Published in final edited form as:

Ocul Immunol Inflamm. 2017 April ; 25(2): 179–189. doi:10.3109/09273948.2015.1092560.

The Role of Alpha-MSH as a Modulator of Ocular Immunobiology Exemplifies Mechanistic Differences between Melanocortins and Steroids

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Abstract

Melanocortins are a highly conserved family of peptides and receptors that includes multiple proopiomelanocortin-derived peptides and five defined melanocortin receptors. The melanocortins have an important role in maintaining immune homeostasis and in suppressing inflammation. Within the healthy eye, the melanocortins have a central role in preventing inflammation and maintaining immune privilege. A central mediator of the anti-inflammatory activity is the non-steroidogenic melanocortin peptide alpha-melanocyte stimulating hormone. In this review we summarize the major findings of melanocortin regulation of ocular immunobiology with particular interest in the ability of melanocortin to induce immune tolerance and cytoprotection. The melanocortins have therapeutic potential because their mechanisms of action in regulating immunity are distinctly different from the actions of steroids.

Keywords

alpha-MSH; eye; glucocorticoids; melanocortins

INTRODUCTION

The melanocortin (MC) system encompasses multiple peptides including α-, β-, γ-melanocyte stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), and five MC receptors (MCR1-5) that are expressed in a multitude of cells and tissues.[1,2] The MC peptides and receptors are highly conserved across multiple species[3] from lower vertebrates to vertebrates and appeared early in evolution[2] but remain largely unchanged,[4] suggesting a critical and ubiquitous role. The role of the MC system in the neuroendocrine control of inflammation is understood and known to be affected by the release of corticotropin-

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DECLARATION OF INTEREST

CMC and JY are employees of Mallinckrodt Pharmaceuticals, and AWT has been a consultant for Mallinckrodt Pharmaceuticals.

releasing hormone in response to infection or stress; this stimulates the production of pro-opiomelanocortin (POMC), which is processed to generate the MC peptides. The myriad functions of the MCs are carried out through their binding to the five known MC receptors, each of which is expressed in specific cell types.[5,6] ACTH stimulates melanocortin receptor 2 (MC2R) on the adrenal cortex to produce glucocorticoids (GCs). Although the anti-inflammatory effects of GCs are well known and are one way in which MCs control inflammation indirectly, there is a growing understanding of the distinct and direct effects of GCs and MCs as immune modulators (Table 1).

It has long been established that GC production is controlled selectively by ACTH, and that ACTH induces steroidogenesis via binding to MC2R. MC2R is abundantly expressed from the adrenal cortex, specifically the zona fasciculata, where the GCs are produced, and the zona glomerulosa, where the mineralocorticoid aldosterone is produced.[7] The essential role of MC2R in steroidogenesis is clear as mutations in MC2R result in familial GC deficiencies[8] and *Mc2r* null mice lack adrenal gland development and steroid production.[9] The MC receptors have varying affinities for the different MCs, but all recognize a highly conserved sequence (HFRW) that is common to all MC peptides.[10] Unlike the other MC receptors, MC2R exclusively binds ACTH[7,11] and this specificity is conferred by peptide sequences that are unique to ACTH.[12] Animal studies confirm that α-MSH is not capable of stimulating GC secretion[13,14] and only ACTH was able to restore wild-type GC production in a *Pomc* null model.[15] Thus, the anti-inflammatory effects of α-MSH are not due to the induction of GC production.

To dissect the direct, non-steroid-mediated effects of MCs in whole organisms multiple approaches have been used. Adrenalectomization,[16–18] MCR knockouts,[19–23] and administration of specific MCs such as α-MSH[24–27] have all been applied to demonstrate the direct pleiotropic effects of the MC system in controlling inflammation. MCs control inflammation through specific downstream modulation of immune cells, processes, cytokines, and chemokines.[2,4,28] These studies have helped to uncover how MCs utilize different MCRs in specific cells and tissues to regulate acute, systemic, and chronic inflammation and provide a strong foundation for their use to treat a variety of inflammatory conditions.

ADVERSE EFFECTS OF GLUCOCORTICOIDS ON THE EYE

Although GC therapy has been a mainstay in the treatment of inflammation for decades, it affects many different cells beyond the immune system. Acting via the GC receptor, GCs utilize both transactivation of target genes and transrepression mechanisms to regulate a number of transcription factors including NFkB, AP-1, and p38 MAP kinase[29,30] and influence a number of different pathways including stress responses, metabolism, and development. As such, the profile of undesirable side effects from prolonged systemic GC therapy is significant and includes bone loss, diabetes, muscle wasting, impaired wound healing, gastric ulcers, weight gain, cardiovascular disease, and neuropsychiatric issues.[31,32]

In the eye, the adverse effects of GCs include increased intraocular pressure (IOP), which is directly associated with the development of glaucoma.[33–35] IOP is regulated in part by

outflow of the aqueous humor via the trabecular meshwork (TM), and increased resistance in this outflow pathway is one of the primary causes of elevated intraocular pressure that can lead to glaucoma.-[36] GCs are known to increase outflow resistance of the TM in some individuals.[37,38] This GC sensitivity could be due to variation in the relative levels of alternatively spliced GC receptor isoforms in the TM.[39,40] GCs have numerous effects on the TM, including changes in TM morphology, gene expression, extracellular matrix, and cytoskeleton as well as inhibition of phagocytosis, proliferation, and migration of TM cells.[41] Also, GC treatment causes apoptosis in bovine TM cells,[38] and in human TM cells at high concentrations.[42] While the exact mechanism by which GCs increase IOP is unclear, it has been reported that 40–60% of patients undergoing chronic GC therapy develop ocular hypertension.[43] These adverse effects are also dependent on the type of GC therapy. A recent study on the treatment of uveitis with steroid implants[44,45] found that 65% of patients treated with these implants developed increased IOP and 23% developed glaucoma. In comparison, increased IOP was noted in 49% of patients undergoing periocular GC injections,[46] and 24% of those receiving systemic therapy, composed of GCs and immunosuppressive medications, developed increased IOP.[45]

Beyond influencing intraocular pressure, GC therapy has been linked to cataract formation, primarily posterior subcapsular cataracts.[47–51] Lens epithelial cells are known to express GC receptors[52] and GC treatment induces significant gene expression changes in these cells.[53,54] The exact mechanism by which GC treatment induces cataract formation is probably complex. GCs have been shown to induce apoptosis in lens epithelial cells,[55,56] but GC treatment also disrupts the differentiation and proliferation of lens cells and causes their aberrant migration to the posterior pole of the lens.[57] These factors, as well as changes to the lens environment, via GC effects on other ocular tissues, may all contribute to cataract formation. One meta-analysis of several studies reported that approximately 22% of patients undergoing systemic treatment with GCs developed cataracts, which was correlated with the dosage and duration of treatment.[49] Similarly, 20% of patients receiving periocular GC injections developed cataracts within 12 months.[46] However, a recent study found that 91% of patients receiving steroid implants for uveitis developed cataracts within 24 months.[44]

α-MSH AND THE EYE

The microenvironment of the eye is immune privileged in that it has several mechanisms to suppress the action of inflammation. Over the past couple of decades it has become clear that melanocortin pathways have an important role in maintaining immune privilege.[58–60] The melanocortin pathways are involved in suppressing proinflammatory signals and, unlike steroids, promote the immune system to regulate itself within the ocular microenvironment. Aqueous humor, the fluid filling the anterior chamber of the eye, suppresses the *in vitro* activation of immune cells that mediate hypersensitivity;[61] moreover, these aqueous humor-treated immune cells are able to suppress other hypersensitivity-mediating T cells.[62] At the molecular level this immunoregulatory activity of aqueous humor is mediated by α-MSH. Although TGF-β2 is the most abundant anti-inflammatory factor in aqueous humor,[63–65] it exists in a latent form and must be activated before it can affect immune cells whereas the effects of α-MSH are more immediate. *In vitro* studies have demonstrated that TGF-β2 is an enhancer of the immune regulating activity induced by α-MSH.[66]

In the healthy eye there is constitutive expression of α-MSH. In aqueous humor the physiological concentration is around 30 pg/mL and the level of α-MSH is relatively constant among mammals. The sources of α-MSH production in the eye are not fully known; however, retinal pigment epithelial (RPE) cells have been shown to be a source of α-MSH.[60] In culture, RPE cells produce about 2 ng of α-MSH in 24 hours[58,60] and express the necessary endopeptidases and post-translational enzymes to process a functional α-MSH peptide from POMC.[67] Other cells in the eye, such as the cells of the iris and ciliary body, also express these enzymes, suggesting that they are also potential sources of α-MSH.[68] At ocular physiological concentrations under serum-free conditions *in vitro*, as found within the ocular microenvironment, α-MSH is highly potent and suppresses most signals of inflammation while stimulating regulatory activity.[26,58,60,62,66,69] Evidence suggests that there is a loss of α-MSH expression in eyes with autoimmune disease or damaged retinas.[60] Treatment of mice suffering from ocular inflammation (uveitis) with α-MSH suppresses the inflammation, and may re-establish some features of immune privilege and immune regulation.[22,70–72] The finding of α-MSH activity within the eye has not only promoted examination of the role of neuropeptides in regulating immunity but, more importantly, has also provided molecular mechanisms for the anti-inflammatory activity seen within the immune privileged eye.

Activated effector T cells treated with aqueous humor or α-MSH produce their own TGF-β, are FoxP3 positive, and function as $CD4^+CD25^+$ inducible Treg (iTreg) cells.[69,73] In addition, these α-MSH-induced iTreg cells require reactivation to their cognate antigen to mediate suppression, although the mechanism of suppression mediated by the α-MSH–induced iTreg cells is non-specific and will suppress all inflammatory activity in their immediate microenvironment. The induction of regulatory immunity instead of complete suppression of inflammation provides the eye with a directed mechanism of protection against autoimmune attack. Induction of regulatory immunity by α-MSH is mediated through its effects on both the antigen presenting cells (APC) and on effector T cells through their expression of melanocortin receptors 1, 3, and 5.[26,72,74–77] The induction of regulatory immunity and signaling through melanocortin receptors other than MC2R provides a strong indication that α-MSH might be an alternative non-steroidogenic therapeutic approach to regulate immunity.

The RPE, through α-MSH together with another neuropeptide NPY, promotes the differentiation of macrophages into suppressor cells that suppress inflammation and immunity.[60] This regulation also appears to convert the retinal microglial cells into suppressor cells. The benefit of such cells is that, although they occupy a tissue microenvironment that is hypoxic and full of oxidized byproducts, they are not activated to mediate inflammation;[60,78,79] on the contrary, they suppress the activation of inflammation and effector T cells. RPE cells from wounded retinas are diminished in α-MSH production and support the activation of macrophages that mediate inflammation.[60] Therefore, in ocular disease, changes in RPE production of α-MSH may contribute to the disease pathology. The RPE-induced suppressor cells are not themselves suppressed in immune activity. While they continue to phagocytize opsonized materials, α-MSH suppresses the activation of phagolysosomes.[80,81] The implication is that although α-MSH-affected cells can clear materials through phagocytosis, they cannot process or degrade the materials through

conventional acidic-lysosome pathways. This may be a mechanism of immune privilege by which processing of recognizable autoantigen peptides for MHC presentation is prevented. One interesting phenomenon is that, without α-MSH, healthy RPE cells induce apoptosis in macrophages.[60,81] While the mechanism by which RPE induces apoptosis in the macrophages is unknown, this unique finding suggests that a macrophage responding to α-MSH is protected from apoptosis;[82] however, such a rescued macrophage will now be a suppressor cell. This could be part of a mechanism of immune privilege to select for immune cells that can be manipulated to be suppressor cells within the healthy retina. This mechanism is highly dependent on the production of α-MSH by the RPE.

There is increasing evidence that specific melanocortin receptors may be associated with different actions of α-MSH (Figure 1). While the suppression of pro-inflammatory signals on innate immune cells by α-MSH is thought to occur most often through MC1R and MC3R,[74,75] the activation of regulatory activity appears to be through MC5R.[26,77] The role of MC5R in regulation is seen in the difference between wild-type mice and *Mc5r* knockout mice that have recovered from experimental autoimmune uveitis (EAU).[83] Mice, unlike humans, recover from EAU without medical intervention. Post-EAU spleens of wild-type mice exhibit regulatory immunity that provides resistance to reactivation of the autoimmune uveitis.[77,84] Mice without MC5R recover from EAU on their own, but they lack this regulatory immunity in the spleen.[84] If the post-EAU *Mc5r* knockout mice are reimmunized to reactivate EAU, they display an immediate reactivation of uveitis that becomes extremely severe. If the spleen cells from post-EAU wild-type mice are adoptively transferred to *Mc5r*-knockout mice before the reimmunization, the second episode is suppressed. This finding demonstrates that mice possess a melanocortin-dependent induction of regulatory immunity that prevents a memory immune response to autoantigen of the retina and a systemic resistance to retinal autoantigens.

The MC5R-dependent regulatory immunity can be induced during uveitis by injecting α-MSH peptide into the EAU mice.[22,72,77] This has also been demonstrated in the mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis.[85,86] Both antigen presenting cells (APC) and effector T cells express MC5R, and can be the target of α-MSH induction of regulatory activity. As described above, treating activated effector T cells with α-MSH induces the expansion and activation of inducible Treg cells.-[26,69] Blocking MC5R or using T cells from immunized MC5R knock-out mice prevents α-MSH induction of regulatory activity. α-MSH upregulates expression of FoxP3 in T cells, indicating that α-MSH promotes T cell differentiation into regulatory cells.[69] There is very little cytokine production by these α-MSH-treated T cells, other than TGF-β. The cells function as regulatory T cells, and through adoptive transfer, suppress inflammation within the tissue microenvironment where their antigen specificity is presented.[62,77,87] Therefore, by stimulating MC5r with α-MSH peptide or a melanocortin analogue that targets only MC5r, it is possible to create a unique population of Treg cells from antigen-specific T cells that can be used to target tissues of inflammation, graft rejection, and autoimmune disease.

When the spleen cells from the post-EAU mice were examined, it was not the T cells but rather the APC that were MC5R dependent for regulatory activity.[77] These APC are unique in that they express markers of both myeloid and granulocytic cells. They are found in the

spleens of mice, but mediate regulatory immunity only after EAU and only if MC5R is expressed. Resting APC stimulated by α-MSH express the ectoenzymes that convert ATP into adenosine.[72] There is also an increase in their expression of PD-L1, a surface adhesion protein that regulates T cell activation.[73] They process and present antigen and, when mixed with antigen specific effector T cells, the APC promote regulatory activity by the T cells. These Treg cells have the characteristics of inducible Treg cells, suggesting that α-MSH, through MC5R, upregulates APC generation of adenosine and expression of PD-L1 to promote the counterconversion of effector T cells into inducible Treg cells.[72,73] Therefore, as part of the resolution of EAU, there is a melanocortin-dependent pathway that localizes in the spleen a unique population of APC that promote the activation of protective autoreactive T cells (Figure 2). This pathway can be induced by α-MSH therapy and, since expression of the melanocortins is conserved, has the potential to be a new therapeutic approach to suppression of autoimmune disease in humans. It will be of interest to see whether this is a pathway that, while spontaneously activated in mice, needs to be awakened in humans with a melanocortin-based therapy.

These studies have shown that the MCs have an extremely important role in preventing inflammation within the eye. In addition, there is strong potential for use of the MC system in therapy for uveitis. Also, therapeutic benefits of using the MCs may go beyond immune regulation within the eye. Through MC1R, α-MSH protects the RPE from oxidative stress-induced apoptosis.[88] In addition, α-MSH may have neurotrophic activity that promotes photoreceptor survival.[89] This suggests that, besides the anti-inflammatory and immune regulating activity of α-MSH therapy, there will be an additional benefit of maintaining and promoting the health of other cells of the retina. Therefore, the MCs hold an important role in maintaining an anti-inflammatory microenvironment and in the general health of the retina. Moreover, the anti-inflammatory and immune-regulating activity of the melanocortins has the potential to provide a novel therapeutic approach to many autoimmune and inflammatory diseases. This approach contrasts with the general suppression of immunity by GCs and with the biologic therapies that target one specific proinflammatory cytokine at a time. MC therapy manipulates the immune cells to function in a manner that suppresses inflammation and promotes immune tolerance and cell survival to potentially regenerate a healthy ocular microenvironment (Figure 3).

MELANOCORTINS AS ALTERNATIVES TO GLUCOCORTICOIDS

GCs have been the primary therapeutic option for the treatment of ocular inflammatory disorders for over 60 years.[90] Despite the popularity of GCs for treatment, they have a number of side effects that cause serious complications. As mentioned above, a significant portion of the population is susceptible to increased IOP from treatment with GCs. In addition to the well-documented relationship of GCs with glaucoma and cataracts, GC therapy can also lead to a number of other adverse effects in the eye including viral retinitis-[91] and central serous chorioretinopathy,[92,93] which is characterized by serous fluid accumulation in the retina resulting in localized detachment of the neurosensory retina.[94] GC therapy is also associated with an increased risk of infection, impaired wound healing, and thinning of the cornea.[95,96]

In contrast, α-MSH is present in the aqueous humor of the eye and acts to prevent inflammation that could be damaging to the eye.[58,97] α-MSH has the ability to influence T cells in a positive immune modulating capacity by suppressing immune response through the release of inhibitory cytokines, metabolic inhibition, or cytolysis of effector T-cells and by suppressing the maturation of dendritic cells.[58,59,66,69,98,99] α-MSH suppresses production of proinflammatory cytokines, including IFN-γ[58] and TNFα,[100] while increasing production of anti-inflammatory cytokines such as IL-10.[101] In addition to its anti-inflammatory actions, α-MSH has been shown to suppress apoptosis in a number of cell types.[82,102–104] The immune modulation exhibited by α-MSH, coupled with its distinctive cytoprotective effect, makes α-MSH a potentially advantageous alternative treatment and has generated a number of mechanistic studies to examine α-MSH as a therapeutic tool in the treatment of ocular inflammation. Use of α-MSH and its analogs to treat uveitis in a variety of model systems has shown them to be effective in reducing the severity and promoting resolution of inflammation.[22,70,105] In addition to the treatment of inflammatory disorders, topical α-MSH has been shown to transiently lower intraocular pressure,[106] which contrasts with the increase in pressure often seen with GC treatment. While the anti-inflammatory actions of GCs suppress the immune system, MCs appear to have multipathway immunomodulatory properties to handle the acute inflammation with pro-resolving properties that alter the phenotype of immune cells, allowing them to be more modulatory.[20]

MCs have potent anti-inflammatory and cytoprotective functions in reducing inflammation and inducing resolution in other tissues and conditions. α-MSH normalizes oxidative stress, diminishes apoptosis, and reduces retinal damage in diabetic retinopathy.[104,107] In rodent model systems, MCs promote restoration of nerve damage from spinal cord injury,[108,109] modulate inflammation, and attenuate apoptosis and damage after traumatic brain injury.[110] Recently, α-MSH has been demonstrated to protect against brain damage and cognitive decline in murine models of Alzheimer's disease.[111–113]

The neuroprotective functions of α-MSH can also reduce the severity of autoimmune encephalomyelitis (EAE) in rodent models.[85,114] This contrasts with GCs, which have been found to increase apoptosis of retinal nerve ganglion cells in EAE models.[115] EAE is an inflammatory demyelinating disease of the central nervous system which, importantly, is a model system for multiple sclerosis (MS). ACTH has been known to be effective in the treatment of MS for many years.[116] Historically, the effects of ACTH therapy in MS were thought to be due to the promotion of steroidogenesis through binding of MC2R. However, several studies now indicate that ACTH functions in alleviating MS exacerbations via binding to other MC receptors rather than by the induction of steroid production.[117] This, along with results from model systems such as EAE, suggests that MS may be successfully treated with MC peptides.

MCs also exhibit cytoprotective properties that oppose the damaging effects of GCs. A significant side effect of systemic GC therapy is osteoporosis.[118] Although ACTH induces steroidogenesis, this results in a lower plasma level of GCs than typical steroid administration[119,120] and, moreover, has a cytoprotective effect on bone and can protect against osteonecrosis induced by GCs.[121] In addition, while GC therapy can increase the

risk of infection, α-MSH and its analogues have been shown to have significant antimicrobial activity.[122,123]

The differences noted above suggest that MCs may offer a less toxic alternative to GCs for the treatment of inflammation. Toxicity studies found that massive doses of α-MSH, 5000-fold greater than the dose necessary to affect thermoregulation in rabbits, were required before toxicity became lethal in some animals.[124] Furthermore, α-MSH and analogues have been shown to have no significant adverse effects in clinical studies, especially in comparison to other anti-inflammatory therapies.[125–131]

CONCLUSION

Melanocortins have shown promise in the treatment of a number of autoimmune disorders. α-MSH administration reduces disease activity in model systems of rheumatoid arthritis,[132] systemic lupus erythematosus,[133] and inflammatory bowel disease.[134] Recent evidence has shown that ACTH is effective in lupus,[135] dermatomyositis or polymyositis,[136] infantile spasms, MS, and nephrotic syndrome.[137] These are all indications in which steroids are generally considered the mainstay of treatment, and where their toxic side effects often require an alternative therapy. Importantly, in several of these indications, MCs have shown to be efficacious where steroids alone have been ineffective,[137–139] further suggesting their mechanism of action is distinct from steroids (Table 1).

Acknowledgments

Writing support for this manuscript was provided by Kelly P. Smith, and financial support for AWT was provided in part from the Massachusetts Lions Eye Research Foundation.

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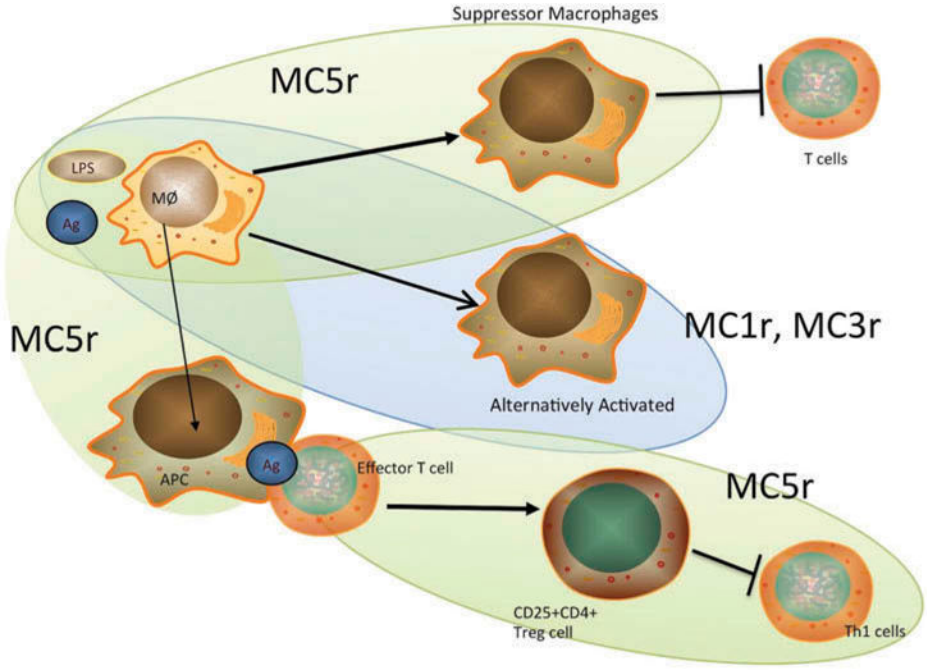

FIGURE 1.

Effects of different melanocortin receptors on immune activity. Through MC1r, MC3r, and MC5r, α-MSH suppresses inflammation and promotes the activation of anti-inflammatory activity and regulatory immunity. In macrophages, through MC1r and MC3r, α-MSH mediates alternative activation by which the macrophages suppress inflammation.[74,75] Through MC5r, α-MSH mediates the activation of suppressor cell activity in macrophages that suppresses effector T cell activation and viability.[58,60] Through MC5r on T cells, α-MSH promotes the activation of regulatory T cell activity and the suppression of effector T cells.[26,69] In addition, through MC5r, α-MSH induces antigen presenting cells to promote activation inducible Treg cells[72, 77] (see Figure 2). Ag, antigen; LPS, lipopolysaccharide; MØ, macrophage.

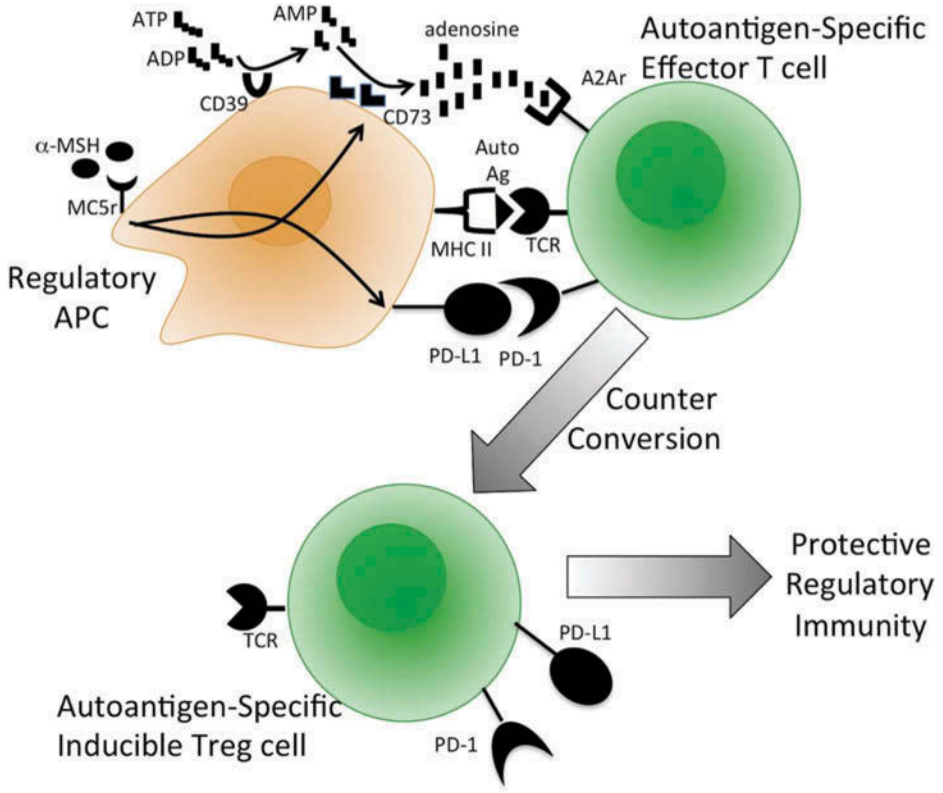

FIGURE 2.

Melanocortin-driven induction of autoantigen-specific protective immunity. Self-resolution or α-MSH treatment of experimental autoimmune uveitis in mice is followed by the induction of autoantigen-specific Treg cells that provide resistance to the recurrence of uveitis.[72,84] This is driven by the action of α-MSH, through MC5r on macrophages, to induce antigen presenting activity that counter-converts autoantigen-specific effector T cells into inducible Treg cells.[2,77] α-MSH upregulates APC generation of adenosine and expression of PD-L1.[72] This process requires autoantigen-specific effector T cells expressing the adenosine 2A receptor.[72] Ag, antigen, CD39, ecto-nucleoside triphosphate diphosphohydrolase 1; CD73, ecto-5′-nucleotidase; MHC II, major histocompatibility class II antigen; TCR, T-cell receptor.

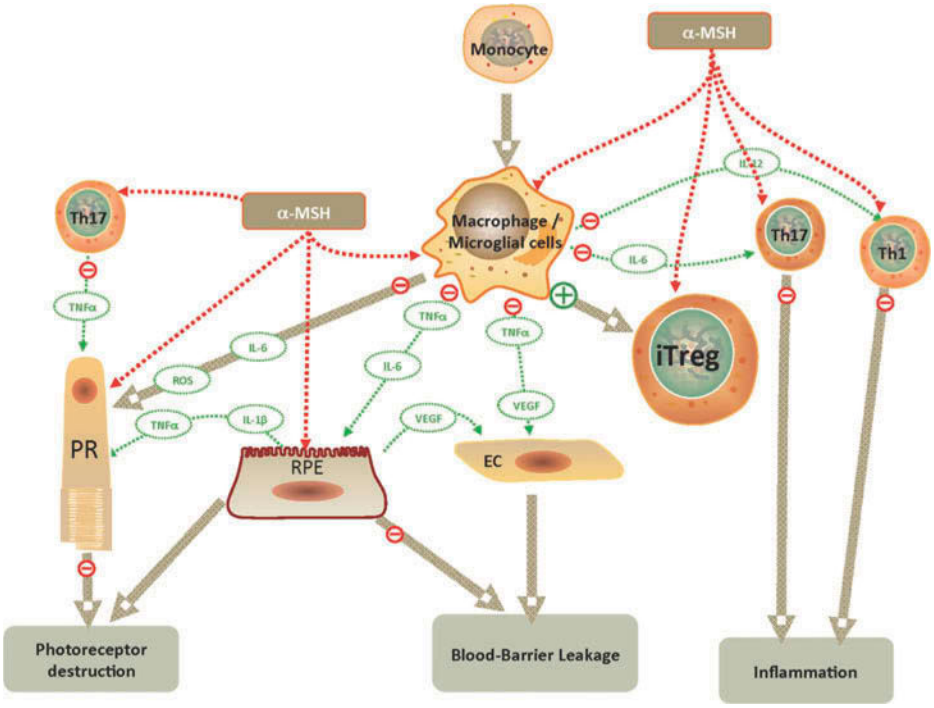

FIGURE 3.

Effects of α-MSH on uveitis and retinal cell health. Therapeutic application of α-MSH has the potential to suppress inflammation, induce immune tolerance, and promote retinal cell survival (see text). α-MSH can directly influence immune cells through their expression of melanocortin receptors to suppress activation of effector T cells (Th1, Th17 cells), while promoting iTreg cell activation. In macrophages, α-MSH suppresses production of proinflammatory cytokines and promotes antigen presenting activity that converts effector T cells into functional iTreg cells. In addition, RPE and photoreceptors express melanocortin receptors through which α-MSH promotes cell survival. EC, endothelial cell; IL-1β, -6, -12; interleukin-1beta, -6, -12; iTreg: inducible Treg cells; RPE, retinal pigment epithelial cells; PR, photoreceptor cell; ROS, reactive oxygen species; Th: T helper cells; TNFα; tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

TABLE 1

Effects of glucocorticoids and α–MSH on the eye.

	Glucocorticoid	α–MSH
Immune effects	• Suppresses proinflammatory signals • Suppresses immune cell activity	• Suppresses proinflammatory signals • Promotes production of anti-inflammatory cytokines • Induces suppressor antigen presenting cells • Induces the activation of regulatory T cells • Natural regulator of immunity in healthy eyes
Optic nerve effects	• Indirect damage of optic nerve due to increased intraocular pressure • May sensitize nerve cells to disease-induced apoptosis	• Transiently lowers intraocular pressure • Can protect neuronal cells from damage
Adverse effects	• Causes cataracts • Induces increased intraocular pressure and glaucoma • Many other adverse effects	• No known adverse effects