EXPERT REVIEWS

Boosting controlled autoimmunity: a new therapeutic target for CNS disorders

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In most tissues, the immune system plays an essential role in protection, repair and healing. Although immunologically privileged, the CNS remains subject to a highly regulated form of immunosurveillance that is of increasing interest. There is evolving evidence that repair mechanisms within the CNS may be enhanced by exploiting an innate process of protective immunity. Understanding the regulation of protective autoimmunity within the CNS is likely to lead to novel therapeutic approaches to neuroinflammatory and neurodegenerative diseases.

KEYWORDS: beneficial autoimmunity • CNS injury • neuroprotection • protective autoimmunity

The unique 'immunological privilege' of the CNS has been long recognized. Evolving evidence suggests that some repair mechanisms within the CNS may comprise a unique form of innate immunomodulation. The regulation of this innate protective immunity and the relative roles of activated microglia, and systemic T and B cells remain poorly understood.

The contention that an autoimmune response within the systemic immune system can be beneficial implies that natural autoimmune T cells have undergone positive selection at some stage, and that they are tolerated under physiological conditions without the development of an autoimmune disease [1,2]. Accordingly, autoimmune T cells may act as a reservoir in 'standby' mode, ready for protective action when required in times of stress or tissue crisis [1]. The challenge from a basic research perspective is to identify mechanisms by which the ensuing inflammatory response can be harnessed for anti-inflammatory and neuroprotective purposes.

This review examines the evidence for the existence of a protective autoimmunity within the CNS, and discusses the likely therapeutic benefits that might be derived from modulating and exploiting this process.

Protective autoimmunity is a physiological response to both CNS trauma & neurodegenerative disorders

The CNS is anatomically separated from the systemic circulation by the BBB, and as such is considered to be immunologically privileged. The unique status of the CNS also means that an initial injury is at risk of generating an immune-mediated self-propagating process of secondary degeneration. However, there is a recent and emerging body of evidence from laboratory animals pointing to the presence of a modulatory system of protective immunity that can limit the extent of this destructive process (FIGURE 1) [3–5]. This system involves recruitment of an anti-inflammatory and neuroprotective T-cell-dependent immune response [6]; an innate CNS immune response comprising activated microglia [7] and components of humoral immune response [8,9].

The biological importance of protective immunity in the CNS has been most comprehensively studied using an optic nerve crush model of tissue injury [3,4,10]. Transfusion of myelin-specific T cells significantly increases the number of surviving neurons in treated compared with untreated animals. Treatment

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with T cells activated with non-myelin-based antigen is less effective than treatment with T cells activated with specific antigen, as evidenced by the number of surviving neurons following optic nerve crush in treated animals [3,6,11]. This ability of specific autoimmune T cells [11–14] or other cells associated with innate immunity to diminish the post-traumatic neuronal degeneration has also been confirmed by both morphological and functional studies in other experimental models of injury, including spinal cord trauma and animal models of demyelination [7,8,15,16].

In the optic nerve crush model, the number of surviving neurons is significantly higher if the nerve crush is purposely preceded by a spinal cord injury. This neuroprotective effect can also be transferred to recipient rats by *ex vivo* activated splenocytes against myelin basic protein. By contrast, adult rats thymectomized at birth express no endogenous protective autoimmunity, indicating that protective autoimmunity is not a phenomenon induced by experimental or therapeutical interventions, but is a physiological response to CNS injury [3].

Neonatal rats rendered tolerant to myelin antigens have a significantly reduced ability to resist axonal injury as adults. This indicates that the spontaneous T-cell dependent protection is an evoked myelin-specific reaction to injured myelinated axons [17,18].

The discovery that neuroprotective immunity can be demonstrated in transgenic mice overexpressing a T-cell receptor for myelin basic protein peptide, but not mice overexpressing a T-cell receptor for ovoalbumin, supports the hypothesis that antigenic specificity is essential for the observed neuroprotection [3].

Furthermore, in optic nerve injury experiments using adult Lewis rats thymectomized at birth and lacking endogenous T cells (including Tregs), transplant with myelin-specific T cells does not protect the damaged nerve [5]. This suggests that protective autoimmunity includes both autoreactive and regulatory T cells [3,4,18].

Autoimmunity & neuroprotection

Autoimmune disease is known to occur when the regulatory mechanisms for tissue repair are absent, deficient or impaired [10]. In the CNS, there appears to be an inverse relationship between the rate of neuronal survival after CNS damage and likelihood of developing an autoimmune condition. This relationship is mediated by an injury-induced beneficial T-cell response in animals that are genetically resistant to experimental autoimmune encephalomyelitis (EAE), but not in genetically susceptible animals. This suggests that a protective T-cell-dependent response and resistance to autoimmune disease are both regulated by a common mechanism [4].

Similarly, the limited recovery from optic nerve injury in EAE-susceptible rats and mice demonstrates that EAE-susceptible animals have a limited spontaneous ability to generate a protective autoimmune response to CNS injury. In these susceptible animals, the rate of post-injury neuronal survival is lower than in animals resistant to EAE [4].

The microenvironment is crucially important. T cells can be either beneficial or detrimental for neurons depending on the regulatory environment. Thus, T cells might be both potentially protective and potentially destructive, and the ability to protect neuronal tissue correlates with a well-controlled constitutive autoimmune response, mediated by the interaction of adaptive immune T cells with activated innate immune microglia [19,20]. Additionally, protective effects of humoral immunity would also be considered. Both antibodies and complement may have protective effects in autoimmune demyelination [21,22].

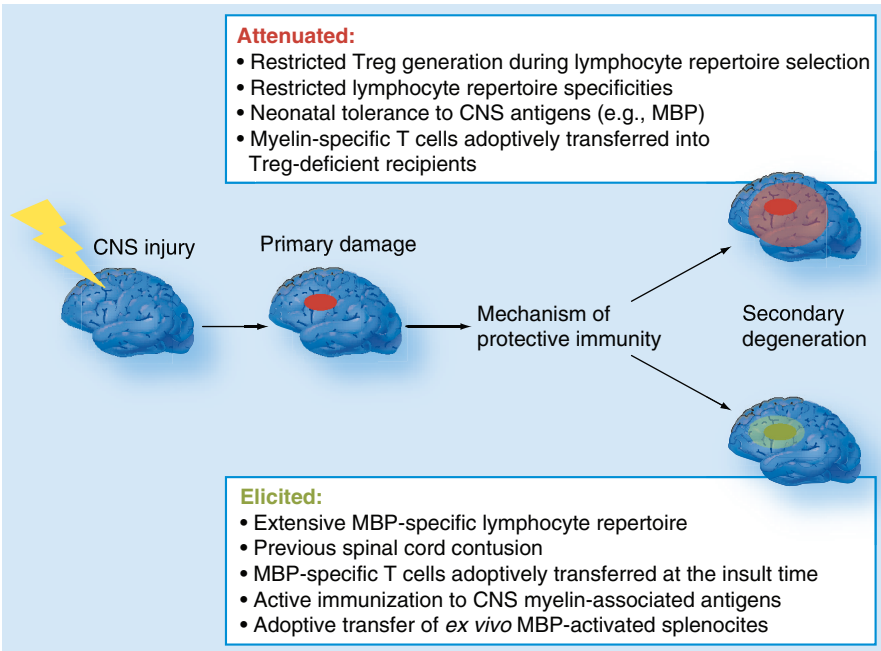

Figure 1. Primary damage caused by a CNS injury is followed by a secondary degeneration of initially spared neurons. Protective immunity reduces the magnitude of this delayed degeneration through different mechanisms [3–6,11,17,18,21].

Activation of protective immunity

Microglia

Microglia have been increasingly recognized as primary agents of innate immunity within the CNS. They are the primary sensors of change in the brain microenvironment, and respond to pathogens in a nonantigen-specific fashion similar to the actions of systemic macrophages. They produce TNF-α that acts in an autocrine/paracrine manner to activate the population of immune cells in the brain.

Microglia also possess TLRs that recognize molecular sequences found on microbes and can trigger NF-κB signaling and production of proinflammatory cytokines [23,24]. In fact, TNF-α can enhance TLR2 expression in microglia, mediated, in part, by activation of the NF-κB pathway [24]. Recent data also suggest that nonpathogenic molecules released by trauma can trigger inflammation via TLR2 and TLR4 [25]. There is evidence to support both neuroprotective and neurodegenerative roles for microglia, and the relative properties of activated microglia dictated by endogenous host ligands. For example, in mSOD1 transgenic mice, bone marrow transplants from wild-type donor-derived microglia slowed motor neuron loss, and prolonged disease duration and survival when compared with mice receiving $mSOD1^{G93A}$-expressing cells [26]. Furthermore, studies using the Cre-Lox system reduced the expression of mSOD1 in microglia and reached a similar conclusion, namely that the reduction of mSOD1 in microglia prolongs disease duration and survival [27]. *In vitro* studies have documented the association of neurotoxic effects of the mSOD1 microglia with production and release of superoxide anion, nitrous oxide and hydrogen peroxide, while the neuroprotective effects of wild-type microglia can be explained by downregulation of the toxic effects and upregulation of IGF-1 as well as other neurotrophins [26,28,29]. Furthermore, the toxic effects of microglia can be induced *in vitro* by application of microglial activators such as lipopolysaccaride, while the protective effects can be modulated by IL-4, which is known to be released from T cells [28]. Thus, modulation of microglia through surface receptors such as TLRs play an important role in the regulation of innate protective immunity, and accordingly modulate the balance between neuroprotective and neurodestructive inflammatory cascades.

Neurotrophins

Neurotrophic factors comprise a family of proteins that mediate neuron survival and regulate other neuronal and glial cell activities, including growth of axons and dendrites, synaptic plasticity and neurotransmitter expression.

At least three families of neurotrophic factors have been characterized including NGF-related neurotrophic factors (NGF), BDNF, NTF-3 and NTF-4/5, GDNF family and the neuropoietic cytokines CNTF and LIF.

Neurotrophic factors can influence various immune cell functions, including migration, differentiation and antigen presentation. The neuroactive effects of activated microglia, autoimmune B cells and T cells is in part mediated by the release of immunomodulatory and neuroprotecive factors such as BDNF and LIF, which are produced and act within the immune system by means of autocrine/paracrine mechanisms. These factors act on injured and degenerated nerve cells and regulate the response of neurons to traumatic or degenerative processes [30]. On this basis, a bidirectional dialog can be sustained between the nervous and the immune systems [31].

Translational implications of protective immunity

A greater understanding of the importance of immune regulation within the CNS, and the potential role for protective immunity can be exploited to therapeutic advantage. Based on the evidence from animal models, it is likely that the relative contribution of protective immunity may differ between individuals. It may be that those who are genetically resistant to autoimmune disease have greater access to innate and biologically useful protective CNS autoimmunity, which would then promote a favorable outcome following CNS injury. In animal models, susceptibility to autoimmune disease after active immunization with self-antigens is linked to the existence and functionality of Tregs. These regulatory cells maintain a balance between the generation of an autoimmune response required for neuroprotection and the need to prevent autoimmune disease [17]. Knowledge of an individual's protective immunological potential could be harnessed for therapeutic purposes and individualized treatments tailored, as individuals with an ability to regulate the autoimmune response would be more likely to benefit from exogenous exploitation of a protective autoimmune response [20,21,32]. Moreover, emergent evidences on the role of cytokines (e.g., IL-2) in the generation and expansion of Tregs encourage further evaluation boosting controlled autoimmunity therapeutically [33].

Active vaccination may also be a possible and attractive path to protect individuals from the effects of secondary degeneration. Unlike the antibody response, the response of T cells to immunization with a suitable antigen can begin within hours. In the animal model of optic nerve injury, vaccination with immunodominant antigens from the region is neuroprotective [20,34,35]. As vaccination would be designed to protect the individual from the insult-induced endogenous toxicity, the antigen would be a self-protein and the immune reaction would therefore be a self-limited autoimmune response [5].

Vaccination with nonpathogenic peptides, such as those derived from myelin basic protein, or synthetic polymers that cross-react with self-proteins, have been shown to improve motor recovery without the development of an autoimmune disease in spinally injured rats [32,36] and in experimental models of optic nerve chronic injuries [37–39]. Pilot studies to this effect in multiple sclerosis (MS) are promising [40].

Vaccination as a neuroprotective strategy is also worthy of investigation as an acute management strategy following trauma. Immediately after the injury to the CNS, therapeutic vaccination could be used to ensure recruitment of immunocompetent cells, thus making it possible to protect the individual from the pathological consequences of the damage. Furthermore, dendritic cells would also be considered as a possible target. These cells are essential for antigen presentation and in mediating the effects of vaccination [41]. A further therapeutic option will be to capitalize on the crosstalk between immunomodulatory and neuroprotective peptides, to generate an immune-based therapeutic approach that exploits

neuroprotective properties within the CNS. A number of groups are currently experimenting with the introduction of genetically modified autologous bone marrow-derived stem cells containing neurotrophic factors as a means of increasing the concentration of neurotrophins within the CNS [42].

Recognizing the role of protective autoimmunity in disease

T-cell receptors have long been recognized as a potential target that could be exploited for therapeutic purposes in demyelinating diseases. The therapeutic aim is to abrogate the autoimmune T cell, and to shift the balance from presumed pathogenic Th1/Th17 cells toward an expected beneficial phenotype (e.g., Th2) [43,44]. However, immune regulation within the CNS is a complicated system and the pathophysiology of neurodegeneration in an immune-mediated neurological disease such as EAE and MS remains poorly understood [19,22]. The progression of disability in MS does not correlate well with the neuroinflammatory response, at least as demonstrated on neuroimaging. And while it is known that currently available immunomodulatory and immunosuppressive treatments of MS have an effect on the degree inflammatory activity as evidenced on neuroimaging, their long-term effect on the progression of disability is less impressive [45]. It is also the case that nonselective immunosuppressive treatment does not produce a lasting clinical benefit [46,47]. It may be that nonspecific immunosuppression limits a process of immune-mediated neuroprotection that could otherwise be beneficial. For example, it is known that activated lymphocytes from MS patients have increased expression of BDNF, which is potentially neuroprotective [48]. The presence of neuroprotective elements in the inflammatory response in MS plaques is reminiscent of animal models of nerve injury, where a neuroprotective effect is mediated by the release of neurotrophic factors from autoimmune T cells, B cells and activated microglia. [49–51]. Detailed immunohistochemical analysis of active MS plaques has also shown an upregulation of BDNF and its receptor [52]. This endogenous expression of such neurotrophins is higher in 'fresh' MS lesions, compared with chronic established plaques. The downregulation of neuroprotective agents such as BDNF seems to correlate with the process of axonal degeneration evident in the secondary progressive stage of the disease [30]. However, it is not yet well defined whether the production of neurotrophic factors, such as BDNF within the CNS by immune cells is always beneficial. Recognition of the potential to exploit the positive features of neuroprotective autoimmunity will have consequences on our understanding of both the pathogenesis and treatment of MS. From a pathogenic perspective, it remains unclear as to whether there is a phase of the disease in which the inflammatory response may be seen as favorable rather than as evidence of a poor prognosis [30]. From a treatment perspective, it will be essential to preserve and exploit neuroprotective and immunomodulatory aspects of the immune response while attempting to attenuate the proinflammatory and neurodegenerative components.

Expert commentary

Neuroprotective immunity has the potential for therapeutic exploitation. The aim is to manipulate the neuroprotective components of the immune system to beneficial effect (i.e., one that limits neuronal damage). Each tissue has its own set of specific self-antigens that signal the immune system. Evolving research into innate immunity within the CNS, although still in its infancy, points to a series of intriguing new therapeutic options including the possible development of a therapeutic vaccination with self-antigens or with cross-reactive antigens that can be used to drive a protective immune response.

Key issues

- The original concept of immunological privilege within the CNS is changing.
- The CNS contains a well-developed system of innate immunity.
- There is a modulatory system of protective immunity, meditated by antigen-specific T cells, B cells and microglia that can limit the extent of secondary neuronal injury in response to trauma or injury.
- The importance of microglia as active participants in regulating the CNS microenvironment is increasingly recognized. There is evidence to support both neuroprotective and neurodegenerative roles for microglia, and the relative properties of activated microglia are dictated by endogenous host ligands.
- The neuroactive effects of activated microglia, autoimmune B cells and T cells is in part mediated by the release of neurotrophic factors, such as BDNF and LIF. These and other neurotrophic factors act on injured and degenerated nerve cells, and regulate the response of neurons to traumatic or degenerative processes. Neurotrophic factors thus contribute to a dialog between the nervous and the immune systems.
- Knowledge of an individual's protective immunological potential could be harnessed for therapeutic purposes, and vaccination as a neuroprotective strategy is worthy of investigation.
- Recognition of the potential to exploit the positive features of neuroprotective autoimmunity will have consequences with respect to our understanding of the pathogenesis and treatment of neuroinflammatory conditions, such as multiple sclerosis, and neurodegenerative conditions, such as amyotrophic lateral sclerosis.

Current immunomodulators such as steroids and immunosuppressives have been disappointing as therapies for non-infectious inflammatory disorders, as they are not sufficiently selective.

There is a wealth of basic research that points to an important role for innate immunity and its modulation by adaptive immunity in both neuroinflammatory and neurodegenerative diseases. Further exploitation of this previously under-investigated field is likely to lead to exciting new therapeutic options. However, caution with respect to clinical application must be taken. The conditions to separate protective and detrimental immune responses and to selectively stimulate the protective immune response are far from being clear so far. Premature clinical application of this concept may therefore be detrimental for the patients and for the field in general.

Five-year view

There is an increasing recognition of the importance of microglia within the CNS. Dissecting the processes that regulate activated microglia will no doubt yield pathways that can be targeted for drug discovery. Similarly, pathways that upregulate T-cell-mediated protective immunity could be exploited for therapeutic benefit.

Ultimately, the challenge will be to develop mechanisms that activate and enhance the anti-inflammatory and neuroprotective elements of innate immunity within the CNS, while seeking to limit the proinflammatory and neurodegenerative cascades that make up the major part of the immune response.

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