Review

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Immune mechanisms in inflammatory and degenerative eye disease

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It has recently been recognized that pathology of age-associated degenerative eye diseases such as adult macular degeneration (AMD), glaucoma and diabetic retinopathy, have strong immunological underpinnings. Attempts have been made to extrapolate to age-related degenerative disease insights from inflammatory processes associated with non-infectious uveitis, but these have not yet been sufficiently informative. Here we review recent findings on the immune processes underlying uveitis and those that have been shown to contribute to AMD, discussing in this context parallels and differences between overt inflammation and para-inflammation in the eye. We propose that mechanisms associated with ocular immune privilege, in combination with paucity of age-related antigen(s) within the target tissue, dampen what could otherwise be overt inflammation and result in the para-inflammation that characterizes age-associated neurodegenerative disease.

Introduction

The eye is a prototypic immune privileged tissue that resists immunogenic inflammation through multiple mechanisms [1,2]. Inflammatory and immune-mediated diseases in the eye must therefore be viewed against the backdrop of ocular immune privilege. Nevertheless, the eye is subject to inflammatory and para-inflammatory processes. Noninfectious uveitis describes a group of potentially blinding inflammatory ocular conditions of obscure etiology; disease progression in uveitis is thought to be driven at least in part by autoimmune mechanisms. Current concepts in ocular inflammation and the mechanisms that drive it stem largely from studying uveitis in animal models. More recently, it has been recognized that processes that had once been believed to be purely degenerative, such as AMD, diabetic retinopathy, and glaucoma, also involve inflammatory and immune elements [3]. Moreover, studies in patients and in animal models have implicated autoimmune processes in degenerative diseases of the eye [4,5], suggesting some anti-inflammatory therapies that are effective for uveitis may be useful for the treatment of AMD.

However, the inflammation observed in uveitis is different from that associated with degenerative conditions in the eye. While uveitis has a major adaptive immune component, AMD and similar degenerative conditions primarily involve innate immune elements [6–8]. While uveitis is associated with overt inflammation, AMD is slow and insidious (para-inflammation), and acute inflammation is characteristically absent. Here, we critically examine the processes of inflammation and para-inflammation in the eye, comparing and contrasting the associated cellular and molecular mechanisms [9,10]. Synthesis of the available evidence suggests that (i) autoimmune processes are involved as drivers (if not etiologic triggers) of both the overt inflammatory disease known as uveitis, and the para-inflammatory disease typified by AMD; (ii) unlike retinal antigens, the target AMD antigens in the retina are scarce, which limits the adaptive immune response but not innate immune processes; and (iii) the inhibitory ocular microenvironment as part of ocular immune privilege is able to dampen innate immune responses, but is less effective in limiting the function of effector T cells. This in turn enables effector T cells that encounter abundant target antigen in the eye to break down ocular immune privilege and precipitate the development of overt inflammation typical of uveitis.

Ocular immune privilege as a throttle of inflammation in the eye

Immune responses affecting the eye and vision must be viewed against the backdrop of ocular immune privilege. The term was coined in the 1940s by Sir Peter Medawar [11]. It has since been studied intensively, with major conceptual contributions by the late J. Wayne Streilein and his colleagues [1,2,12,13]. The concept that has emerged, and that continues to guide the field today, is that the ocular environment has evolved to limit local immune and inflammatory responses in order to preserve vision. Although specifics are still being debated, it appears clear that immune privilege involves a complex combination of local and systemic mechanisms. These can be thought of as constituting successive layers of defense that are deployed as they are needed. The first line of defense is separation between the immune system and the eye by an efficient blood–retina barrier and little, or no, direct lymphatic drainage of the inside of the globe, which is maintained as long as the eye is intact. If that is breached (as in the case of physical trauma to the eye) and immune cells from the blood enter the eye, the immunoinhibitory ocular microenvironment, composed of diverse soluble and cell-bound molecules, steps in to control them. If that is not

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sufficient and inflammation develops, the eye elicits systemic regulatory mechanisms, experimentally modeled by anterior chamber associated immune deviation (ACAID) and post-recovery eye-dependent tolerance, that can limit the damage. These aspects of immune privilege have been reviewed thoroughly [1,2,12–15] and are summarized in Table 1.

The concept that we wish to bring forward is that, as part of immune privilege, the inhibitory ocular microenvironment serves as a throttle of inflammation in the eye, exerting significant measure of control over both innate and adaptive immune elements. Past and recent studies have uncovered inhibitory effects of the ocular microenvironment on both innate and adaptive immunity. However, a difficulty has been that many of the studies from which the central concepts of immune privilege arose had been performed *in vitro* with ocular fluids and cells, extrapolating to an *in vivo* situation. This was an inevitable consequence of the lack of appropriate tools for an *in vivo* readout. Nevertheless, where available, we try to point out conclusions based on *in vivo* data. In keeping with the issues examined in this review, which emphasize the local expression of immunity in the eye, we concentrate on those aspects of immune privilege that act within the ocular microenvironment, rather than systemic aspects.

Immune privilege versus innate immunity

Activation and function of innate immune elements such as natural killer (NK) cells, monocyte–macrophages, neutrophils, and complement are all dampened by the ocular microenvironment [reviewed in [16,17]. Ocular fluids contain at least two factors that suppress NK cell function: macrophage migration inhibitory factor (MIF) and transforming growth factor (TGF)-β2. These can be shown to turn off NK cells *in vitro*. It is hypothesized that, together with nonclassical MHC antigens that are expressed by ocular cells, they may also turn off NK cells *in vivo*, although direct evidence to support this is lacking. Indirect support is provided by the well-documented fact that MHC-unmatched corneal grafts, which by all expectations should have activated NK cells to kill the corneal cells, nevertheless persist and are accepted with high frequency both experimentally and in the clinic [13]. A particularly interesting molecule that has been connected to ocular immune privilege *in vivo* is FasL, which interacts with both innate and adaptive immune cells. Membrane-bound FasL is expressed in the cornea, iris/ciliary body epithelium and retinal pigment epithelium (RPE). It causes apoptosis of Fas-expressing effector leukocytes and promotes tolerance to antigens within the eye [18]. Ocular fluids also contain α-melanocyte stimulating hormone (MSH) and may contain soluble FasL, a cleavage product of membrane FasL with antagonistic properties [19,20]. Both these substances inhibit activation of neutrophils (although membrane FasL would activate them [21]).

A major population of innate inflammatory cells that has been described in most cases of intraocular inflammation is the macrophages [22,23]. Their activation and function can be dampened by the neuropeptides α-MSH and calcitonin gene-related peptide (CGRP) that are present in ocular fluids. Interleukin (IL)-10 coming from γδ T cells appears to be important for systemic manifestation of immune privilege known as ACAID [24,25], but it is currently unknown whether a role can be ascribed to IL-10 produced by γδ T cells within the ocular milieu. The fact that IL-10 is associated with the regulation of infiltrating ocular macrophages and polarization to the regulatory M2 phenotype, reaffirms the concept of ocular immune regulation of innate responses [22,23]. The appearance of macrophages with inhibition of neovascularization in the retina in laser-induced damage models, suggest that this is the case [26]. How the role of macrophages is directed in tissue destruction versus regeneration is still unknown, but certainly, the ocular microenvironment has the ability to signal these cells to regulate their function through messengers such as Toll-like receptor (TLR) ligands and macrophage-specific cytokines as well.

Finally, activation of the complement cascade, either by the classical or by the alternative pathway, generates mediators that directly damage target cells by forming a membrane attack complex, and also attract and activate innate immune cells. Data indicate that a low level of complement activation is constantly present in the eye, and may be needed to protect from pathogens. To counterbalance this and control excessive complement activation that would be damaging to the tissue, the ocular fluids and cells express a number of complement regulatory proteins, including the complement factor H (CFH) and the cell bound molecules decay accelerating factor (DAF) and complement-related receptor gene Y (Crry) (reviewed in [27,28]).

Table 1. Three successive layers of immune privilege[a,b]

SEPARATION	**BRB**: prevents free traffic of cells and molecules into and out of the eye **No lymphatic drainage** (as long as BRB is intact)
Inhibition	**Immunoinhibitory and Treg-inducing ocular microenvironment:** soluble mediators (e.g., cytokines and neuropeptides: TGF-β, α-MSH, VIP, CGRP, soluble FasL) cell-bound molecules(e.g., FasL, TSP1, PD-L1) **Soluble and cell-bound complement regulatory proteins** (e.g., CFH, DAF, Crry)
Regulation	**Eye-driven systemic regulatory processes** (ACAID, post-recovery eye dependent tolerance)

[a]Adapted from [12].

[b]Abbreviations: BRB, blood–retina barrier; Crry, complement-related receptor gene Y; PD-L1, programmed death ligand-1; VIP, vasoactive intestinal polypeptide.

Immune privilege versus adaptive immunity

The adaptive immune elements that can express effector function in the eye are $CD4^+$ and $CD8^+$ T cells and antibodies. It is currently unknown whether B cells, which play a systemic role in induction of ACAID, exert any function within the eye besides antibody secretion. $CD8^+$ T cells share many effector characteristics with NK cells and may be controlled in part by similar mechanisms. $CD8^+$ T cells also can act as regulatory cells, whose generation is at least in part driven by interactions dependent on NKT cells in the spleen [29]. The role of $CD4^+$ T cells as effectors and as regulators in the various aspects of immune privilege has similarly been studied extensively in the past. These studies showed that processes that inhibit innate immunity in the eye can often also control adaptive immune cells, and