Negative regulators that mediate ocular immune privilege

Andrew W. Taylor and Tat Fong Ng

Boston University School of Medicine, Boston, Massachusetts, USA

Abstract

The ocular microenvironment has adapted several negative regulators of inflammation to maintain immune privilege and health of the visual axis. Several constitutively produced negative regulators within the eye TGF- β 2, α -melanocyte stimulating hormone (α -MSH), Fas ligand (FasL), and PD-L1 stand out because of their capacity to influence multiple pathways of inflammation, and that they are part of promoting immune tolerance. These regulators demonstrate the capacity of immune privilege to prevent the activation of inflammation, and to suppress activation of effector immune cells even under conditions of ocular inflammation induced by endotoxin and autoimmune disease. In addition, these negative regulators promote and expand immune cells that mediate regulatory and tolerogenic immunity. This in turn makes the immune cells themselves negative regulators of inflammation. This provides for a greater understanding of immune privilege in that it includes both molecular and cellular negative regulators of inflammation. This would mean that potentially new approaches to the treatment of autoimmune disease can be developed through the use of molecules and cells as negative regulators of inflammation.

Keywords

anti-inflammatory; eye; Immunosuppression; neuropeptides; regulatory T cells; suppressor macrophages; tolerance

1 INTRODUCTION

The eye is an immune privileged tissue that has adapted several negative regulators to prevent the activation of inflammation within its tissue microenvironment. Ocular immune privilege was originally described by the indefinite survival of histoincompatible grafts placed within the anterior chamber.^{1,2} Today, immune privilege is described also by soluble and cell membrane bound molecules constitutively produced by cells of the ocular microenvironment. These molecules suppress inflammation, and trigger checkpoints in immunity.³⁻⁶ Moreover, these molecules do not just suppress inflammation, but program monocytes, and T cells to mediate tolerance.

Correspondence Andrew W. Taylor, Department of Ophthalmology, Rm L915, Boston University, School of Medicine, Boston, MA 02118, USA, awtaylor@bu.edu. **AUTHORSHIP** Drs. Taylor and Ng wrote and edited this manuscript.

DISCLOSURES

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The mechanisms of ocular immune privilege can be separated into physical, molecular, and cellular barriers to the induction of inflammation. The physical barriers are the tight junctions of endothelial cells, and the retinal pigment epithelial (RPE) cell monolayer that form the blood–ocular barrier.^{7,8} This barrier is sufficient to inhibit the migration of immune cells from the circulation into the eye.⁹ Also, it allows the eye to bathe its own cells with molecules needed for metabolism, neuroretinal function, regulation of intraocular pressure, and the accumulation of anti-inflammatory factors. In addition, there are no known direct lymphatic drainage of the ocular microenvironment further isolating the ocular microenvironment from conventional pathways to induce inflammation and immunity.¹⁰ These were once considered the sole reason for survival of the incompatible grafts placed into the anterior chamber of the eye because of an exclusion of peripheral immune cell migration, and sequestration of Ags in the ocular microenvironment. However, it is clear that the immune system is very much aware of Ags placed in the ocular microenvironment.^{11–14}

Inoculation of Ags into the eye does not induce inflammatory immune responses, but instead induce tolerance that is specific to the Ag.¹¹ This is exemplified by treating APC with aqueous humor (the fluid filling the ocular anterior chamber), or with conditioned media of primary RPE cell cultures.^{15–23} These ocular influenced APC process and present Ag in a manner that induce Ag-specific regulatory CD4 and CD8 T cells.^{24–26} In addition, contact with RPE cell causes naive T cells to produce anti-inflammatory cytokines, and when adoptively transferred these T cells mediate tolerance.^{27–29} The same is seen with APC and T cells treated with aqueous humor.^{17,24} This demonstrates that part of the mechanisms of ocular immune privilege are soluble negative regulators of inflammation that make the immune system regulate itself.

These mechanisms allow for medical interventions that are not possible in other tissues. The most noted is that blood typing is not needed for a successful corneal transplant in low risk patients.^{30–32} This has been linked to the ocular microenvironment to generate specific tolerance to alloantigen expressed in the transplanted cornea.^{30,33,34} Clinical trials of AAV2 delivery of hRPE65 genes show little to no immune response against the virus even with multiple applications of the virus into the eye.^{35–37} Direct evidence as to why has not been reported, but the injection of viral proteins into the ocular microenvironment may be inducing systemic tolerance to viral Ags. This is a phenomenon called immune deviation, and would permitting multiple injections of AAV without immune response.^{11,38,39} In addition, long-term survival of embryonic stem cells has been seen in clinical studies with the cells injected into the subretinal space.^{37,40,41} It has been found that transplanted RPE cells can create immune privileged microenvironments; therefore, transplanting retinal cells may themselves produce factors that prevent rejection.^{42–44} In contrast, ocular immune privilege may cause complications in patients infected with Ebola virus. Even during recovery there is a persistence of virus in the eye taking advantage of the ocular microenvironment to hide from the substantial immune response raging against it.^{45–47} Understanding the mechanisms of ocular immune privilege will provide the knowledge into what is necessary to maintain, and in disease to restore a healthy ocular microenvironment.

2 ESSENTIAL NEGATIVE REGULATORS OF IMMUNITY IN IMMUNE PRIVILEGE

The uniqueness of the ocular microenvironment is that negative regulators of inflammation are constitutively expressed under healthy conditions. The source of the soluble regulators are the iris and ciliary body cells that generated aqueous humor, and recently it has become clear that RPE cells are another source of the regulators.^{19–22,27,48–52} These regulators are growth factors, neuropeptides, cytokines, and complement inhibitors. Collectively, these regulators suppress the activation of inflammatory activity, induce production of anti-inflammatory cytokines, and promote immune tolerance activity in monocytes and T cells.^{17,19,20,23} Individually these regulators affect different cells of inflammation (Table 1A). Also, they mediate the activation of tolerogenic APC, and regulatory T cells (Tregs), which in turn act as cellular negative regulators of inflammation (Table 1B). The most noted regulators are the immunosuppressive cytokine TGF- β 2, the immunomodulating neuropeptide alpha-melanocyte stimulating hormone (α -MSH), and the check point membrane expressed molecules PD-L1 and Fas ligand (FasL).^{16,53–58}

2.1 Transforming growth factor- β 2

The initial work done to understand the molecular negative regulators of immune privilege was done studying the effects of aqueous humor on APCs.²³ When F4/80 positive macrophages are treated with aqueous humor while processing Ag, they induce systemic Ag-specific tolerance.⁵⁹ These tolerogenic APC migrate to the marginal zones of the spleen and promote the activation and expansion of Ag-specific CD8⁺ Tregs.^{23,60,61} This is similar to the phenomena of anterior chamber-associated immune deviation (ACAID). The ACAID response is the induction of Ag-specific systemic tolerance caused by injecting foreign Ag into the anterior chamber of the eye.⁶² A very similar ACAID-like response is seen when the Ag is injected into the subretinal space. This is mediated by TGF- β 2 in aqueous humor that induces an alternative activation of Ag presenting activity in macrophages.^{23,53–55}

There is very little to no detection of the other isoforms of TGF- β , other than TGF- β 2 in healthy aqueous humor.^{53,55} In addition, the TGF- β 2, as it is in all tissues, is latent requiring activation.^{63,64} The activation can be through proteinases near cell membranes, and in the eye thrombospondin-1 (TSP-1) has an important role in intraocular TGF- β activation.^{19,65,66} Mice with TSP-1 knocked out do not express the ACAID phenomena; moreover, autoimmune-induced inflammation in the retina does not resolve on its own as seen with wild-type (WT) mice.¹⁹ These findings have demonstrated a potentially important role for TSP-1 in maintaining a low level of activated TGF- β 2 in the immune privileged ocular microenvironment.

Macrophages treated with TGF- β 2 express the characteristics of the aqueous humor-treated macrophages that mediate ACAID.^{23,67} The TGF- β 2 treated macrophages increase their surface expression F4/80 and CD1d, while reducing expression of coreceptors for T cell activation.^{60,68–70} The macrophages express TGF- β 1.⁶⁵ When adoptively transferred the TGF- β -treated macrophages migrate to the marginal zones of the spleen, and form cellular cluster with NKT cells, CD8⁺ and CD4⁺ T cells.^{25,60} The result is expansion and activation

of efferent CD8⁺ Treg cell that suppress in an Ag-specific manner hyper-sensitivity and autoimmune disease.

When the activity of TGF- β 2 is neutralized or left latent, aqueous humor is still able to suppress effector T cell activation.^{24,63,71} The T cells produce only TGF- β 1, and act as Treg cells.²⁴ This had demonstrated that other soluble negative regulators are active within the ocular microenvironment.^{16,54,72} This is the role of immunomodulating neuropeptides.

2.2 Neuropeptide α -MSH

Several immunomodulating neuropeptides are found in aqueous humor, and are produced by RPE.^{16,17,21,22,24,73–75} The neuropeptide α -MSH has demonstrated to have an important central role in modulating immune activity within the eye. It is a prototypical neuroimmunomodulating neuropeptide that with its melanocortin receptors is highly conserved in nature, and is potent in suppressing multiple innate and adaptive immune pathways of inflammation.^{74,76–79} The effects of aqueous humor on immune cells is very similar to the effects of α -MSH peptide treatment on immune cells.^{16,17} This 13 amino acid long neuropeptide originally described for its melanin-inducing activity in frogs, has a fundamental role in modulating inflammatory responses in mammals.^{80–83} There is constitutive expression of α -MSH in healthy aqueous humor and in the conditioned media of cultured RPE cells at concentrations that are highly anti-inflammatory.^{16,21}

Tissue or systemic injections of α -MSH suppress inflammation mediated by endotoxin, and proinflammatory cytokines IL-1 α and TNF- α .^{84–90} At the cellular level α -MSH suppresses macrophage, dendritic cell, and neutrophil generation of reactive oxygen intermediates, nitric oxide, proinflammatory cytokines, and migration.^{91–96} Also, there is induction of an anti-inflammatory autocrine loop where α -MSH enhances its own receptor expression and production in macrophages.⁹⁶ Macrophages treated with α -MSH and stimulated through TLR4 with endotoxin are suppressed in NF- κ B activation.^{97–102} Suppression of inflammatory activity stimulated through other TLRs may also be suppressed by α -MSH.^{103,104} The α -MSH-treated macrophages have enhanced expression of IL-1R associated kinase (IRAK)-M that blocks MyD88 intracellular pathways of inflammation.¹⁰⁵ Recently reported is that α -MSH suppress phagocytic uptake of bioparticles through scavenger-receptor mediated pathways, but not through FcR-mediated pathways.¹⁰⁶ Although uptake of opsonized-Ag is not suppressed by α -MSH, the activation of the phagolysosome is suppressed.¹⁰⁶ In addition, this is further enhanced by the cotreatment of macrophages with α -MSH and Neuropeptide Y (NPY), another neuropeptide found constitutively present in the eye and produced by RPE cells.^{21,106} This has suggested that within the immune privileged ocular microenvironment there is a mechanism to allow phagocytes to remove harmful materials without induction of inflammation. Also, this is done without conventional processing and presentation of Ag that could be recognized by autoreactive effector T cells expanded in the periphery. The effects of α -MSH are not just suppression of inflammatory activity, α -MSH programs anti-inflammatory activity in stimulated macrophages.^{20,107,108} Similar effects have been seen in activated macrophages treated with aqueous humor or conditioned media of cultured RPE cell mediated by α -MSH.^{20,23}

Aqueous humor suppresses CD4⁺ T cells production of IFN- γ , and this is mediated by α -MSH.¹⁰⁹ The suppression of the proinflammatory cytokines is through up-regulation of INF- γ protein ubiquitination within the α -MSH-treated T cells.¹¹⁰ Like with macrophages, α -MSH is not just suppressive, it promotes TGF- α 1 production by the T cells, which in turn act as Treg cells.^{74,108,111,112} These α -MSH-induced Treg cells are CD25⁺ and FoxP3⁺. The α -MSH induced Treg cells must be stimulated by their own presented cognate Ag to mediate suppression of other T cells.^{17,108} When these α -MSH-induced Treg cells are generated in vitro they can be used in adoptive transfer experiments to suppress autoimmune uveitis, and promote retinal allograft survival.^{108,111,112}

The effects of α -MSH on immune cells are through the melanocortin receptors.^{79,99,103,104,108,113,114} The suppression of proinflammatory activity by α -MSH is mediated through the Melanocortin 1 and 3 receptors (MC1r and MC3r) expressed on macrophages, and the α -MSH-induced immune regulatory/tolerogenic activity is through MC5r on the T cells and macrophages. MC5r is expressed on macrophages and promotes suppressor activity.^{79,113,115} Through constitutive presence of neuropeptides like α -MSH, the mechanisms of immune privilege not only work to suppresses inflammation, but also promote anti-inflammatory and regulatory behavior in immune cells.

2.3 Membrane bound negative regulators

T cells express regulatory activity when they come in contact with cultured RPE.^{42,52,57,116} This is mediated by several possible mechanisms. Besides the soluble factors expressed above, RPE cells express soluble CTLA-2 α and retinoic acid that promote regulatory activity.^{28,50} Fixed cultured RPE cells also induce naive T cells to act as Treg cells.⁵² This is a contact dependent mechanism by membrane bound TGF- α on the RPE cells. In addition, under conditions of inflammation, RPE cells express enhanced levels of PD-L1 and possibly MHC class II.^{57,117} This has demonstrated the potential for RPE cells to promote Treg cell activation even during uveitis.

Cells throughout the ocular microenvironment express FasL, and it has been suggested that it is a major contributor to immune privilege, because its expression is necessary for graft survival within the eye.⁵⁶ However, the presence of soluble FasL in aqueous humor significantly blocks membrane FasL mediated apoptosis.^{118,119} Immune privilege may in part depend on a balance between soluble and membrane bound FasL.¹¹⁹ The constitutive expression of FasL can contribute to a selective mechanism within the ocular microenvironment to permit the presence of regulatory immune cells at the exclusion of other types of proinflammatory immune cells. The expression of PDL1 and FasL along with the physical barrier created by the tight junctions of the RPE and endothelial cells form the immune barrier of the ocular microenvironment.

2.4 Cellular negative regulators of inflammation

The negative regulators of inflammation expressed within the eye, not only suppress production of proinflammatory cytokines, but also program immune cells to suppress inflammation and promote tolerance. This makes immune privilege more than the

constitutive presence of molecular regulators of inflammation, but also immune cells that act as cellular negative regulators of inflammation.

The effects of aqueous humor on macrophages, the ACAID phenomena, and the activation of Treg cells by retinal dendritic-like cells¹²⁰ demonstrate that Ag presentation within the immune privileged eye does not follow conventional pathways that lead to effector T cell activation. Although there remains much that is not understood about APC activity in the healthy eye, there is during uveitis an up-regulation from very low levels in the healthy retina of MHC class II on infiltrating macrophages and microglial cells.¹²¹ This suggests that in uveitis there is conventional processing and presentation of Ag, but not in the healthy retina. In the spleen of mice that have recovered from EAU there is a defined population of APCs that counter-convert Ag-specific effector T cells into Ag-specific inducible Treg (iTreg) cells.¹¹⁵ These iTreg cells provide protection from reactivation of uveitis and prevent recall immunity to retinal autoantigens. Therefore, during the resolution of EAU there is a tolerogenic APC that has processed and presented Ag in a conventional manner to affect autoantigen-specific effector T cells. Mice without MC5r, like WT mice, self-recover from EAU, but do not have this defined population of suppressor APC in their spleens; therefore, do not generate the protective iTreg cells.^{73,79,115} When the MC5r knockout mice are reimmunized to the retinal autoantigen after recovery from EAU they display a recall response with rapid development and severe uveitis.¹²² This is in contrast to reimmunized WT mice recovered from EAU that show a naive immune response with delayed and mild uveitis. As the eyes recover from uveitis, they appear to be using the mechanisms of immune privilege and tolerance to restore an anti-inflammatory microenvironment. It is not clear if this is possible in every human with uveitis, but the negative regulators of immunity within the eye are evolutionarily conserved in expression and function. It is possible that species variance in the strengths of these regulatory pathways are associated with susceptibility and recovery to autoimmune disease.

Microglial cells of the retina are potential cellular regulators of inflammation.^{21,123–125} Microglial cells are resident immune cells of the brain and retina that are derived from yolk sac blood islands.^{126–128} Although they have the potential to express MHC class II, they do so at a very low level.^{124,129} Microglial cells perform immune surveillance, and activate upon pathologic changes.^{130–132} Even the slightest changes like bright light injury, microglial cells adopted an amoeboid shape and moved to the site of retinal injury.¹³³ In the inflamed retina macrophages and microglial cells up-regulate their expression of iNOS and produce of proinflammatory cytokines including TNF- α , IL-1, CCL22.^{21,134,135} However, microglial cells in the healthy retina may have a more anti-inflammatory function mediated by the negative regulators of α -MSH and NPY produced by RPE, and by CD200 expressed on neural and epithelial cells of the retina.^{21,136} When microglial cells in healthy retinas were stained for the proinflammatory enzyme iNOS and for the anti-inflammatory marker enzyme Arginase-1 they costained for both.²¹ The coexpression of iNOS with Arginase-1 is a characteristic of myeloid suppressor cells.^{137,138} When the retina is injured this coexpression is lost, and corresponds with diminished production of α -MSH by RPE.²¹ This makes the microglial cells sentinels of immune privilege. Their expression of myeloid suppressor cell activity means that they prevent T cell activation and suppressive activity that would induce inflammation. Changes in their activity would have a significant effect on the

ocular microenvironment to prevent inflammation and autoimmune disease. Since the RPE produce negative regulators of inflammation that induce suppressor activity in the microglial cells, it indicates that there is an important communication link between the cells to maintain ocular immune privilege and retinal health.

3 CONCLUSIONS

Our understanding of the mechanisms of ocular immune privilege has moved beyond the original description of a tissue site that is isolated from the immune system by a blood barrier and lack of direct lymphatic drainage.^{1,10} The ocular microenvironment actively suppresses the induction of inflammation through soluble and membrane bound negative regulators. Moreover, the ocular microenvironment is not just anti-inflammatory. Although the negative regulators suppress activation of inflammation, the same negative regulators promote and possibly select for immune cell behaviors of suppressors of inflammation and immune tolerance. Therefore, immune privilege is a biologic adaptation of a tissue to suppress inflammation, and select immune cell activity to protect and preserve itself from the damage of inflammation. In the eye, it is to preserve and protect the ocular microenvironment to maintain clear vision.

The studies of ocular immunobiology present the possibility that the mechanisms of immune privilege are mediated by the constitutive expression of a specific pattern of molecular negative regulators. Supporting this idea is that in each study of a soluble or membrane bound regulators, when an individual regulator is neutralized or knocked-out there is significant loss in various mechanisms and characteristics of immune privilege.

^{16,51,79,113,115,139–141} It is not clear if all of the regulators need to be expressed; however, of the negative regulators of inflammation discussed in this review, TGF- β 2, α -MSH, PD-L1, and FasL affect multiple pathways of inflammation. They are also associated with inducing anti-inflammatory and immune tolerance activity in macrophages, APCs, and T cells.

Within the healthy eye only a few immune cells are seen and are mostly myeloid cells and microglial cells. These cells are programed to suppress inflammation and promote immune tolerance. Such cells can be generated in vitro by the soluble negative regulators produced within the eye.^{23,74} They can be adoptively transferred, as well as the cells from the eye to confer suppression of inflammation and immune tolerance.^{26,108} It could be argued that immune privilege is not solely the presence of specific negative regulators, but also the presence of cellular negative regulators of inflammation. This would suggest that a cell base therapy involving the generation of suppressor myeloid cells presenting ocular Ags, or Treg cells specific to ocular Ags would be as effective in suppressing inflammation and reestablishing ocular immune privilege as using the molecules of immune privilege.

Of the negative regulators of inflammation found in the eye, α -MSH is one of the few ocular regulators that suppresses inflammation and induces regulatory and tolerogenic immunity. Treatment of uveitic mice with α -MSH not only suppresses uveitis it promotes expansion of APC that convert autoantigen-specific effector T cells into Treg cells. It is as if α -MSH therapy had reset the immune response in its recognition of retinal self-Ags.

^{73,75,113,115,142–144} This therapy has the capacity of generating immune tolerance with

potential long-term immunosuppression.^{73,115,144} Whether α -MSH reestablishes all mechanisms of immune privilege is to be seen; moreover, as research progresses the potential of other negative regulators being important in reestablishing ocular immune privilege will definitely be found. The advantage of using the eye's own negative regulators of inflammation is that the eye is already well tolerant to these molecules, and is already set to be receptive to their anti-inflammatory activity.

It has been almost 70 years since Peter Medawar used the phrase immune privilege to describe the immunobiology of the ocular microenvironment.¹ Although we still have much more to go in understanding the actions of immune cells within the healthy and diseased eye, we have a much clearer understanding of the molecular and cellular negative regulators of inflammation within the immune privileged eye. It still remains whether it is possible to use these molecules and cells to restore immune privilege in uveitic eyes, and to whether they can be used to impose immune privilege on other tissues to suppress autoimmune disease and allograft rejection.

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Abbreviations

α-MSH	α -melanocyte stimulating hormone
ACAID	anterior chamber-associated immune deviation
FasL	Fas ligand
iTreg	inducible Treg
RPE	retinal pigment epithelial
Tregs	regulatory T cells
TSP-1	thrombospondin-1
WT	wild-type

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Table 1

The effects of molecular negative regulators of ocular immune privilege

(A) Molecular negative regulators that suppress inflammation by:	
Innate immune cells	
<i>α</i> -MSH ^a , VIP, CGRP, SOM, MIF, PEDF, CRP	
Activated M1 macrophages	
TGF- <i>β</i> 2, <i>α</i> -MSH, CGRP, VIP, NPY	
Th1, Th2, and Th17 cells	
TGF- <i>β</i> 2, <i>α</i> -MSH, VIP, SOM, FasL	
(B) Molecular negative regulators that activate:	
Tolerogenic APC	
TGF- <i>β</i> 2, TSP-1, <i>α</i> -MSH	
Treg cells	
TGF- <i>β</i> 2, <i>α</i> -MSH, PD-1L, CTLA-2 <i>α</i> , RA	

^a*α*-MSH (alpha-melanocyte stimulating hormone),^{16,17,73–75,78,92,96,106,108,111–113,115,143,145} CGRP (calcitonin gene related peptide),^{140,146,147} CRP (complement regulatory proteins),^{148–150} CTLA-2*α* (cytotoxic T-lymphocyte associated protein-2alpha),²⁸ MIF (migration inhibitory factor),¹⁵¹ NPY (neuropeptide Y),^{21,106,152–155} PEDF (pigment epithelial derived factor),^{51,156} RA (retinoic acid),⁵⁰ SOM (somatostatin),^{51,141,157,158} TSP-1 (thrombospondin-1),^{19,125} TGF-*β*2^{19,23,53,159},VIP (vasoactive intestinal peptide).^{139,160,161}