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In This Issue: Immunology of the Eye—Inside and Out

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In recent years, our perspectives on many processes and diseases that affect the eye and vision have undergone extensive revision, and are in part reflected in the series of reviews that follow. While, due to space restrictions it is not possible to provide a complete coverage of the field, we have tried to bring to the reader a representative crosscut of topics ranging from the ocular surface to the neural retina that lines the back of the eye and is directly responsible for transduction of the visual signal.

The eye, similar to other tissues, is subject to both immune protection and attack. However, in many ways the eye is a unique tissue immunologically, in part due to a complex structure. The external surface of the eye is a mucosal tissue that is exposed to the environment, and is subject to constant challenges both in terms of microorganisms as well as a hostile external environment. Yet, normally the delicate ocular surface remains clear and healthy. Protection of the ocular surface and antibacterial activity is the role of substances present in the tear film, mucins, and antibacterial substances produced by immune cells and ocular surface structural cells. Perturbation of immune homeostasis by environmental stress and/or infectious agents can lead to immune-mediated damage to the ocular surface that threatens vision, a topic covered in this issue by Stern and by Pearlman [1, 2].

In contrast, the internal compartments of the eye present a sterile environment separated from the immune system by a highly efficient blood-retinal barrier (BRB). The latter prevents free trafficking of cells and even of larger molecules into and from the eye. Furthermore, the eye has the ability to actively regulate immune responses both locally and systemically. This regulatory function, together with the physical barrier of the BRB, is known as ocular immune privilege, and it affects many if not all aspects of the eye's relationship with the immune system. Clinically, immune privilege is exploited in retinal transplantation, where approximately 90% graft retention is seen at the end of one year without tissue matching. Future technologies hope to harness immune privilege to allow stem cell transplantation into the eye, as well as therapeutic gene delivery using potentially immunogenic vectors which carry genes for proteins that themselves may be targeted by the immune system. The reviews by Stein-Streilein and by Niederkorn [3, 4] deal with these issues. The flip side of the coin is that immune privilege also affords protection to intraocular tumors, a topic that could not be covered in this issue, but has been reviewed elsewhere [5–7].

There has recently been a resurgence of interest in innate immunity. This has led to an increased understanding of the processes and molecules that trigger assembly and control

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the function of the inflammasome. Dysregulation of these pathways is now felt to be involved in ocular inflammation and may underlie the etiology of a group of so-called "autoinflammatory" diseases, as discussed by Rosenbaum [8]. Innate immune cells responding to environmental or autologous stimuli also are largely responsible for establishing the milieu that instructs adaptive immunity resulting in protective versus pathogenic self-reactivity in the eye. Accordingly, regulatory T cells (Treg) and effector Th17 cells have joined the ranks of cells intensely studied with regard to immune and autoimmune tissue damage that can compromise vision. In some ways, immune privilege is a double-edged sword because the BRB limits access of the immune system to the healthy eye, thereby impeding the establishment of peripheral tolerance to tissue-specific antigens localized within the eye. This results in the persistence of non-tolerant T cells that can respond to ocular antigens. A chance encounter with an activating stimulus, whether microbial (mimic) or endogenous (e.g. released by trauma, especially if an infectious agent is also present and provides an adjuvant effect), may activate these autoreactive T cells and lead to an autoimmune attack on the eye [9]. Why, then, does ocular immune privilege, which protects the eye from consequences of minor day-to-day insults and traumas, and efficiently promotes acceptance of non-tissue-matched corneal grafts, unable to prevent such an autoimmune attack? The answer may lie in our recent findings showing that, while the living eye is able to control uncommitted retina-specific T cells by converting them *in situ* to Tregs or by suppressing their effector lineage commitment, it cannot control T cells that had already been activated prior to entering the eye. Such T cells resist the inhibitory effects of the ocular environment and instead induce inflammation [10].

Finally, it has lately become more and more clear that diseases once considered as purely degenerative, in fact contain an important immune-mediated component. This includes such entities as adult macular degeneration, glaucoma, diabetic retinopathy and other retinopathies. While these diseases do not exhibit classical inflammation as in uveitis, immune effectors are detected in lesions, and genetic associations with immune system elements have been defined. Both innate and adaptive responses may participate. On the one hand, tissue repair involves macrophages that scavenge tissue breakdown products. On the other hand, dysregulation of this process may result in pathology involving inappropriate activation of complement and polarization of the "healing" macrophages to pathogenic Type 1 (inflammatory) or Type 2 (neovascularization promoting) phenotypes. Finally, one can imagine also that when degenerative processes cause disruption of the BRB and release ocular constituents into the periphery, giving access to innate and adaptive immune components to the retina, secondary immune/autoimmune responses can also be induced thereby promoting T cell and B cell pathogenic responses. Current efforts are aimed at dissecting the role of immunity in what might constitute pathogenic as opposed to repair processes, and also at targeting these processes therapeutically [11].

In summary, despite the immunologically privileged status of the anterior and posterior poles of the eye [3] and the protective mucosal environment of the ocular surface, there are many threats to vision. These include (i) external environmental stresses and infections which can interfere with the transparency of the cornea [1, 2], necessitating corneal transplantation [4], (ii) intraocular inflammation known as uveitis driven by innate stimuli and/or by autoreactive T cells [8, 9] and (iii) degenerative/immune processes like AMD, glaucoma and diabetic retinopathy [11]. It is hoped that the current compendium of topics will not only inform the readers of the current status of thinking on these subjects, but also will encourage them to seek further information about the fascinating dialog between the eye and the immune system.

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