The privileged immunity of immune privileged organs: the case of the eye

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INTRODUCTION

Over the past decades, the mammalian central nervous system (CNS), including the eye, brain, and spinal cord, were believed to be sealed from the circulation. This assumption was based on the current belief that immune privileged organs, including the eye and the brain, are acutely rejected (Medawar, 1948). These organs are thus acutely rejected (Medawar, 1948). Over the past decades, immune privileged organs, including the eye and the brain, have been believed to be acutely rejected (Medawar, 1948). However, studies spanning more than a decade have demonstrated that acute insults to the retina, or chronic conditions resulting in retinal ganglion cell loss, such as in glaucoma, result in an inferior outcome in immunocompromised mice; likewise, steroid treatment was found to be detrimental under these conditions. Moreover, even conditions that are associated with inflammation, such as age-related macular degeneration, are not currently believed to require immune suppression for treatment, but rather, are thought to benefit from immune modulation. Here, we propose that the immune privilege of the eye is its ability to enable, upon need, the entry of selected immune cells for its repair and healing, rather than to altogether prevent immune cell entry. The implications for acute and chronic degenerative diseases, as well as for infection and inflammatory diseases, are discussed.

Keywords: immune privilege, visual system, immunomodulation, neuroprotection and neuronal repair, inflammation

Understanding of ocular diseases and the search for their cure have been based on the corromor assumption that the eye is an immune privileged site, and the consequent conclusion that entry of immune cells to this organ is forbidden. Accordingly, it was assumed that when immune cell entry does occur, it reflects an undesired outcome of breached barriers. However, studies spanning more than a decade have demonstrated that acute insults to the retina, or chronic conditions resulting in retinal ganglion cell loss, such as in glaucoma, result in an inferior outcome in immunocompromised mice; likewise, steroid treatment was found to be detrimental under these conditions. Moreover, even conditions that are associated with inflammation, such as age-related macular degeneration, are not currently believed to require immune suppression for treatment, but rather, are thought to benefit from immune modulation. Here, we propose that the immune privilege of the eye is its ability to enable, upon need, the entry of selected immune cells for its repair and healing, rather than to altogether prevent immune cell entry. The implications for acute and chronic degenerative diseases, as well as for infection and inflammatory diseases, are discussed.

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The early innate immune response involves cells that are needed for cleaning the lesion site, yet the activity of these cells must be followed by immune cells that terminate this initial response and subsequently contribute to the repair. Both stages involve innate immune cells of distinct phenotypes; the cells that contribute to the termination of the local early response are largely monocyte-derived macrophages that acquire and exert a local anti-inflammatory function (Kigerl et al., 2009; Shechter et al., 2009; London et al., 2011). The obvious question is how such a response can be reconciled with the traditional view of the eye as an immune privileged site; do these findings change our understanding of the privilege, or do they require breaking of privilege under severe conditions? Here, focusing on the eye, we will discuss a different view of the physiological meaning of the CNS as an immune privileged site, and its manifestations under pathological conditions.

THE EYE AS AN IMMUNE PRIVILEGED ORGAN

Immune privileged organs were operationally defined as sites in the body where foreign tissue grafts can survive for extended, often indefinite periods of time, whereas similar grafts placed at regular sites in the body are acutely rejected (Medawar, 1948). These organs include the eye and the brain, as well as the pregnant uterus, testis, and several others (Streilein, 2003b; Niederkorn, 2006). Such immune privilege is thought to be an evolutionary adaptation to
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Inflammation is beneficial only on the condition that it ends in active resolution (Grosset, 2010). Studies on wound healing outside the CNS have characterized distinct subsets of macrophages that infiltrate the site of injury and display different functions corresponding to the changing needs of the tissue along the course of healing; these include the clearing of dead cells and tissue debris at the first stage, and the secretion of anti-inflammatory cytokines and growth factors at the later stage, to aid tissue regeneration and restoration of immune homeostasis (Arnold et al., 2007; Nahrendorf et al., 2007). Recently, our team demonstrated that a subset of monocyte-derived macrophages, which manifests an immune-resolving phenotype, is essential for the resolution of inflammation after sterile insults, in models of spinal cord injury and retinal glutamate intoxication (Shechter et al., 2009; London et al., 2011). In both of these cases, such macrophages were found to be crucial for recovery, as was measured by a functional motor scale after spinal cord injury, and directly in terms of cell survival in the retina. Thus, despite the classification of these organs as immune privileged, they nevertheless derive benefit from the controlled recruitment of innate immune cells from the circulation, to assist in their healing. Notably, while the CNS contains its own population of immune cells, the resident microglia, we have shown that infiltrating blood-derived macrophages are nonetheless crucial for neuroprotective and anti-inflammatory activities at the injury site; we have therefore proposed that the infiltrating cells fulfill specialized functions in the recovery process, which the resident immune cells either fail to display, or at least do not manifest at the right time or at sufficient levels (Shechter et al., 2009). In animal models of optic nerve injury, it was found that macrophages can modify the non-permissive nature of the optic nerve for regeneration in vitro (David et al., 1990), and that transplantation of activated macrophages into the injured optic nerve can facilitate retrogrowth in vivo (Lazarov-Spiegler et al., 1996). In line with these observations, the important contribution of a macrophage-derived molecule, oncomodulin, to the regeneration of the optic nerve, was identified by Benowitz and colleagues (Yin et al., 2006, 2009; Cui et al., 2009), who coined the term “inflammation-induced regeneration.” Collectively, these results attribute to innate immunity an important role in eye repair, and reveal the ability of macrophages to orchestrate neuroprotection and axonal regeneration.

The beneficial role of adaptive immunity in neuroprotection was initially observed in animal models simulating different aspects of glaucoma, where it was found that the extent of retinal ganglion cell loss is increased in immunocompromised animals relative to immunocompetent ones (Kipnis et al., 2001; Schori et al., 2001, 2003; Yoles et al., 2001). Similarly, recent studies have demonstrated that well-regulated immune responses in the CNS, rather than immune ignorance, are optimal for the recovery of the tissue after insult, whether sterile or immune-induced (Kert et al., 2008; Shechter et al., 2009; Caspi et al., 2011; London et al., 2011; London et al., under revision). Thus, it is becoming increasingly clear that immune privilege is not aimed at entirely suppressing immune responses in the target organ, but rather at maintaining a specialized, tightly regulated immunological niche to preserve the integrity of especially vulnerable organs, such as the brain and the eye (Streilein, 2003b; Niederkorn, 2006).

**REGULATED IMMUNE RESPONSES ARE BENEFICIAL IN MITIGATING EYE PATHOLOGIES**

Inflammation is the body’s adaptive response to any insult, be it mechanical, biochemical, or immune-mediated. However, inflammation is beneficial only on the condition that it ends in active resolution (Grosset, 2010). Studies on wound healing outside the CNS have characterized distinct subsets of macrophages that infiltrate the site of injury and display different functions corresponding to the changing needs of the tissue along the course of healing; these include the clearing of dead cells and tissue debris at the first stage, and the secretion of anti-inflammatory cytokines and growth factors at the later stage, to aid tissue regeneration and restoration of immune homeostasis (Arnold et al., 2007; Nahrendorf et al., 2007). Recently, our team demonstrated that a subset of monocyte-derived macrophages, which manifests an immune-resolving phenotype, is essential for the resolution of inflammation after sterile insults, in models of spinal cord injury and retinal glutamate intoxication (Shechter et al., 2009; London et al., 2011). In both of these cases, such macrophages were found to be crucial for recovery, as was measured by a functional motor scale after spinal cord injury, and directly in terms of cell survival in the retina. Thus, despite the classification of these organs as immune privileged, they nevertheless derive benefit from the controlled recruitment of innate immune cells from the circulation, to assist in their healing. Notably, while the CNS contains its own population of immune cells, the resident microglia, we have shown that infiltrating blood-derived macrophages are nonetheless crucial for neuroprotective and anti-inflammatory activities at the injury site; we have therefore proposed that the infiltrating cells fulfill specialized functions in the recovery process, which the resident immune cells either fail to display, or at least do not manifest at the right time or at sufficient levels (Shechter et al., 2009). In animal models of optic nerve injury, it was found that macrophages can modify the non-permissive nature of the optic nerve for regeneration in vitro (David et al., 1990), and that transplantation of activated macrophages into the injured optic nerve can facilitate retrogrowth in vivo (Lazarov-Spiegler et al., 1996). In line with these observations, the important contribution of a macrophage-derived molecule, oncomodulin, to the regeneration of the optic nerve, was identified by Benowitz and colleagues (Yin et al., 2006, 2009; Cui et al., 2009), who coined the term “inflammation-induced regeneration.” Collectively, these results attribute to innate immunity an important role in eye repair, and reveal the ability of macrophages to orchestrate neuroprotection and axonal regeneration.

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**REGULATED IMMUNE RESPONSES ARE BENEFICIAL IN MITIGATING EYE PATHOLOGIES**

Inflammation is the body’s adaptive response to any insult, be it mechanical, biochemical, or immune-mediated. However,
FIGURE 1 | An evolving view of immune involvement in the eye.

Ocular pathologies are initiated by multiple factors, and take on various manifestations. Glaucoma, a slowly progressing neurodegenerative disease, is characterized by loss of retinal ganglion cells and damage to the optic nerve. In posterior uveitis, retinal atrophy, and neuronal death are commonly induced by autoimmune inflammation, and age-related macular degeneration presents with drusen (“dry” AMD) and choroidal neovascularization (“wet” AMD). While the traditional dogma stated that immune privilege implies the exclusion of immune activity from the eye under any circumstances, our evolving understanding of immune privilege proposes that boosting beneficial immunity in the eye, in a well-regulated manner, rather than general immune suppression, is most favorable for coping with ocular pathologies, regardless of their initiating factors.

The beneficial involvement of immune cells in the eye is also observed in diseases that are immune-induced, such as autoimmune posterior uveitis, a potentially blinding inflammatory condition affecting the retina and the choroid of the eye. Studies in experimental autoimmune uveitis (EAU), an animal model of human posterior uveitis, demonstrate the heterogeneity of immune cells along this disease. Beside the well-characterized pro-inflammatory cells known to initiate EAU, the uveitic eye is also endowed with regulatory immune populations (Robertson et al., 2002; Kerr et al., 2008; Caspi et al., 2011; London et al., under revision). These cells, including subsets of macrophages and T cells, act to limit inflammation, presumably bringing the disease to a state of equilibrium and remission.

An additional pathology in which the immune system has been shown to fulfill various, perhaps opposing functions, is age-related macular degeneration (AMD), the leading cause of blindness in the elderly. Naturally, the etiology of AMD is very diverse; the disease is associated with numerous immune-related factors. Here too, the role of macrophages has been a matter of debate; on the one hand, it was found that aging is accompanied by a pathological shift to M2 macrophages, which are known to promote angiogenesis, and would therefore seem likely candidates for promoting choroidal neovascularization (CNV), the process by which abnormal blood vessels develop beneath the retina (Espinosa-Heidmann et al., 2003; Sakurai et al., 2003; Cao et al., 2011). On the other hand, studies have also shown that prevention of macrophage entry into the eye promotes CNV, whereas injection of macrophages inhibits it (Apte et al., 2006). Patel and Chan (2008) reviewed the seemingly contradictory
functions of macrophages in AMD, and proposed that these con-
icting findings relect a dual role of macrophages in this pathol-
gy, where the uncontrolled pro-inammatory M1 macrophages
induce tissue damage, and the M2 macrophages, which are
recruited to terminate the M1 response and to clear drusen
and other age-related deposits, could also adversely aect dis-
ease progression by displaying pro-angiogenic activity. Among
the additional factors associated with AMD pathogenesis and pro-
gression, a pivotal role has been attributed over the past several
years to the complement system and its dysregulation (Klein et al.,
2005; Patel and Chan, 2008; Anderson et al., 2010). These findings
emphasize the need for a regulated immune response, in terms of
timing, duration, and phenotype, and further support the argu-
ment that there are no “good” or “bad” immune cells; it is all
a matter of their control and coordination. Moreover, the accu-
mulating evidence on beneicial immune involvement in AMD
and in the other ocular pathologies mentioned above give further
reinforcement to the current contention that although the eye is
an immune privileged site, it can enjoy the beneits of immune
support, and thus immune regulation, rather than immune
suppression, is the key to disease resolution, as in other parts of
the body (Figure 1).

A DIFFERENT VIEW OF IMMUNE PRIVILEGE

Immune privilege is an evolutionary adaptation aimed at protect-
ing especially vulnerable organs from overwhelming inammation
that could abolish their functions and jeopardize the well-being
of the individual. As vision is crucial for survival, it is under-
standable why the eye would be particularly protected from
these risks (Streilein, 2003a). However, we propose that the
immune privileged designation of the eye means that it has the
privilege to enable selective immune responses most suitable
and effective for its proper function in health and pathology. We
 contend that this is true for all other parts of the CNS, as well.

As many CNS pathologies are associated with local inammation,
they are generally treated with anti-inammatory and immuno-
suppressive drugs. However, this treatment approach has
shown limited success in animal models of ocular pathologies
and other neurodegenerative disorders, as well as in the clinic,
and in some cases was even found to exacerbate disease (Levin
et al., 1999; Solberg et al., 1999; Bakalash et al., 2003; Ohlsson
et al., 2004; Dimitriu et al., 2008; Schwartz and Shechter, 2010).
The beneits of those drugs, if any, are often temporary, as they
help relieve some of the symptoms but do not address the under-
laying pathological processes (Giosnert, 2010). Bearing in mind
the heterogeneity of immune cells and their changing functions
along the course of disease, together with the delicate balance
of counter-regulatory signals required for effective resolution
of inammation (Giosnert, 2010), we suggest that a more efcient
approach to treating such disorders would be to manipulate spe-
cic immune subsets in a timely manner, rather than to globally
inhibit the immune response (Figure 1).

Finally, our interpretation of the privilege of immunity in
immune privileged sites does not negate the possibility that under
certain conditions, immune privilege is breached in order to pre-
serve the life of the individual, at the expense of local loss of
function; this is the case in certain microbial infections, or in the
presence of highly immunogenic tumors (Morrison et al., 1989;
Niederkorn, 1991; Li and Niederkorn, 1997; Streilein et al., 1997;
Saint Andre et al., 2002; Niederkorn and Stein-Streilein, 2010),
in which a powerful immune response is essential, and the risk
of blindness is accepted for the sake of survival (Niederkorn and
Stein-Streilein, 2010).

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