

Ocular immune privilege

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F1000 Biology Reports 2010, **2**:3 (doi:10.3410/B2-3)

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Abstract

The eye attempts to limit local immune and inflammatory responses to preserve vision. This phenomenon, known as ocular immune privilege, is mediated by a combination of local and systemic mechanisms. While immune privilege is believed to protect the eye from day-to-day inflammatory insults, it is not absolute and its mechanisms are still incompletely understood.

Introduction and context

The eye has a special relationship with the immune system, known as immune privilege. The term was coined in the 1940s by Sir Peter Medawar, who noticed that foreign tissue grafts placed in the anterior chamber (AC) of the eye were not rejected [1]. While the concept of immune privilege is simple, research into its nature has revealed its highly complex character, which is still incompletely understood (reviewed in [2]). Multiple mechanisms combine to maintain immune privilege:

(a) Physical barriers (efficient blood-retina barrier and lack of efferent lymphatics) prevent free entry and exit of cells, and even larger molecules, into and out of the eye. The integrity of the blood-retinal barrier is routinely measured in the clinic by the fluorescein test and provides a widely accepted measure of ocular health. Nevertheless, the concept of sequestration of the eye from the immune system has recently been debated, mostly on the basis of the phenomenon known as anterior chamber-associated immune deviation (ACAID). (See item (c) below).

(b) The inhibitory ocular microenvironment, composed of cell-bound and soluble immunosuppressive factors within the eye, inhibits the activity of immune-competent cells. The soluble factors include transforming growth factor-beta (TGF- β) (which can also be membrane-bound), neuropeptides such as alpha-melanocyte-stimulating hormone (α -MSH), vasoactive intestinal peptide, and others. Ocular resident cells directly inhibit immune cells (at least in

culture) by secreting soluble factors and by contact-dependent mechanisms. Retinal glial Müller cells were the first to be identified, but their inhibitory surface molecules of the retina (RPE) and the iris/ciliary body (IPE) not only inhibit T cells, but also induce them to become T regulatory (Treg) cells [4]. Surface-bound molecules involved in these processes include CD86 [which engages cytotoxic T lymphocyte antigen 4 (CTLA-4) on T cells], FasL, thrombospondin, and galectins [4,5].

(c) Finally, the eye actively regulates systemic immune responses. The classic example is ACAID, a unique and highly orchestrated immune response to antigens injected into the AC. It involves migration from the eye to the spleen of F4/80⁺ antigen-presenting cells that interact with invariant natural killer T cells and B cells and culminates in elicitation of systemic regulatory immunity through induction of CD4⁺ afferent and CD8⁺ efferent Treg cells (reviewed in [4,6]). Proteins and even cells or cellular fragments were shown to pass from the AC directly into the blood through a highly porous structure known as the trabecular meshwork. While some regard this as negating the concept of ocular antigen sequestration, elicitation of ACAID requires puncturing of the eye with a needle and perturbation of ocular integrity. It is therefore likely that ACAID is more representative of a response to trauma rather than of a mechanism of tolerance to tissue-specific antigens contained in the healthy eye. A less controversial example is post-recovery tolerance, in which spleen cells from mice

that have recovered from experimental autoimmune uveitis (EAU) contain regulatory activity, whose generation is dependent on the presence of eye [7-9]. This type of tolerance was shown to involve the melanocortin pathway and cannot be induced in melanocortin-5 receptor knock-out mouse, but whether it is α -MSH from the eye that is involved has not been determined.

A highly successful application of the ocular immune privilege is corneal transplantation. Corneal allografts are up to 90% successful without tissue matching and without systemic immunosuppressive therapy [10]. On the downside, however, ocular immune privilege may leave the eye vulnerable to autoimmunity by impeding peripheral tolerance to eye-specific antigens sequestered behind the blood-retinal barrier [8].

Major recent advances

While some effects of neuropeptides that help maintain the immunoinhibitory ocular microenvironment may be exerted directly on lymphoid cells [5], neuropeptides may also regulate production of TGF- β within the eye. A recent study demonstrated that immune privilege of the eye, as evaluated by rejection of allogeneic tumor cells, development of ACAID, and maintenance of high TGF- β levels in aqueous humor, was lost following removal of functional sympathetic fibers [11]. Thus, although some neuropeptides in ocular fluids might be produced by ocular cells themselves, sympathetic innervation of the eye is critical for maintenance of the above-mentioned manifestations of immune privilege. This could stem from the observed effects on TGF- β as there is no evidence from previous studies for direct effects of neuropeptides on ACAID and related phenomena.

Recent studies addressing local regulation by pigmented ocular epithelia identified previously unrecognized molecular pathways by which they mediate T-cell suppression and their conversion to Treg cells. Ligands for the T-cell inhibitory receptor programmed death-1 (PD-1) were detected on human as well as mouse RPE cells. Both the human ARPE-19 line and primary human RPE express both PD-L1 and PD-L2, and expression on primary human RPE was enhanced by interferon-gamma (IFN- γ). In murine RPE, PD-L1 was below detection in primary cells but was induced by IFN- γ . PD-L1 expression was functionally relevant and negatively regulated cytokine production by T cells. This could be reversed by blocking antibodies to PD-L1 or by PD-1 deficiency [12,13]. RPE cells also were found to constitutively produce CTLA-2 α , a cathepsin L (CathL) inhibitor. CD4⁺ T cells exposed to CTLA-2 α -expressing RPE cells or to recombinant CTLA-2 α converted to CD25⁺FoxP3⁺ Treg cells. Importantly, this pathway was functional also *in vivo* and provided protection

from autoimmune uveitis in the mouse EAU model, as demonstrated using anti-CTLA-2 α antibodies and CTLA-2 α -deficient mice. CTLA-2 α directly lowers CathL activity in T cells and also promotes activation of TGF- β by facilitating Treg conversion [14,15]. Thus, PD-1 pathway may function in suppression of the Th1 responses and CTLA-2 α may additionally convert T cells that 'slipped through' the PD-1 pathway into Treg cells. In contrast, the T cell inhibitory activity of human IPE was shown to be driven by a contact-mediated TGF- β -dependent mechanism that could be reversed by TGF β 2-siRNA (short interfering RNA) or anti-TGF- β antibodies [16].

Future directions

The elaborate and highly redundant nature of mechanisms comprising ocular immune privilege seems undisputed. If things are so good, then why are they so bad? It seems unreasonable that in the face of immune privilege and in the absence of physical trauma, the eye remains vulnerable to autoimmune uveitis in both its clinical and experimental forms. As amply demonstrated by experimental models of induced uveitis, privilege is easily broken by even small numbers of activated T-effector cells that have been primed in the periphery or adoptively transferred [8]. Why are they not inactivated or converted to Treg cells by the ocular microenvironment but allowed to induce destructive inflammation? Furthermore, spontaneous uveitis develops when there is increased frequency of retina-specific T cells, such as in mice lacking the transcription factor AIRE (AutoImmune REgulator) which do not delete retina-specific cells in the thymus or in mice expressing a foreign protein in the retina and having T cells that carry the specific T-cell receptor [17,18]. If retinal antigens are indeed sequestered, where are the T cells being primed? And if they are not sequestered, why has privilege not resulted in systemic tolerance? It would seem that the concept of immune privilege needs to be further studied, refined, and perhaps revised.

Abbreviations

α -MSH, alpha-melanocyte-stimulating hormone; AC, anterior chamber; ACAID, anterior chamber-associated immune deviation; CathL, cathepsin L; CTLA, cytotoxic T lymphocyte antigen; EAU, experimental autoimmune uveitis; IFN- γ , interferon-gamma; IPE, iris pigment epithelium; PD-1, programmed death-1; RPE, retina pigment epithelium; TGF- β , transforming growth factor-beta; Treg, T regulatory.

Competing interests

The authors declare that they have no competing interests.

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Evaluated by Matthias von Herrath 07 Dec 2006, Bruno Kyewski 08 Dec 2006, Arthur Hurwitz 14 Feb 2007

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