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Immunology of Corneal Transplantation

M. G. FALCON

INTRODUCTION

There was considerable interest in corneal surgery, including grafting, in the early nineteenth century, but failure was universal because of a lack of understanding of immunology and corneal physiology. With improvements in asepsis and anaesthesia later in the same century, some progress was made, and the first successful human lamellar graft was performed in 1886 by von Hippel. The next 50 years saw further interest in the possibilities of corneal transplantation, and further (though rather crude) progress; but it was not until after the Second World War that most of the major advances were made, leading to a far greater chance of success. None of these advances has been more important than the development of immunology. Indeed, the cornea has been an excellent model for transplantation immunology in general. Following Maumenee’s recognition that clinical rejection can occur, and the experimental work of Khodadoust and Silverstein that evaluated this in detail, we realize today that corneal graft rejection is the commonest cause of graft failure, and (now that most other difficulties have been largely overcome) it is by far the most taxing problem that remains.

This chapter is designed to cover the relevant background of transplantation immunology with particular reference to the cornea, and it examines the pathogenesis and clinical forms of rejection. The clinical management and pharmacological treatment of rejection are considered, and some selected areas are discussed where further advances seem promising.

Corneal structure and function relevant to transplantation

The cornea is, of course, very specialized and unusual in its anatomy and physiology, and this has an important bearing on transplantation. There are three principal layers (Figure 4.1). The epithelium is composed of stratified squamous non-keratinized cells about five layers thick, which are produced by the active basal cells at the limbal (corneoscleral) region. Within the epithelium are Langerhans cells, which are particularly concentrated at the

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Figure 4.1 Schematic horizontal section of the eye. A, conjunctiva, with vessels; B, corneal epithelium; C, corneal stroma; D, corneal endothelium, and Descemet's membrane; E, sclera; F, drainage angle of anterior chamber; G, ciliary body; H, anterior chamber; I, lens

limbus, and they can also be found in vascular endothelium (corneal or other). The Langerhans cells are macrophage-derived antigen-presenting cells (APC), whose function is critical to transplantation immunology. Probably identical in function are the stromal interstitial dendritic cells, and the APC in the conjunctival epithelium associated with the localized lymphoid tissue in the conjunctival submucosa, known as CALT (conjunctiva-associated lymphoid tissue).

Beneath the epithelium there is a condensation of stroma termed Bowman's layer. The rest of the stroma, accounting for the most of the corneal thickness and strength, is composed of closely-packed and regularly-arranged lamellae of specialized collagen (which allows light transmission) embedded in a ground substance within which are keratocytes. The proteoglycans in the ground substance account for the considerable tendency of the stroma to swell osmotically. The stroma is devoid of lymphatics and blood vessels in health, but it can acquire them when diseased (corneal vascularization being a particularly common response to a variety of insults). Peripherally, the stroma joins the sclera at the limbus. It has a small component of interstitial dendritic cells. Other inflammatory cells such as polymorphs can move into and within the stroma (from the limbus or the aqueous humour), and this is greatly facilitated by certain pathological conditions.

On the internal limit of the stroma is Descemet's membrane, a tough, thin sheet of specialized collagen that is secreted by the endothelium throughout life. The endothelium (probably derived from neural crest) is a monolayer of epithelial cells that, in humans, normally have no capacity for mitosis. It has the critical function of pumping fluid out of the stroma into the anterior chamber, to maintain corneal transparency. If the endothelium fails, through (surgical) trauma, rejection or any other disease process, then corneal swelling will occur, and corneal transparency will be lost. Peripherally, the endothelium becomes involved, at the root of the iris, with the drainage mechanism that allows aqueous to leave the eye. This should normally balance aqueous production by the ciliary body and thus keep intraocular