Immunological Basis of Symptomatology in Ocular Diseases

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Abstract

Hypersensitivity reactions are our own immune responses to various triggering factors. These immune responses result in different clinical presentations of various ocular diseases. Various cytokines, interleukins are responsible for a myriad of symptoms and thus our therapy should be targeted on specific immunological pathways. In this article we have summarized various ocular diseases with the causative immune pathways thus simplifying the underlying cause. This article will help in understanding why similar looking diseases may have requirement for different modalities of treatment or why similar medications may work in different ocular diseases.

Keywords: ocular immunology, hypersensitivity reactions, ocular mast cells, immune reactions

Introduction

Human beings live in an environment with substances capable of producing immunologic responses. These responses are protective many times but can also be damaging to tissues. Various reactions produced from the exposure to exogenous or endogenous antigens are termed as Hypersensitivity Reactions. The mast cells play a major role as these cells are the source of various mediators of immune reactions. Therefore, ocular diseases can be classified accordingly and their presentations can be different because of the underlying immunologic reactions (Table 1).

Table 1: Classification of Hypersensitivity Reactions

| Types | Prototypes |
|-------|------------|
| Type I Reactions | Allergic conjunctivitis |
| | Vernal keratoconjunctivitis (VKC) |
| | Atopic keratoconjunctivitis (AKC) |
| | Acute urticaria |
| Type II Reactions | Anaphylactic reactions |
| | Idiopathic anaphylaxis (IAP) |
| | Ocular pemphigus vulgaris |
| Type III Reactions | Anaphylactoid endophthalmitis (AE) |
| Type IV Reactions | Phymatous keratoconjunctivitis |
| | Sympathetic ophthalmia |

Ocular Mast Cells

The mast cells play a major role in pathogenesis of immune reactions. The ocular mast cells are present mainly in substantia propria of the conjunctiva, although they are also found in in lesser numbers in the choroid stroma and meninges of the optic nerve (perivascular location). Mediators released by mast cells can be classified into two groups:17,18

1. Preformed / Primary mediators: these are
   - Histamine,
   - Proteoglycans,
   - Neutral Proteases (trypsin, chymase, cathepsin G, human mast cell carboxypeptidase) and
   - basic Fibroblast Growth Factor (bFGF).
2. Newly generated / Secondary mediators: these are
   - Prostaglandins (PG)D2

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Immune Reactions

A. Type I Reactions:

These are mediated mainly by Histamine secreted by mast cells. When the ocular surface is exposed to environmental exogenous allergen, the resident TH2 cells activate naïve B cells. This results in increased production of IgE B cells which secrete IgE. These in turn get cross-linked to the IgE receptors present on mast cell surface. It causes degranulation of mast cells. Histamine released acts via three receptors (Figure 1). Among other primary mediators, Neutral Proteases acts by cleaving the peptide bond and symptoms depend on the types.16 (Figure 2). Cytokines (LT-C4, IL-4,5 6,13) have their

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main role in VKC and AKC (Figure 3). These ongoing immunological reactions in conjunction also bring some other characteristic features in the clinical scenario e.g. papilla, Tranta’s spots (Figure 4).

Giant Papillary Conjunctivitis (GPC)
It’s a classical example of type 1 reaction. It is also termed as Contact lens associated papillary conjunctivitis because of its high incidence in contact lens wearers. These patients are predisposed to develop GPC and usually have a history of other atopic conditions. Contact lenses develop rapidly a complex coating of various substances e.g. cellular debris, lipids etc after insertion onto the eye. Even with the best of cleaning regimens, coating cannot be removed completely. This coating acts as an antigenic stimulus in GPC patients (Figure 5).

B. Type II Reactions:
These reactions are mediated by antibodies directed towards antigens present on the cell surface and extracellular matrix.

a) Complement and Fc- receptor mediated inflammation
In these reactions, antibodies get deposited in extracellular matrix such as basement membranes (BM) and matrix thereby causing inflammation induced tissue injury. A prototype of this reaction in ocular diseases is Pemphigoid. In Bullous pemphigoid, antibodies are against β-4 integrin and laminin of extracellular matrix (ECM) or basement membrane zone (BMZ) of conjunctival cell surface. This creates a difference in symptomatology of the two diseases.

b) Antibody mediated cellular dysfunction
In these types of reactions, antibodies are directed against cell surface receptors. This causes impairment or dysregulation of cellular function. A prototype of this type is Ocular pemphigus vulgaris in which there is formation of flaccid bullae.

c) Mooren’s ulcer
The pathogenesis of Mooren’s ulcer is not very clear. These patients have circulating antibodies which are thought to be directed against an unknown molecule in the stroma of the cornea. The peripheral cornea is a prone area because the limbal capillary arcade serves as a source of cells (Figure 8).

C. Type III Reactions (Arthus Reactions):
Arthus reaction is a localized area of tissue necrosis resulting from acute immune-complex vasculitis. As the antigen diffuses into the vascular wall, it binds with the preformed circulating antibody. Large immune-complexes are formed locally which precipitate in the vessel walls and trigger an inflammatory reaction.

Scleritis
In this disease, immune-complexes get deposited in the episcleral and scleral perforating capillaries and postcapillary venules. It leads to complement activation and platelet aggregation. In some cases, Type IV reaction subsequently ensues (Figure 9).

Phacoanaphylactic endophthalmitis
Phacoanaphylactic endophthalmitis is a non-granulomatous type of uveitis but along with type III reactions, type II and IV reactions also play a role in its pathogenesis. Other non-granulomatous uveitis e.g. atopic uveitis, seasonal uveitis come under type I reaction. These different types of uveitis have a final common pathway (Figure 10).
Despite having same immunological reactions, the symptoms and signs are more marked in uveitis. This is because of high vascularity and loose architecture of uveal tissue.

D. Type IV Reactions:
They are initiated by antigen activated (sensitized) T lymphocytes (TH1 cells). On subsequent exposure, antigen presenting cells (APCs) take the antigen to previously sensitized TH1 cells. This leads to activation of TH1 cells44 (Figure 11).

Phlyctenular Keratoconjunctivitis
It is usually due to delayed hypersensitivity to tuberci, exotoxins of Staphylococcus. In some cases Chlamydia, Candida, Cryptococcus may be the underlying cause. Clinical presentation depends on the involved location12-14 (Figure 12).

Sympathetic Ophthalmia
It is a rare granulomatous uveitis of insidious or acute onset.
It affects the fellow eye usually within 3 months of severe trauma to the other eye involving the uveal tissue. The characteristic features are mutton fat keratic precipitats (KPs), moderate to severe vitritis and multiple yellowish-white choroidal lesions. It represents an autoimmune inflammatory response against choroidal melanocytes mediated by T cells.\(^1\) (Figure 13).

**Summary**

This article summarizes various immunologic reactions by simplified flowcharts. These flowcharts illustrate the underlying cause of clinical spectrums of various ocular diseases. Different ocular diseases have a different underlying immune reaction and thus need a different treatment strategy. We can plan our treatment strategy under the underlying immune reaction and thus need a different ocular diseases. Different ocular diseases have a different characteristic features of clinical spectrums of various.

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