Harnessing immune privilege in the eye to combat autoimmune uveitis

Dr Andrew Taylor, Boston University School of Medicine, investigates how we can manipulate the immune system of the eye to treat autoimmune uveitis. Understanding the molecular mechanisms underlying autoimmune uveitis will provide potential opportunities to use naturally produced molecules to suppress the disease, instead of drugs with unpleasant side effects. His findings could be extrapolated to other autoimmune diseases.

IMMUNE PRIVILEGE IN THE EYE

The phrase immune privilege was first used by Sir Peter Medawar to describe the lack of an immune response against allografts (a transplant between genetically different individuals of the same species) placed into the ocular microenvironment. Now, the term refers to the ability of an organ to suppress responses against what would normally be considered a foreign antigen. This occurs through physical barriers, such as the blood-ocular barrier, and through biochemical signals.

The mechanisms of ocular immune privilege include a blood-ocular barrier, a lack of direct lymphatic drainage, the development of a form of tolerance to foreign antigens placed in the ocular microenvironment and a specific repertoire of immunosuppressive molecules. Breakdown of one or more of these mechanisms can make an eye susceptible to uveitis.

The process of immune privilege prevents the activation of proinflammatory activities of immune cells. In the eye, immune privilege can prevent antigen presenting cells from activating self-antigen responsive T-cells, which in turn prevents the T-cells from mounting an autoimmune response. Although the mechanisms of immune privilege in the eye are not fully understood, it is thought that the presence of soluble factors produced within the eye may play a role in suppressing the expression of inflammatory cytokines by immune cells. These soluble factors promote the activation and expansion of T-cells with regulatory activity (Treg cells), while suppressing effector T-cells, which are involved in active immune responses and inflammation.

The current therapies for autoimmune uveitis suppress the symptoms and block the key cytokines involved in inflammation, but do not directly alter the behaviour of the immune cells responsible for causing disease. In contrast, harnessing mechanisms of immune privilege would provide the potential to change the programming of the immune cells to promote anti-inflammatory and self-regulating activity.

NEUROPEPTIDES AS POTENTIAL THERAPEUTICs

The ideal therapeutic approach must activate immune regulation within the eye, actively promote immune tolerance, and re-establish ocular immune privilege.

The endogenous neuropeptide α-Melanocyte Stimulating Hormone (α-MSH), a member of the highly conserved melanocortin family of peptides and receptors, is a potent suppressor of inflammation. In 1992, Taylor, Cousins and Streilein first reported that α-MSH suppresses inflammation in the aqueous humour of the eye and holds an important role in maintaining ocular immune privilege in healthy eyes. It is likely that α-MSH represents just one of many immunosuppressive factors in the aqueous humour and identifying further molecules would both further understanding about immune privilege in the eye and provide novel therapeutic drugs. These molecules target a range of different immune cells at different stages during the induction of an immune response.

The sources of α-MSH in the eye are not fully known, although it has been documented that several types of cell in the eye, such as retinal pigment epithelial cells, as well as cells of the iris and ciliary body, may be sources of the neuropeptide. Evidence suggests that there is a loss of α-MSH in autoimmune disorders of the eye, or damaged
The retina looks nearly normal (as in Image 1).

Indeed, preliminary studies done by Taylor and his group using α-MSH peptide therapy have shown that this treatment does suppress rodent models of autoimmune uveitis. Alpha-MSH treatment also appeared to lead to retinal pigment epithelial cells regaining their immunoregulatory activity.

A previous study by Taylor and Lee demonstrated that α-MSH is capable of inducing conversion of effector T-cells into Treg cells. Interestingly, α-MSH did not induce regulatory behaviour in T-cells which have not been exposed to antigens; this phenomenon was confined to the effector T-cell population, demonstrating that α-MSH mediates action of inducible Treg cells. Recently, Taylor and Lee found that α-MSH takes effect through inducing antigen presenting cells to mediate contra-conversion of effector T-cells into inducible Treg cells.

Further data from Taylor’s lab suggest that receptor-specific agonists to melanocortin 1 and 5 receptors (MC1r and MC5r) both suppress an experimental model of autoimmune uveitis. In mice, this suggests a strong possibility that MC5r stimulation is necessary for α-MSH suppression of experimental autoimmune uveitis, and the possibility of reactivating ocular immune privilege.

Dr Taylor also hypothesises that there is a role for ocular neuropeptides in the regulation of macrophage activity in the healthy eye, particularly in promoting suppressive and anti-inflammatory activity. These macrophages respond to pathogens without mediating inflammation or activating T-cells. Moreover, the macrophages produce anti-inflammatory cytokines, and suppress and possibly induce death in activated T-cells. Taylor has evidence that this is mediated by the neuropeptides neuropeptide Y and α-MSH produced within the eye.

PUBLIC HEALTH RELEVANCE

Examining the mechanisms of ocular immune privilege promotes the importance of interactions between the nervous and the immune systems and may provide opportunities to use these interactions to beneficially manipulate immune responses.

The work of Dr Taylor’s lab has demonstrated that the melanocortin pathway, which acts through the neuropeptide α-melanocyte stimulating hormone and its melanocortin receptors, is essential for ocular immune privilege. Therefore, as the group has shown, it is possible to stimulate the melanocortin pathway to provide a therapeutic option for suppressing inflammation and autoimmune disease. Ultimately, there is the potential to develop a new approach to uveitis therapy that would use the body’s own natural anti-inflammatory activities, mediated by the neuropeptide α-MSH, to combat the disease.

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