis of GPC. These include mechanical irritation of the conjunctiva by the contact lens. The chronic microtrauma by the lens and lens deposits may disrupt tight junctions between the conjunctival epithelial cells, allowing allergens to penetrate. GPC could also be a manifestation of an immune reaction against a protein or residue deposited on the lens.

The allergic mechanism in GPC is a combination of a type IV delayed hypersensitivity reaction and possibly a type I humoral component. The low-grade chronic contact-lens-induced injury to the conjunctival epithelial cells stimulates the production of neutrophil chemotactic factors. These have been found to be increased in the tear fluid from patients with GPC³⁵ and are thought to play a role in the inflammatory response that occurs.

Eosinophil MBP is also found in increasing amounts in the conjunctiva (but not in tears) of patients with GPC and most likely has a contributory role.³⁶ Eosinophil MBP is responsible for mast-cell degranulation and possesses cytotoxic effects that may enhance the conjunctival inflammatory reaction.

The T-helper cells, integral to the type IV hypersensitivity reaction, are also thought to play a role. However, this is not well elucidated and overall GPC is characterised by a lack of significant cytokine changes in tears when compared with VKC and AKC.

Histopathologically, GPC is associated with an abnormal distribution of cells, with an increased number of mast cells and basophils present in the conjunctival epithelium and substantia propria. An associated infiltration of eosinophils, plasma cells, and lymphocytes is also present, suggesting a mixed mast-cell and lymphocyte-mediated process. The giant papillae of GPC are thought to occur as a result of the inflammatory mediators. These tend to accumulate as a result of delayed tear clearance in patients with GPC.³⁷

CONCLUSION

Ocular allergic disease presents with a spectrum of clinical manifestations and recent advances in the immunology of allergic diseases have contributed significantly to our understanding of the eye manifestations. Considerable useful information has been obtained about the role of the various cell types in the pathogenesis of allergic eye disease and it is evident that besides an IgE-mediated reaction, a complex chronic inflammatory response is also involved. Our knowledge of the key role of the TH2 cytokines and the other immunological mechanisms that underly allergic eye disease continues to grow.

An understanding of the underlying immunopathology provides future avenues for pharmacological targeting of the unique features of allergic eye disease. Appropriate therapies can be directed at the specific inflammatory cell constituents primarily responsible for the disease process.³⁸

Declaration of conflict of interest

The author has no conflict of interest.

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