

## Introduction

Peripheral ulcerative keratitis (PUK) is a destructive inflammatory disease of the juxta-  
limbal corneal stroma that is associated with an  
epithelial defect, the presence of inflammatory  
cells in the stroma and progressive stromal  
melting [1]. It could be associated with various  
ocular and systemic infectious and noninfectious  
diseases [2]. The exact pathophysiologic mech-  
anism of PUK is not known. Although different  
etiologies are suspected, the overall mechanisms  
are thought to be identical in all forms of PUK.  
A number of systemic conditions are known to  
be associated with PUK. These include collagen  
vascular diseases such as rheumatoid arthritis,  
Wegener's granulomatosis, systemic lupus ery-  
thromatosus, relapsing polychondritis, pol-  
yarteritis nodosa, and infectious conditions such  
as syphilis and hepatitis C [1]. Some noninfec-  
tious local conditions such as Mooren's ulcer can  
also cause PUK.

The peripheral cornea is unique in both its  
morphological as well as immunological char-

acteristics that predisposes it to inflammatory  
reactions. The central cornea derives oxygen  
from ambient air, through the tear film and  
aqueous humor. In contrast, the peripheral cornea  
receives additional oxygen and nutrients from the  
perilimbal capillary arcades. The perilimbal  
vascular and lymphatic arcades primarily act as a  
reservoir for immunocompetent cells such as  
macrophages, lymphocytes, Langerhans, and  
plasma cells. The proximity of corneal tissue to  
these arcades readily exposes the peripheral  
cornea to inflammatory cells and mediators [1],  
which can result in peripheral ulcerative keratitis.

Morphologically, the corneal extracellular  
matrix comprises highly organized lamellae of  
collagen fibrils embedded in the framework of  
glycosaminoglycans. The predominant cells that  
lie in between these lamellae are flattened  
fibroblasts, although there are occasional pres-  
ence of polymorphonuclear leucocytes, macro-  
phages and lymphocytes as well. Corneal  
fibroblasts (keratocytes) play a crucial role in the  
maintenance and turnover of the corneal matrix.  
The principal mechanism involved in the rate of  
matrix turnover is the optimal balance between  
collagenases and their tissue inhibitors [2]. Col-  
lagenases are primarily produced by fibroblasts  
and invading mononuclear cells [3]. It is postu-  
lated that there is a local imbalance between  
levels of a specific collagenase (MMP-1) and its  
tissue inhibitor (TIMP-1) in PUK. This imbal-  
ance could be responsible for rapid keratolysis, a  
hallmark feature in this condition [4]. However,

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it remains uncertain whether these factors could possibly initiate PUK. Research tends to suggest that both humoral-mediated and cell-mediated autoimmune processes are involved.

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### **Predisposition to Immune Reaction**

The peripheral cornea has distinct morphologic and immunologic characteristics that predispose it to immune reaction. The limbal vasculature is known to accumulate IgM, immune complexes, C1 (first component of the complement cascade) as well as other high molecular weight molecules [5]. Immune complex deposition activates the classical pathway of the complement system. This process, in turn results in chemotaxis of inflammatory cells including neutrophils and macrophages to the peripheral cornea. These inflammatory cells release the enzymes collagenases and proteases that can potentially disrupt the cornea stroma [6–8]. Stromal destruction can further be accelerated by the release of cytokines such as interleukin-1 from these inflammatory cells that enables stromal keratocytes to produce matrix metalloproteinase-1 & 2 [9].

PUK may occur in patients with some autoimmune diseases, especially rheumatoid arthritis, which is often associated with severe necrotizing scleritis. These lesions have a vasculitic pathogenesis whereby immune complexes are situated in the peripheral cornea as well as in the limbal vessels. There is also chemotaxis of inflammatory cells, particularly neutrophils and histiocytes in addition to enzyme liberation from inflammatory cells. As a result there is collagen and proteoglycan destruction.

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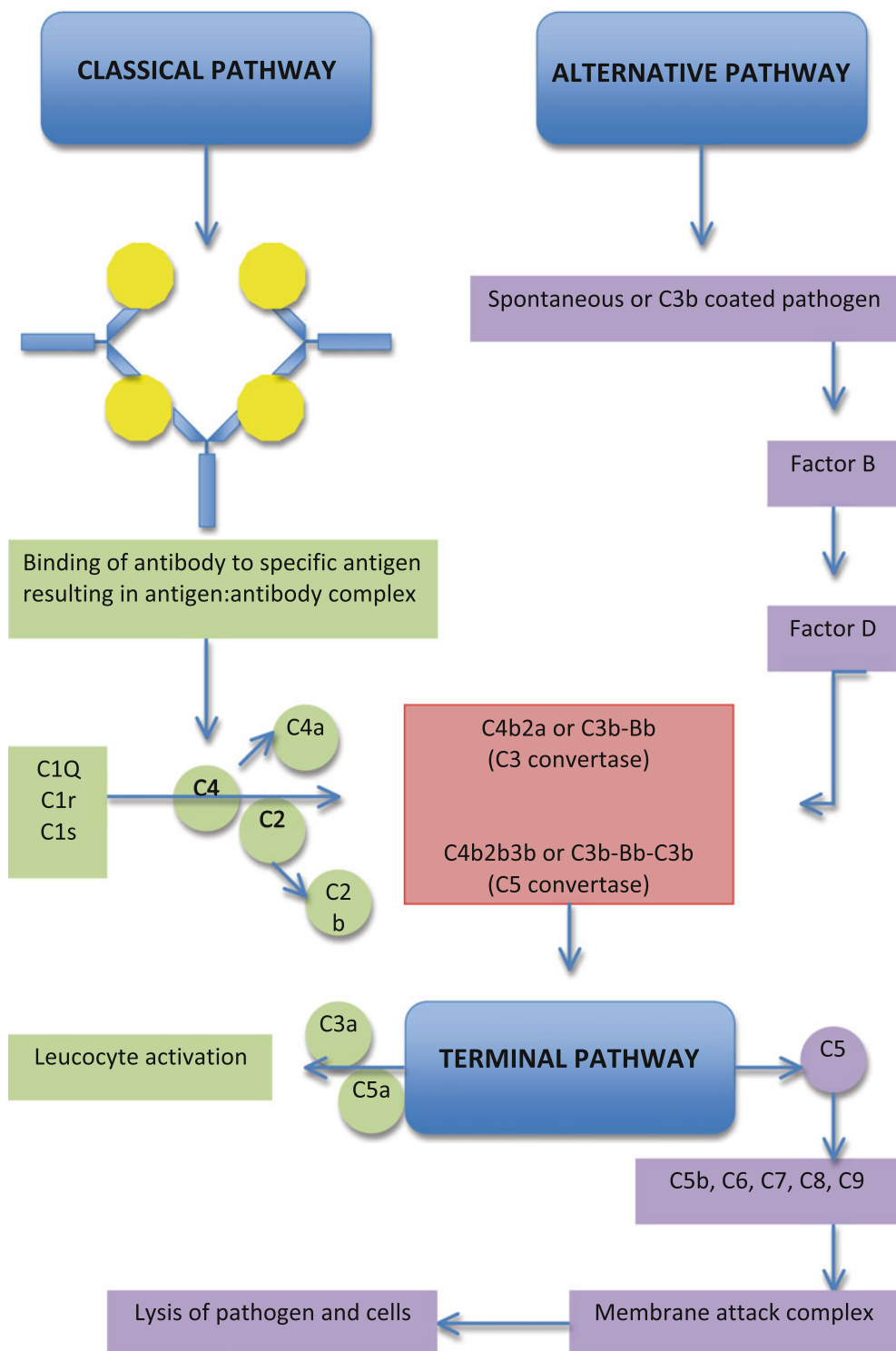
### **Pathogenesis**

Exposure to a foreign antigen activates an adaptive immune response that leads to the production of antigen-specific antibodies. The antigen-antibody combination creates immune complexes that neutralize the foreign antigen and allow it to be cleared safely by the reticuloendothelial system.

This complex system, however, has the potential to fail. If the antibody response is just adequate, these immune complexes may escape early detection and become deposited in the vascular endothelium. These immune complexes can then activate compliments leading to severe local inflammation. The immune complexes within the blood vessels result in vasculitic reactions. Vasculitis frequently leads to cellular destruction, resulting in damage to the vascular structures and compromising blood flow to the organ supplied. Immune complexes are not necessarily pathogenic. Their immunogenicity is determined by several factors including antigen load, antibody response, the efficiency of reticuloendothelial system in clearance of immune complexes, pre-existing damage of vascular endothelium and the solubility of the immune complexes themselves.

Immune complex solubility is determined by the antibody-antigen ratio. When they are present in equal proportion, large immune complexes are formed, which are identified easily and removed by reticuloendothelial system. When there is an excess of antibody, small immune complexes are formed, which remain in solution and do not elicit any immune response. When there is slight excess of antigen, however, the immune complexes precipitate from the solution and become trapped in the capillary beds or in the previously damaged vascular endothelium. Once immune complexes precipitate in the tissue, they fix the complement, leading to intense immune reaction. Complement fixation and local inflammation recruit neutrophils, which make an attempt to engulf the immune complexes. During this process, the neutrophils degranulate, releasing lysosomal enzymes and oxygen-free radicals that cause tissue necrosis [10].

Complement is a group of serum proteins, majority of which are produced by liver. Complement can be activated (fixed) by antigen-antibody complexes or other substances which may result in variety of biological effects including cytolysis, anaphylatoxin activity, chemotaxis, opsonization, and tissue damage. The consequences of complement activation can be broadly categorized in two groups:



**Fig. 2.1** Both classical and alternate pathways of the complement system are activated resulting in the production of “membrane attack complex” in the terminal

pathway. Membrane attack complexes create pores in the cell wall leading to cellular lysis

- (A) Facilitating antibody function (destruction and removal of foreign material): This is done by either lysis of the target cells or by immune clearance. Both classical and alternate pathways of complement fixation produce “membrane attack complex (MAC)” which in its final state creates pores in the cell wall leading to cellular lysis (Fig. 2.1). Immune clearance, on the other hand, is a critical function facilitated by the presence of receptors on the surface of leucocytes and erythrocytes. This is a special process by which the soluble immune complexes are removed from the serum.
- (B) Development of inflammation: Complement components that are activated in plasma and body fluids are engaged in the regulation of virtually all phases of an acute inflammatory reaction, including changes in the vascular flow and caliber, the increase in vascular permeability, extravasation of leucocytes and chemotaxis. Several regulatory functions of complement affect other inflammatory mediators, whereas other complement activities are associated with the direct action of complement proteins on target cells. Because of its variety of activating mechanisms, complement can independently participate in the regulation of inflammation, in either presence or absence of an infection.

Mooren’s ulcer, a relatively uncommon painful peripheral corneal ulceration without associated scleral involvement deserves a special mention in this regard. Although there are sufficient evidences to suggest the autoimmune nature of the disease, the precise pathophysiological mechanism remains unclear. High levels of proteolytic enzymes have been demonstrated in the affected conjunctiva [11]. Foster and colleagues had established the presence of numerous activated neutrophils in the affected cornea and eventually proposed that these neutrophils were the source of proteolytic enzymes [12]. Researchers also noted that systemically, helper T cells outnumbered suppressor T cells in patients with Mooren’s ulcer. It was proposed that

unregulated helper T cells could induce production of autoantibodies, resulting in deposition of immune complexes, complement activation followed by inflammatory cell infiltration and release of proteolytic enzymes [13, 14].

However, it is important to remember that inflammatory involvement of adjacent conjunctiva, episclera, and sclera is not a feature of all types of PUK. A simple hypersensitivity reaction to exogenous antigens may induce marginal keratitis and phlyctenular keratitis in the peripheral cornea that has an excellent prognosis when compared to immune diseases-related PUK.

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## Conclusions

Any inflammatory stimulus in the peripheral cornea, be it a microbial invasion, immune complex deposition as in systemic immune diseases, malignancy, or trauma, all result in neutrophil recruitment and activation of both classical and alternative pathways of complement in tissues and vessels. Activated components increase the vascular permeability and produces chemotactic factors for neutrophils such as C3a and C5a. These neutrophils infiltrate in peripheral cornea to release collagenolytic and proteolytic enzymes as well as many other pro-inflammatory substances. An inflamed limbal conjunctiva itself has the capability to generate collagenase enzymes. Therefore, the final result is disruption, dissolution, and tissue necrosis of corneal stroma followed by progressive thinning, a typical feature of PUK.

## Compliance With Ethical Requirements

### Conflict of Interest

Manotosh Ray and Hwei Wuen Chan declare that they no conflict of interest.

### Informed Consent

No human studies were carried out by the authors for this article.

### Animal Studies

No animal studies were carried out by the authors for this article.

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