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Ocular immune privilege and ocular melanoma: parallel universes or immunological plagiarism?

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Evidence of immune privilege in the eye was recorded almost 140 years ago, yet interest in immune privilege languished for almost a century. However, the past 35 years have witnessed a plethora of research and a rekindled interest in the mechanisms responsible for immune privilege in the anterior chamber of the eye. This research has demonstrated that multiple anatomical, structural, physiological, and immunoregulatory processes contribute to immune privilege and remind us of the enormous complexity of this phenomenon. It is widely accepted that immune privilege is an adaptation for reducing the risk of immune-mediated inflammation in organs such as the eye and brain whose tissues have a limited capacity to regenerate. Recent findings suggest that immune privilege also occurs in sites where stem cells reside and raise the possibility that immune privilege is also designed to prevent the unwitting elimination of stem cells by immune-mediated inflammation at these sites. Uveal melanoma arises within the eye and as such, benefits from ocular immune privilege. A significant body of research reveals an intriguing parallel between the mechanisms that contribute to immune privilege in the eye and those strategies used by uveal melanoma cells to evade immune elimination once they have disseminated from the eye and establish metastatic foci in the liver. Uveal melanoma metastases seem to have "plagiarized" the blueprints used for ocular immune privilege to create "*ad hoc* immune privileged sites" in the liver.

Keywords: anterior chamber, eye, immune privilege, stem cells, uveal melanoma

INTRODUCTION

The roots of immune privilege reach back two centuries to an observation made by the Dutch ophthalmologist van Dooremaal (1873). In an attempt to identify the etiology of cataracts van Dooremaal inserted a variety of foreign objects and tissues into the eyes of rabbits and dogs. Although he failed to discover the cause of cataracts, he observed a significant prolongation in the survival of mouse skin grafts placed into the anterior chamber (AC) of the dog eye (van Dooremaal, 1873). Another 75 years would pass before Medawar "rediscovered" the prolonged survival of foreign tissue grafts placed into the AC of rabbits and coined the term "immune privilege" to describe this phenomenon (Medawar, 1948). Medawar concluded that the apparent absence of lymphatic drainage from the AC resulted in a sequestration of antigens in the eye resulting in a condition that contemporary immunologists might call "immunological ignorance." The late 1970s ushered in a new era in immune privilege research that was led by Streilein and colleagues who made the remarkable observation that antigens introduced into the AC of the eye not only gained access to the peripheral lymphoid tissues, but in the process, induced a systemic down regulation of antigen-specific cell-mediated immunity (Kaplan et al., 1975; Kaplan and Streilein, 1977, 1978). This immunoregulatory phenomenon was termed AC-associated immune deviation (ACAID; Streilein and Niederkorn, 1981). The discovery of ACAID kindled a renewed interest in immune privilege research that has led to numerous insights over the past 35 years. This body of work has revealed that immune privilege is the product of multiple anatomical, physiological, and immunoregulatory processes that share a common feature – restriction of immune inflammation in an organ whose tissues have a severely limited capacity to regenerate.

In addition to the AC of the eye, there are other notable immune privileged sites in the body including the testis, hair follicle, placenta, and brain. The eye is part of the brain, both anatomically and embryologically, and like the brain, has a severely limited capacity to regenerate its tissues. Thus, immune privilege is believed to be an adaptation to protect the eye and the brain from injury inflicted by immune-mediated inflammation. By contrast, the testis, hair follicle, and placenta are sites where stem cells reside. Protecting stem cells from immune-mediated elimination has obvious survival benefits for the host and in the case of the placenta, for the survival of the species. It is noteworthy that many of the mechanisms that sustain immune privilege in the central nervous system (i.e., eye and brain) are also employed in sites where stem cells reside (e.g., testis, hair follicle, and placenta) and by stem cells themselves (Arck et al., 1997; Moffett-King, 2002; Aluvihare et al., 2004, 2005; Niederkorn, 2006; Robertson et al., 2007; Fujisaki et al., 2011; Kinori et al., 2011; Meinhardt and Hedger, 2011; Mital et al., 2011).

The immune system is functionally divided into two basic components: (a) innate immunity and (b) adaptive immunity. The innate immune response is characterized by its rapid activation

and its conspicuous absence of antigen specificity and memory. Components of the innate immune apparatus include natural killer (NK) cells, macrophages, granulocytes, and the alternative pathway for complement activation. Elements of the innate immune response serve as "first responders" to infections and provide a nimble, albeit limited level of protection, which is replaced by the adaptive immune response. The adaptive immune system is characterized by its exquisite antigen specificity and memory. Although slower to develop, the adaptive immune response provides a comprehensive protection that persists longer than the innate immune response and possesses memory that allows for a rapid reactivation to future encounters with pathogens. Both innate and adaptive immune responses are capable of inflicting irreparable injury to ocular tissues and stem cells.

IMMUNE PRIVILEGE AND THE INNATE IMMUNE RESPONSE

Innate immune responses have the potential to inflict significant irreparable damage to the eye. Granulocytes and macrophages elaborate a variety of proteases and reactive oxygen species (ROS) that are known to damage innocent bystander cells. However, the aqueous humor (AH) that fills the AC is endowed with a variety of anti-inflammatory and immunosuppressive cytokines, as well as free radical scavengers that buffer or neutralize proinflammatory cytokines and ROS (Taylor, 2007). Moreover, AH contains factors that induce apoptosis of neutrophils and macrophages (D'Orazio et al., 1999). The complement cascade can be activated through the alternative pathway through exposure to bacterial products and under such conditions it functions as a component of the innate immune system. Complement activation culminates in the generation of a membrane attack complex (MAC) that punches holes in the plasma membrane, which leads to osmotic lysis of both bacterial and mammalian cells. Activation of the complement cascade also generates soluble factors that recruit and activate neutrophils. However, injury inflicted by complement activation is minimized by complement regulatory proteins (CRPs) that are present in the AH and that also decorate the membranes of cells lining the AC (Lass et al., 1990; Bora et al., 1993; Goslings et al., 1996, 1998; Sohn et al., 2000a).

Natural killer cells are members of the innate immune system and are believed to protect against viral infections and neoplasms while the adaptive immune response is still being generated. Cytotoxic T lymphocytes (CTLs) are important elements of the adaptive immune response to viral infections and neoplasms. CTLs recognize viral antigens and tumor antigens that are displayed on major histocompatibility complex (MHC) class I molecules. MHC class I molecules act as the "docking station" that facilitates the binding and cytolytic activity of CTLs. However, to evade CTL-mediated killing many tumors and viruses down-regulate MHC class I molecules and thereby render the cancer cells and virus-infected cells invisible to CTLs. To compensate for this evasive strategy, the immune system enlists the aid of NK cells, which are programmed to kill any cell failing to express MHC class I molecules. However, the corneal endothelial cells that line the AC of the eye and cells in the various layers of the retina express little or no MHC class I molecules and are therefore potentially vulnerable to NK cell-mediated cytolysis. Moreover, corneal endothelial cells and cells of the retina are amitotic and cannot regenerate. However, the AH contains two cytokines that inhibit NK cell-mediated cytolytic activity. Macrophage migration inhibitory factor (MIF) produces an immediate inhibition of NK cell-mediated cytolysis of corneal endothelial cells (Apte and Niederkorn, 1996). Transforming growth factor-β (TGF-β) also inhibits NK cell-mediated cytolysis, but does not produce maximal inhibition for 22–24 h (Apte and Niederkorn, 1996). Thus, the AH is endowed with molecules that produce both immediate and delayed inhibition of NK cell activity. In addition to soluble inhibitory factors, the cells lining the AC express non-classical MHC class Ib molecules such as HLA-E in humans and Qa-2 in mice, which can transmit "off" signals to NK cells (Niederkorn et al., 1999; Le Discorde et al., 2003). The importance of intraocular inhibition of NK cell activity was confirmed in studies in which NK-sensitive human uveal melanoma cells were transplanted either subcutaneously (SC) or into the AC of nude mice. Although nude mice lack a functional T cell repertoire, they display potent NK cell activity. Human uveal melanoma cells were briskly rejected by an NK cell-dependent process when they were transplanted SC in nude mice, but grew progressively in the eyes, even at doses that were 50-times lower than the doses that were rejected following SC transplantation (Apte et al., 1997).

Immune privilege of innate immune responses is also present in sites where stem cells reside such as the hair follicle, placenta, and testis. MIF is expressed in the hair follicle (Ito et al., 2008), Leydig cells of the testis (Meinhardt et al., 1996; Okuma et al., 2005), and in the placenta (Vigano et al., 2007). Moreover, there is a close association between reduced MIF in the hair follicle and the development of alopecia areata, an autoimmune disease of the skin (Ito et al., 2008). MIF produced by human decidual cells of the uterus inhibits the cytolytic activity of uterine NK cells and is believed to contribute to the immune privilege of the allogeneic fetus (Arcuri et al., 2006; Vigano et al., 2007). As mentioned earlier, non-classical class Ib MHC molecules are expressed in the eye and are believed to be important inhibitors of NK cell-mediated cytolysis. It is noteworthy that non-classical class Ib molecules are also expressed in the testis (Slukvin et al., 1999; Ryan et al., 2002) and in the placenta (Kovats et al., 1990; Ishitani and Geraghty, 1992; Rouas-Freiss et al., 1997, 1999). Thus, both soluble and cell membrane-bound molecules that inhibit innate immune responses are expressed in both the eye and in sites where stem cells reside (**Table 1**).

IMMUNE PRIVILEGE AND THE ADAPTIVE IMMUNE RESPONSE

The adaptive immune response is characterized by exquisite antigen specificity and memory. T cells and antibodies are the central players in adaptive immune responses and each has the capacity to produce injury to the eye. Many of the strategies employed to buffer injurious innate immune responses in the eye and in sites of stem cell residence are effective in blocking adaptive immune responses that have the potential to damage stem cells and ocular tissues that cannot regenerate.

ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE FACTORS

The AH contains at least five factors that inhibit the expression of T cell-mediated inflammation: (a) TGF-β; (b) α-melanocyte stimulating hormone (α-MSH); (c) vasoactive intestinal peptide (VIP);

Table 1 | Factors that contribute to immune privilege in the eye and in sites of stem cell residence.

Molecule	Mode of action	Eye	Placenta	BM	Testis	Hair follicle
TGF-β	Inhibit NK cell activity and promote generation of Tregs	Y	Y	Y	Y	Y
MIF	Inhibit NK cell activity	Y	Y	?	Y	Y
MHC class Ib	Inhibit NK cell activity	Y	Y	?	Y	Y
IDO	Deplete tryptophan and induce T cell apoptosis	Y	Y	?	Y	Y
FasL	Induce apoptosis of T cells	Y	Y	?	Y	Y/N
TRAIL	Inhibit T cell proliferation	Y	Y	?	?	?
CRPs	Inactivate complement	Y	Y	?	?	?
PD-L1 (B7-H1)	Inhibit T cell proliferation	Y	?	?	Y	?
Tregs	Inhibit T cell immunity	Y	Y	Y	Y	?

BM, bone marrow; Y, yes; Y/N, indirect evidence; ?, not determined.

(d) calcitonin gene-related protein (CGRP); and (e) somatostatin (Granstein et al., 1990; Cousins et al., 1991; Taylor et al., 1994a,b; Taylor and Yee, 2003). Cells lining the AC also produce indoleamine dioxygenase (IDO), an enzyme that catabolizes tryptophan, which is a key amino acid that is necessary for T lymphocyte survival (Beutelspacher et al., 2006; Ryu and Kim, 2007). CRPs are present in the AH and are also expressed on the cell membranes of many cells lining the interior of the eye. CRPs are effective in maintaining immunological homeostasis within the eye. It is believed that a low level of complement activation is always present in the body, including the eye but under normal homeostatic conditions, CRPs act to restrain the untoward effects of complement activation. As evidence in support this, Sohn et al. (2000b) reported that administration of neutralizing antibody to CRPs in rats resulted in spontaneous ocular inflammation.

Immune privileged sites in which stem cells reside express many of the soluble factors that are found in the AH of the eye and are effective in suppressing adaptive immune responses (**Table 1**). TGF-β is produced by Sertoli cells in the testis (Meinhardt and Hedger, 2011), in the hair follicle (Kinori et al., 2011), and by the placenta (Niederkorn, 2006). Moreover, murine embryonic stem cells (ESCs) themselves upregulate TGF-β2 and create an "*ad hoc*" immune privileged niche in the bone marrow (Robertson et al., 2007). The hair follicle, placenta, and Leydig cells of the testis elaborate α-MSH, which also suppresses T cell immunity *in situ* (Niederkorn, 2006; Kinori et al., 2011; Meinhardt and Hedger, 2011). Although it is not a secreted soluble factor, IDO acts to locally suppress T cell-mediated inflammation by depleting tryptophan and starving T cells. Interestingly, IDO is present in the anterior segment of the eye, in Sertoli cells of the testis, and in the placenta (Mellor et al., 2001; Beutelspacher et al., 2006; Fallarino et al., 2009).

Whether stem cells themselves contribute to the immune privilege in sites where they reside or whether they are beneficiaries of the local immunosuppressive properties of these regions remains unresolved. Numerous studies have reported that ESCs express very low levels of MHC class I molecules and virtually no class II and enjoy a significant degree of immune privilege (Drukker et al., 2002, 2006; Li et al., 2004a; Menard et al., 2005; Bonde and Zavazava, 2006). Moreover, adult stem cells (e.g., either mesenchymal or amniotic origin) themselves display immune privilege (Uccelli et al., 2008). By contrast, there is equally compelling evidence that ESCs are not inherently endowed with immune privilege and can undergo immune rejection (Nussbaum et al., 2007; Robertson et al., 2007; Chidgey and Boyd, 2008; Swijnenburg et al., 2008; Wu et al., 2008). Nonetheless, it is clear that many of the niches in which stem cells reside are classical immune privileged sites that provide a milieu that diminishes the likelihood of inflammation and immune-mediated injury.

CELL MEMBRANE-BOUND MOLECULES

Cells that line the interior of the eye express cell membrane-bound molecules that either induce apoptosis or inhibit proliferation of T cells entering the eye. FasL is expressed throughout the eye and purges activated T cells and neutrophils that enter the eye in response to viral infections or corneal transplants (Griffith et al., 1995; Stuart et al., 1997; Yamagami et al., 1997). PD-L1 is another member of the B7 family of membrane proteins that induce down regulation of T cell proliferation and cytokine production and promote apoptosis of inflammatory cells (Dong et al., 2002; Ding et al., 2005; Saunders et al., 2005; Okazaki and Honjo, 2007). PD-L1 is expressed in both the mouse and human eye (Hori et al., 2006; Shen et al., 2007; Yang et al., 2009) and is necessary for the survival of corneal allografts (Hori et al., 2006; Shen et al., 2007). PD-L1 is upregulated in the eyes of patients with sympathetic ophthalmia and in ocular cells exposed to the proinflammatory cytokines such as TNF-α and IFN-γ, which suggests that PD-L1 serves as a buffer for dampening immune-mediated inflammation of the eye (Yang et al., 2009). Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a member of the TNF family and is expressed on cells lining the interior of the eye and is believed to contribute to ocular immune privilege in a manner similar to that invoked by PD-L1 (Lee et al., 2002; Wang et al., 2003).

Cell membrane-bound molecules are also expressed in stem cell niches. FasL is expressed on Sertoli cells of the testis (Bellgrau et al., 1995) and on the cells of the placenta (Niederkorn, 2006). FasL message is down-regulated in the hair follicles in patients with the autoimmune disease alopecia areata, which suggests that FasL is involved in maintaining immune privilege in the hair follicle (Kang et al., 2010). PD-L1 is found on Sertoli cells of the testis (Dal Secco et al., 2008) and on cells of the placenta (Petroff et al., 2003; Petroff, 2005; Holets et al., 2009). Thus, there is an interesting parallel in the mechanisms and molecules that

sustain immune privilege in the eye and that shield stem cells from immune-mediated elimination.

DYNAMIC IMMUNOREGULATORY PROCESSES THAT SUSTAIN IMMUNE PRIVILEGE

In addition to soluble and cell membrane-bound molecules that dampen immune-mediated inflammation, immune privileged sites are designed to promote the generation of dynamic immunoregulatory processes that down-regulate adaptive immune responses. The seminal studies by Streilein and colleagues in the late 1970s introduced the paradigm of ACAID and the concept that immune privilege was also sustained by regulatory cells that deflected the adaptive immune response away from effector mechanisms that imposed extensive injury to collateral tissues. A plethora of studies have revealed the complex nature of ACAID and have demonstrated that at least four organ systems contribute to the generation of ACAID: (a) eye; (b) thymus; (c) spleen, and (d) sympathetic nervous system (Niederkorn, 2006, 2009; Niederkorn and Stein-Streilein, 2010). The induction of ACAID is initiated when antigens are introduced into the AC. Although it was originally believed that injecting antigens into the AC was tantamount to an intravenous (IV) injection, which is a well-known method for inducing immune tolerance (Asherson and Stone, 1965). However, the eye is not a passive participant in this process and the immune deviation induced by AC injection of antigens is fundamentally different from IV-induced immune deviation (Wilbanks and Streilein, 1990, 1991; Kosiewicz et al., 1998; Sonoda et al., 2001). Removal of the eye within 3 days of AC injection of antigen prevents the induction of ACAID. During this obligatory 3-day period, it is believed that antigen is captured by F4/80$^+$ antigen presenting cells (APCs), which under the influence of cytokines in the AH are imprinted to preferentially produce IL-10 and down-regulate the production of IL-12. The ocular APC emigrate from the eye to the thymus and spleen. Within the thymus the ocular APCs evoke the generation of CD4$^-$,CD8$^-$, NK1.1$^+$ T cells (NKT cells), which subsequently emerge from the thymus and migrate to the spleen via the blood vascular route (Wang et al., 1997, 2001). Like the eye and spleen, the thymus is an active participant in the induction of ACAID. Removing the thymus within 3 days of AC injection of antigen prevents the induction of ACAID (Wang et al., 1997). The sympathetic nervous system is also an active player in the induction of AC AID, as chemical sympathectomy prevents the induction of ACAID (Li et al., 2004b). Although it is not clear how the sympathetic nervous system participates in the induction of ACAID, it appears that the generation of ocular F4/80$^+$ APCs is not affected by the sympathetic nervous system (Li et al., 2004b). However, chemical sympathectomy prevents the generation of thymic NK1.1$^+$ T cells and splenic CD8$^+$ T regulatory cells (T regs; Li et al., 2004b). A population of F4/80$^+$ ocular APCs is also believed to migrate from the eye to the spleen where the APCs secrete MIP-2, which attracts CD4$^+$ NKT cells, which in turn interact with the ocular APCs and secrete RANTES. RANTES recruits other cells into the marginal zone of the spleen. Within the marginal zone of the spleen, F4/80$^+$ APCs, NKT cells, B cells, and CD4$^+$ T cells, under the influence of the third component of complement, collaborate to generate antigen-specific CD8$^+$ T (**Figure 1**).

Pigmented epithelial cells of the iris and ciliary body line a portion of the AC and exert important immunoregulatory effects. The ciliary body cells secrete AH, which contains multiple immunosuppressive and anti-inflammatory molecules (Taylor et al., 1992, 1994a,b, 1997; Taylor and Yee, 2003; Taylor, 2007). In addition to secreting AH, iris and ciliary body cells directly suppress T lymphocyte proliferation and block production of IFN-γ by a contact-dependent process that is independent of the AH-borne soluble factors (Yoshida et al., 2000a). *In vitro* studies have shown that T lymphocytes co-cultured with iris and ciliary body cells acquire Treg activity that inhibits T lymphocyte proliferation and antigen-specific DTH (Yoshida et al., 2000b). The *in situ* generation of T regs requires direct contact between T lymphocytes and the iris and ciliary body cells. The locally generated T regs suppress inflammation by secreting active and latent forms of TGF-β. The only blood vessels in the anterior segment of the eye reside in the iris and ciliary body. Thus, inflammatory cells such as T lymphocytes that enter the AC of the eye extravasate via the iris and ciliary body blood vessels and as a result are in direct contact with the pigmented cells of the iris and ciliary body and thus, are subject to *in situ* induction of T reg activity. The *in situ*-generated T regs greet subsequent waves of inflammatory cells that enter the AC and impose their suppressive effects to further dampen inflammation in the AC.

The AC possesses a second pathway for the *in situ* generation of T regs. Soluble factors in the AH, namely α-MSH, can convert T lymphocytes into CD4$^+$CD25$^+$ T regs that suppress DTH and extinguish immune-mediated inflammation such as experimental autoimmune uveitis (EAU; Nishida and Taylor, 1999; Taylor and Namba, 2001; Namba et al., 2002).

Local induction of T reg activity also occurs in sites where stem cells reside. The allogeneic fetus confronts the mother with alien histocompatibility antigens of paternal origin and thus, is at considerable risk for immune rejection. However, a wide array of anatomical, physiological, and immunoregulatory adaptations protect the fetus from immune rejection. The allogeneic fetus induces a form of immune deviation with striking parallels with ACAID. One might even argue that maternal immune privilege is initiated even before fertilization of the ovum. Seminal fluid contains one of the highest concentrations of TGF-β of any bodily fluid (Robertson et al., 2002) and the TGF-β concentration in the uterine luminal fluid increases over threefold immediately after insemination (Tremellen et al., 1998). Semen, like AH, has the capacity to promote the development of immune tolerance and T regs (Lengerova and Vojtiskova, 1963; Robertson et al., 1997; James et al., 2003). In both humans and mice, there is a steep increase in the number of CD4$^+$CD25$^+$ T regs during pregnancy and depletion of CD4$^+$CD25$^+$ T regs induces abortion in mice (Aluvihare et al., 2004; Somerset et al., 2004). Induction of T regs also occurs in the testis. Soluble antigens injected into the testis induce a form of immune deviation that is reminiscent of ACAID (Li et al., 1997; Ditzian-Kadanoff, 1999; Verajankorva et al., 2002). A recent study demonstrated that allogeneic hematopoietic stem cell transplants reside in the bone marrow where immune reactivity exists, yet the stem cell transplants do not undergo immune rejection (Fujisaki et al., 2011). Allogeneic hematopoietic stem cells reside in the bone marrow in close proximity to CD4$^+$CD25$^+$ T regs. Interestingly,

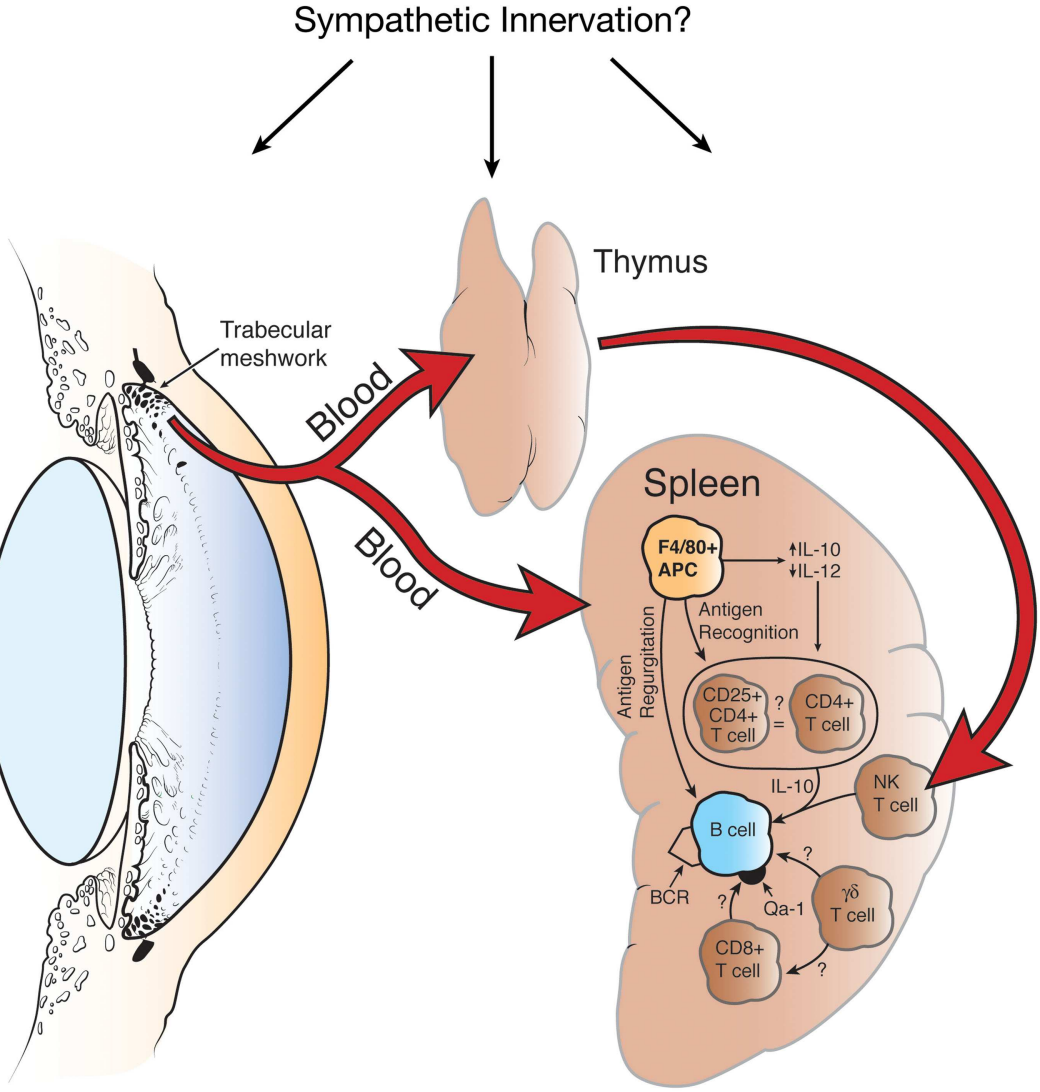

FIGURE 1 | Organ systems involved in the induction of ACAID. Removal of the eye, spleen, or thymus within 72 h of injecting antigen into the anterior chamber prevents the induction of ACAID. Chemical sympathectomy prior to injecting antigen into the anterior chamber also abrogates ACAID. BCR, B cell receptor. Reproduced from Niederkorn (2006), with permission from Nature Publishing Group.

the hematopoietic stem cells are lost if the hosts are depleted of $CD4^+CD25^+$ T regs (Fujisaki et al., 2011). To date no studies have examined if the hair follicle environment promotes the induction of immune deviation or the generation of T regs (Kinori et al., 2011).

OCULAR IMMUNE PRIVILEGE AND OCULAR MELANOMA: PARALLEL UNIVERSES OR IMMUNOLOGICAL PLAGIARISM?

Uveal melanoma is the most common intraocular malignancy in adults and occurs with a frequency of seven cases per million per year in the Western world (Singh and Topham, 2003). There is ample evidence that uveal melanomas are recognized by elements of both the innate and adaptive immune responses. Although uveal melanomas reside within an immunologically privileged site and escape immune elimination in the eye, they metastasize to other body sites, which do not provide the same immunological sanctuary that occurs in the eye. However, growing evidence suggests that uveal melanomas have adopted many of the strategies that contribute to immune privilege in the eye and use them to escape immune rejection after the tumor cells have disseminated from the eye to distant body sites (**Table 2**).

UVEAL MELANOMAS AND IMMUNE PRIVILEGE TO INNATE IMMUNE RESPONSES

Studies in both humans and experimental animals indicate that the innate immune responses, namely NK cells, have an important influence on the growth and metastasis of uveal melanomas (Niederkorn, 2010). *In vitro* studies have shown that human uveal melanoma cells are susceptible to *in vitro* cytolysis by NK cells (Ma and Niederkorn, 1995; Ma et al., 1995; He et al., 2004). However,

Table 2 | Mechanisms and molecules that maintain immune privilege in the eye and are "plagiarized" by uveal melanoma metastases to escape immune surveillance.

Mechanism/ molecule	Mode of action	Eye	Uveal melanoma
TGF-β	Inhibit NK cells	Y	Y
MIF	Inhibit NK cells	Y	Y
IDO	Deplete T cells	Y	Y
FasL	Deplete T cells	Y	Y
TRAIL	Inhibit T cell proliferation and induce T cell apoptosis	Y	Y
CRPs	Inactivate complement	Y	Y
PD-L1	Inhibit T cell proliferation and induce T cell apoptosis	Y	Y
Low level of MHC class Ia	Escape detection by CTLs	Y	Y
MHC class Ib	Inhibit NK cells	Y	Y
Tregs	Inhibit T cells	Y	?

Y, yes; ?, not determined.

the susceptibility of uveal melanoma cells to NK cell-mediated lysis is inversely correlated with the expression of MHC class I molecules (Ma and Niederkorn, 1995; Ma et al., 1995) and is consistent with the "missing self" hypothesis, which posits that NK cells are programmed to kill any cell, malignant or non-malignant, that fails to express MHC class I molecules (Ljunggren and Karre, 1990). However, within the eye uveal melanomas are shielded from NK cell-mediated cytolysis by the buffering effects of the AH, which contains two potent inhibitors of NK cell activity: TGF-β and MIF. Both of these cytokines are present in the AH at concentrations that strongly inhibit NK cell-mediated cytolysis (Apte and Niederkorn, 1996; Apte et al., 1997, 1998). Experiments in nude mice have provided compelling evidence that AH-borne factors prevent NK cell-mediated elimination of uveal melanomas in the eye. Nude mice lack a functional T lymphocyte repertoire, yet have a robust NK cell population. Uveal melanoma cells were briskly rejected following subcutaneous transplantation in nude mice, yet grew progressively if transplanted into the eye, even at doses 50-fold lower than the subcutaneous doses (Apte et al., 1997). Elimination of NK cells by intraperitoneal injection of anti-asialo GM1 antiserum prevented nude mice from rejecting subcutaneously injected uveal melanoma cells and confirmed that the rejection of the subcutaneously injected uveal melanoma cells was indeed mediated by NK cells and also indicated that NK cell-mediated rejection of uveal melanoma cells can occur outside of the eye (Apte et al., 1997).

Uveal melanomas have a propensity to metastasize to the liver and 95% of the patients who die from uveal melanoma have liver metastases (Einhorn et al., 1974; Donoso et al., 1985). Lymphocytes can infiltrate primary uveal melanomas and in some cases, as many as 40% of the tumor-infiltrating lymphocytes (TIL) express NK cell markers (Ksander et al., 1991; Meecham et al., 1992; de Waard-Siebinga et al., 1996). Moreover, NK cells isolated from uveal melanoma-containing eyes display NK cell-mediated cytolytic activity (Ksander et al., 1991). However, as mentioned earlier, the AH of the eye contains MIF and TGF-β, both of which inhibit NK cell-mediated cytolytic activity *in vitro* and *in situ*. However, once in the liver, uveal melanoma cells find themselves in an environment that has the highest concentration of NK cells of any organ in the body (Godfrey et al., 2000; Crispe, 2009; Gao et al., 2009; Nemeth et al., 2009). To compensate for this harsh new reality, uveal melanomas have adopted the strategies employed by the eye to block NK cell-mediated cytolysis. In one study, liver metastases of uveal melanomas produced approximately twice as much MIF as primary uveal melanoma cells (Repp et al., 2000). Uveal melanomas also express TGF-β2, the isoform of TGF-β that suppresses NK cell activity (Esser et al., 2001). Verbik et al. (1997) examined the expression of MHC class I molecules on primary uveal melanomas and liver metastases from the same patient and discovered that liver metastases expressed a 10-fold higher expression of MHC class I molecules compared to the primary melanoma. The susceptibility of tumor cells to NK cell-mediated cytolysis is also affected by the tumor cell's expression of NK cell activating ligands. NKG2D is an activating receptor that is expressed on NK cells and when it interacts with its ligand, MIC-A/B, which is expressed on NK-sensitive tumors, it transmits an activating signal that results in NK cell-mediated cytolysis of the tumor cells. An interesting recent study reported that MIC-A/B was expressed on 50% of primary uveal melanomas, but was undetectable on all 11 metastases specimens tested (Vetter et al., 2004). Thus, uveal melanomas appear to undergo a selection process once they leave the eye that favors the survival of cells that are resistant to NK cell-mediated cytolysis.

UVEAL MELANOMAS AND IMMUNE PRIVILEGE TO ADAPTIVE IMMUNE RESPONSES

Uveal melanomas have also high-jacked strategies used by the eye to create "*ad hoc*" immune privilege against adaptive immune responses in the liver.

IDO AND THE STARVATION OF T CELLS

T lymphocytes are incapable of generating tryptophan and perish if this amino acid is absent. The enzyme IDO catalyzes the degradation of tryptophan and thereby terminates T lymphocyte immune responses (Munn et al., 1999; Frumento et al., 2002; Mellor et al., 2002; Terness et al., 2002). IDO is expressed in many ocular tissues and is believed to contribute to the immune privilege of corneal allografts (Malina and Martin, 1993; Beutelspacher et al., 2006; Ryu and Kim, 2007). IDO is expressed by some tumors and is believed to be a strategy for evading immune surveillance (Uyttenhove et al., 2003). Chen et al. (2007) reported that neither primary uveal melanomas nor liver metastases constitutively expressed IDO. However uveal melanoma cells exposed to IFN-γ, a cytokine produced by both T lymphocytes and NK cells, rapidly upregulated biologically active IDO. Thus, uveal melanoma cells are poised to generate IDO if they perceive the presence of either adaptive or innate immune elements and thereby evade immune elimination in the liver.

COUNTER ATTACK BY PD-L1

PD-L1 is expressed throughout the eye and sustains immune privilege by down-regulating T lymphocyte proliferation and inducing

apoptosis of inflammatory cells expressing its receptor, PD-1. PD-L1 also contributes to the immune privilege of corneal allografts (Hori et al., 2006; Shen et al., 2007). In a recent study, approximately half of the primary uveal melanoma cell lines tested constitutively expressed PD-L1 and only 20% of the metastases cell lines were positive (Yang et al., 2009). However, exposure to the proinflammatory cytokine IFN-γ resulted in the expression of PD-L1 on primary and metastases cell lines. Thus, uveal melanomas have the capacity to sense the presence of an inflammatory response in the form of IFN-γ and respond by upregulating molecules such as IDO and PD-L1 that launch a counter attack that extinguishes immune-mediated inflammation directed against uveal melanomas. However, this escape mechanism can be circumvented. Uveal melanoma cells transfected with the T cell co-stimulatory molecule, CD80, do not upregulate PD-L1 when exposed to IFN-γ and instead, activate T lymphocytes (Haile et al., 2011). This finding suggests that unraveling the mysteries of immune privilege may have important implications for designing therapeutic modalities for managing malignancies such as uveal melanoma that have adopted immune privilege as a strategy for escaping immune surveillance.

BUFFERING EFFECTS CRPs

Complement regulatory proteins are expressed in both soluble and cell membrane-bound forms throughout the eye and act as buffers to limit spontaneous inflammation and complement-mediated cytolysis of ocular cells. Uveal melanomas have high-jacked this strategy and express all three categories of CRPs (CD46, CD55, and CD59), which protect melanoma cells from complement-mediated lysis *in vitro* and presumably *in vivo* (Goslings et al., 1996). There is evidence that at least one proinflammatory cytokine, TNF-α, up regulates CRPs on uveal melanoma cells (Blom et al., 1997). Thus, like PD-L1 and IDO, CRPs have the capacity to be upregulated when inflammation and possibly adaptive immune effector elements are perceived.

CONCLUSION AND PERSPECTIVES

Our understanding of immune privilege has changed significantly over the past 50 years. What was originally perceived as an anatomical anomaly in which the putative absence of lymphatic channels in the eye and brain acted to sequester antigens and create a state of immunological ignorance has evolved into a more complex and dynamic phenomenon that is the sum total of processes and molecules that prevent the induction and expression of both innate and adaptive immunity. It is now widely accepted that immune privilege is an adaptation to protect organs such as the eye and brain, which have limited capacities to regenerate, from immune-mediated injury. However, the same mechanisms and molecules that provide immune privilege to the eye and brain are also present in sites where stem cells reside and by stem cells themselves. Unwitting injury to stem cells by immune-mediated inflammation could have devastating consequences for the host's survival or in the case of the allogeneic fetus, for the survival of the species. Uveal melanomas have "plagiarized" the blueprints used by the eye to establish immune privilege and used them to escape immune surveillance once the tumors leave the eye and metastasize to the liver. Immune privilege in the eye is neither permanent nor absolute. A variety of maneuvers can ablate immune privilege in the eye. Perhaps the next phase of immune privilege research is to take the lessons we have learned in abrogating immune privilege and apply them to the treatment of uveal melanoma metastases.

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