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Innate and adaptive immune responses can be beneficial for CNS repair

Michal Schwartz, Gila Moalem, Raya Leibowitz-Amit and Irun R. Cohen

The limitation of immune responsiveness in the mammalian CNS has been attributed to the intricate nature of neuronal networks, which would appear to be more susceptible than other tissues to the threat of permanent disorganization when exposed to massive inflammation. This line of logic led to the conclusion that all forms of CNS inflammation would do more harm than good and, hence, the less immune intervention the better. However, mounting evidence indicates that some forms of immune-system intervention can help to protect or restore CNS integrity. We have shown that the innate immune system, represented by activated macrophages, can facilitate the processes of regeneration in the severed spinal cord. More recently, we found that autoimmune T cells that are specific for a component of myelin can protect CNS neurons from the catastrophic secondary degeneration, which extends traumatic lesions to adjacent CNS areas that did not suffer direct damage. The challenge, therefore, is to learn how to modify immune interactions in the traumatized CNS in order to promote its post-injury maintenance and repair.

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THE PHENOMENON of 'immune privilege' in the mammalian CNS is thought to derive from an evolutionary adaptation that restricts immune responses within the CNS (Ref. 1). Several mechanisms contribute to the status of the CNS as a site of immune activity of unique and possibly autonomous character. The most prominent element involved in these mechanisms is the blood-brain barrier, an anatomical and physiological barrier that keeps the CNS free from intruders². An additional mechanism is an immunological barrier, mani-

fest by: (1) the reduced expression of major histocompatibility complex class-I and class-II antigens on certain cells in the CNS (Refs 3,4), and (2) an immunosuppressive micro-environment that contains, for example, astrocytes that suppress or anergize invading T cells^{5,6}, and locally produces factors that suppress and regulate the production of immune responses in the CNS (Refs 7,8). These two barriers, which limit both the entry of immune cells into the CNS and their activity there, are thought to protect against remodeling of the dynamic

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and complex neural network of the brain. A unique immunological feature of the CNS, which possibly evolved as partial compensation for the above limitation, is the abundant presence of resident macrophages, the microglia, which occur in resting form and account for approximately 12% of the total brain-cell population^{9,10}.

In tissues other than the CNS, immune responses have a pivotal role in maintenance and repair, which raises the following questions: does the CNS, like other tissues, depend on immune responses for its maintenance and repair, particularly after injury? And, if so, is the restricted activity of CNS-resident immune cells sufficient for this purpose? The data presented in this article suggest that the injured CNS does indeed require immune intervention in order to limit damage and to activate healing, but that under normal circumstances the CNS is relatively inaccessible to such intervention because of the restrictions associated with its immune-privileged status.

The involvement of immune activity in CNS repair and maintenance can be seen, for example, in the case of white-matter injury, that is, injury to axons^{11–14}. Such injury initiates a process of degeneration at the injury site, which is accompanied by an inability of the nerve fibers to regrow and reconnect, and usually culminates in the death of the corresponding cell bodies¹⁵. In addition, undamaged fibers in the vicinity of the injured axons become affected by the lateral spread of damage¹⁶ and consequently undergo secondary degeneration, unless they are treated adequately^{16–20}. This lateral, secondary degeneration appears to be mediated by agents such as glutamate²¹, free radicals or additional mediators of toxicity, some of which might be associated exclusively with CNS axonal injury rather than a direct injury to cell bodies^{21–25}.

Attempts to minimize the spread of degeneration following axonal injury, using the rat optic nerve or spinal cord as a model, have yielded some insights into the mechanisms involved in degeneration and have led to the identification of specific molecules with neuroprotective properties^{26–28}. Thus, for example, the observed reduction in secondary degeneration that followed immediate treatment of an injury with a single dose of methylprednisolone was attributed to the reduction of local inflammation that this compound produced²⁹. Accordingly, inflammatory cells were considered to be harmful to damaged axons³⁰. The beneficial effect of methylprednisolone, either as a result of its anti-inflammatory activity or of its other actions, might be as a neuroprotective agent and, accordingly, it might be exerted only at an early posttraumatic stage. For regrowth, however, inflammatory cells appear to be important^{12,13,31–34}. This would support our suggestion that there could be a conflict between the inflammation that disrupts the maintenance of the CNS and the inflammation required for CNS repair^{35,36}. Similarly, whereas autoimmune T cells are generally considered to be detrimental, under certain posttraumatic conditions they can be beneficial¹⁴. As summarized below, the immune activities of macrophages and T cells in the CNS, although potentially threatening, display positive effects in terms of repair and maintenance following injury.

Implantation of activated macrophages promotes CNS regrowth

In contrast to the CNS, the PNS can regenerate after injury. A comparison of the inflammatory responses of the CNS and the PNS to injury has, therefore, proved to be helpful in defining the factors that are important

for recovery of CNS tissue. For example, macrophage invasion of damaged CNS white-matter sites is slower and less extensive than that observed following similar degrees of PNS white-matter injury³⁷. *In vitro* studies have shown that the phagocytic activity of macrophages is enhanced on their exposure to PNS nerve segments but inhibited by exposure to CNS nerve segments³⁸. Moreover, macrophages that infiltrate the damaged CNS are less efficient at clearing the myelin debris known to inhibit neuronal growth than are PNS macrophages³⁹. Thus, relative to the PNS, the CNS manifests a sluggish macrophage response to injury. In addition, the CNS-resident macrophages, the microglia, have been found to be activated after injury, although their activity is not as high as that of peripheral-blood macrophages and is transient⁴⁰. Can this limitation in macrophage and microglial activity explain, at least in part, the failure of the CNS to regenerate and repair itself?

The above results, together with other findings^{41,42}, have led us to propose that in the injured CNS, as in other injured tissues, activated macrophages are needed at an early stage after injury for healing of the tissue. In addition, CNS healing might be affected adversely by the late arrival of macrophages at the site of injury, their limited spread within the injured tissue and their restricted activity. This hypothesis was substantiated experimentally by incubating peripheral blood macrophages with PNS or CNS tissue *in vitro* and then applying equal numbers of macrophages to the site of injury in the optic-nerve or spinal-cord models. By means of anterograde and retrograde labeling of transected optic nerves of adult rats, we have demonstrated morphologically that PNS-activated macrophages are more beneficial for axonal regrowth than are CNS-activated or non-activated macrophages¹². Regrowth of axons is correlated with the speedy clearance of myelin from the treated axons and with the abundant distribution of PNS-activated macrophages along the distal part of the damaged axons (in contrast to the limited macrophage distribution in transected, untreated axons, or in transected axons exposed to CNS-activated macrophages or to non-activated macrophages)⁴³. The beneficial effect of the macrophages on regrowth is not diminished by treatment with dexamethasone. Some functional recovery has been demonstrated in studies of adult-rat spinal cord, where local application of PNS-activated macrophages to the completely transected spinal cord leads to the partial recovery of otherwise paraplegic rats. Recovery is manifested by acquisition of locomotor activity, which is tested in an open-field by measuring the generation of motor-elicited potential responses in the hind-limb muscles, and by morphological alterations that meet specific criteria¹³.

The above data support three conclusions. First, the CNS is not intrinsically refractory to the processes of healing and regrowth. Second, the ability of activated macrophages to promote CNS healing and regrowth is, in principle, not unlike that promoted by the innate inflammatory response in other organs. Third, the failure of the CNS to regrow can be attributed, at least in part, to a relative inability of the damaged CNS to recruit and activate a restorative inflammatory response to tissue damage. Thus, it appears that the immune-privileged status of the CNS, at least in some circumstances, might be disadvantageous and even detrimental. The remainder of this article contains a review of our recent findings that autoimmune T cells, like activated macrophages, can benefit the damaged CNS.

Passive transfer of CNS-antigen-specific autoimmune T cells limits secondary degeneration

Macrophages do not bear receptors for antigens and they lack immune memory, thus representing the non-adaptive, innate arm of the immune response. T cells, in contrast, respond to specific antigens and ‘remember’ past experience, and so represent part of the adaptive arm of the immune response. When activated, the T cells can kill their target cells or produce signal molecules that activate or suppress the growth, movement or differentiation of other cells. Thus, T cells are involved in protecting the individual against foreign invaders as well as in maintaining body function. The blood–brain barrier of the CNS is normally impermeable to resting T cells, but is permeable to activated T cells. Activated T cells, however, do not accumulate in the healthy CNS unless they recognize and are able to react to their specific antigen there⁴⁴.

Comparative studies of the T-cell response at sites of optic-nerve and sciatic-nerve injury, using T-cell immunocytochemistry, have revealed a significantly greater accumulation of endogenous T cells in the injured PNS than in the injured CNS (Ref. 45). Moreover, the CNS shows a marked propensity for elimination of T cells via apoptosis, whereas this mechanism is less effective in the PNS and is almost absent in other tissues such as muscle and skin⁴⁶. These findings suggest that the T-cell response in the traumatized CNS is both restricted and tightly regulated. Is this limitation in T-cell response disadvantageous to the CNS?

In order to determine whether increasing T-cell accumulation is beneficial or harmful to the injured CNS, we used an experimental model of a partial lesion of the rat optic nerve, which allows the assessment of nerve maintenance after traumatic axonal injury. We found that axonal injury was followed by a transient accumulation of endogenous T cells at the site of the lesion. Passive administration of activated syngeneic T cells specific to a CNS self-antigen such as myelin basic protein (MBP) or to a non-self antigen such as ovalbumin (OVA) resulted in an augmented local accumulation of T cells^{14,47}. Although both T-cell lines accumulated at the site of the lesion, there was a clear difference in their effects on the maintenance of the damaged tissue in terms of their ability to affect the progression of secondary degeneration. Two weeks after injury, the rats injected with the anti-MBP T cells showed significantly less secondary degeneration than rats injected with phosphate-buffered saline (PBS) or with T cells that are specific to the foreign antigen OVA. This neuroprotective property of the anti-MBP T cells was demonstrated using criteria derived from morphometric and electrophysiological studies¹⁴. Thus, both the numbers of retinal ganglion cells and the degree of optic-nerve conduction (measured by its compound action potential) were significantly higher in the rats injected with anti-MBP T cells than in the other groups of rats (Fig. 1). The neuroprotective effect was discernible despite the fact that the transferred anti-MBP T cells induced a transient monophasic paralytic disease known as experimental autoimmune encephalomyelitis (EAE). The EAE started four days after cell injection, peaked on day six and terminated around day ten. It should be emphasized that the adoptive transfer of EAE to Lewis rats by anti-MBP T cells does not involve structural demyelination⁴⁸.

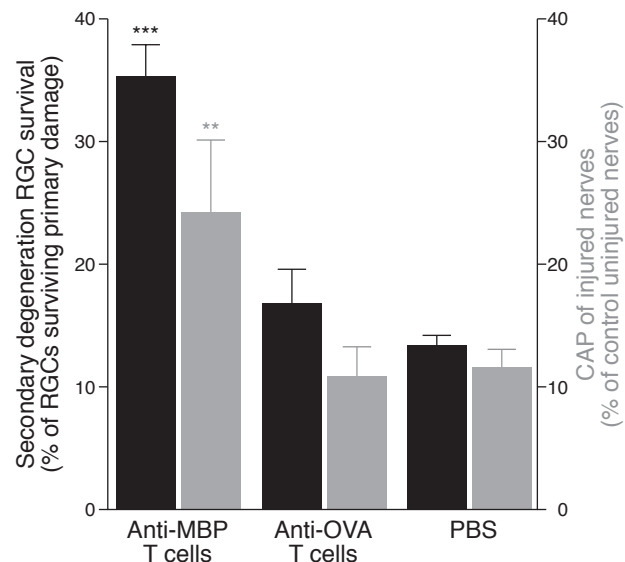


Fig. 1. The neuroprotective effect of autoimmune anti-MBP T cells.

Immediately after partial optic-nerve-crush injury¹⁶, rats were injected intraperitoneally with phosphate-buffered saline (PBS) or with 1×10^7 activated anti-MBP (myelin basic protein) or anti-OVA (ovalbumin) T cells. Two weeks later, neuroprotection was assessed either morphologically or electrophysiologically¹⁴. For the morphological analysis, the neurotracer dye, 4-Di-10-Asp, was applied to the optic nerve distal to the site of the injury. Five days after dye application, the retinas were excised and flat-mounted. Labeled retinal ganglion cells (RGCs) from three to five randomly selected fields in each retina (all located at approximately the same distance from the optic disc) were counted by fluorescence microscopy. The number of RGCs that survived secondary degeneration in each group of injured nerves was expressed as a percentage of the remaining number of RGCs per mm^2 , which were counted immediately after the primary injury (280 ± 51.6 , mean \pm SEM). The mean number of RGCs surviving secondary degeneration (per mm^2) two weeks after the primary injury was 37 in rats injected with PBS, 47 in rats injected with anti-OVA T cells and 99 in the rats injected with anti-MBP T cells. The results represent an average of five experiments, in which each group contained five to ten rats. For the electrophysiological analysis the compound action potential (CAP) was recorded from uninjured optic nerves and from the distal segments of the injured optic nerves two weeks after injury. The nerve ends were connected to two suction Ag–AgCl electrodes immersed in a bathing solution at 37°C. A stimulating pulse was applied through the electrode and the CAP was recorded by the distal electrode. For each nerve, the difference between the peak amplitude and the mean plateau for eight CAPs was computed, and was considered to be proportional to the number of propagating axons in the optic nerve. The mean CAP amplitude of the injured nerves from rats subjected to the different treatments was expressed as a percentage of the mean CAP amplitude of the uninjured nerves in the PBS-injected rats (gray). Each group contained eight to ten rats. The neuroprotective effect of anti-MBP T cells compared with PBS or anti-OVA T cells was significant. ** $P < 0.01$, *** $P < 0.001$ (one-way ANOVA).

Interestingly, the protection of neurons from secondary degeneration was not related to the intrinsic pathogenicity of the anti-MBP T cells. The disease induced by T cells specific to a cryptic epitope of MBP, p51–70, was significantly milder, if seen at all, than that induced by the anti-MBP T cells. Nevertheless, this weakly pathogenic anti-p51–70 T-cell line was as effective in reducing secondary degeneration as the highly pathogenic anti-MBP T-cell line¹⁴. Thus, the induction of clinical autoimmune disease was not a prerequisite for the protection against secondary degeneration mediated by the anti-MBP T-cell lines.

We do not yet know how the anti-MBP T cells arrest the progression of secondary degeneration, although it is known that T cells can synthesize cytokines and

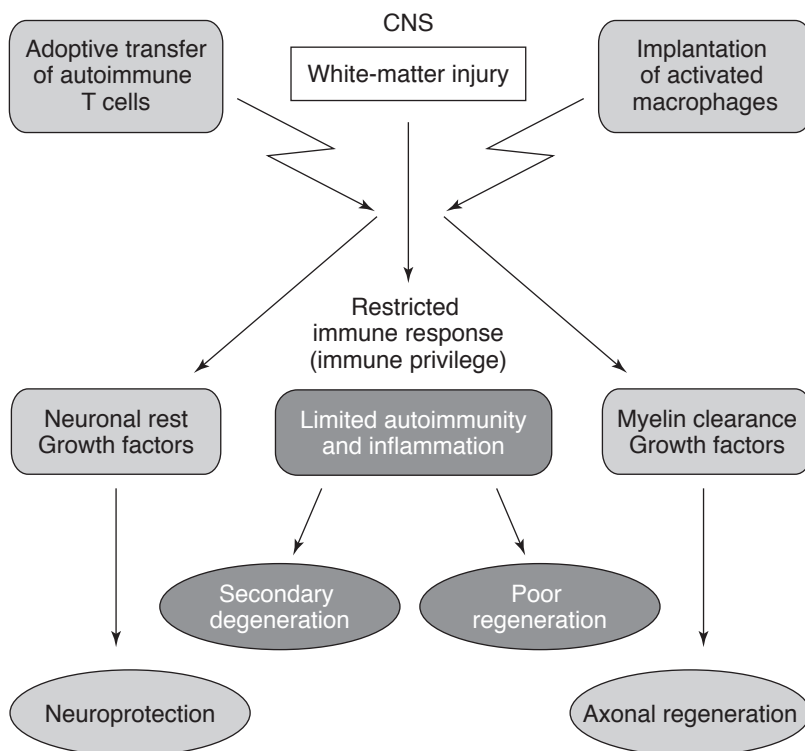


Fig. 2. The innate and adaptive immune responses and their proposed effects on axonal regeneration and neuroprotection. The restricted communication between the CNS and the immune system seems to operate not only in the intact CNS, but also following injury such as axotomy. As a result, the CNS fails to trigger adequate immune reactions needed for protection and regeneration (dark gray). The neuronal environment is not, therefore, modulated so that it can support axonal regrowth or prevent secondary degeneration. However, the obstacle of the restricted immune responses in the injured CNS can be bypassed by implantation of activated macrophages or adoptive transfer of autoimmune T cells (light gray). A model of partial white-matter injury was used for studying neuroprotection and a model of complete transection in the white matter was used for studying regeneration. Macrophage implantation (right) led to the removal of neuronal growth inhibitors by myelin clearance and to growth-factor secretion, resulting in axonal regeneration. Adoptive transfer of autoimmune T cells (left) led to a reduction in energy requirements, caused by transient inhibition of nerve conduction ('neuronal rest'), and to growth-factor secretion, resulting in neuroprotection.

neurotrophic factors^{49–51}. We were unable to detect major differences between the T-cell lines examined in these experiments with respect to their cytokine and neurotrophin production *in vitro* (M. Schwartz, G. Moalem, R. Leibowitz-Amit and I.R. Cohen, unpublished observations), and are currently examining whether antigen recognition at a site of injury induces differential cytokine and neurotrophin secretion *in vivo*. Myelin in the crushed nerve undergoes degradation and its exposure could, therefore, stimulate the anti-MBP T cells to secrete neuroprotective factors. Alternatively, or in addition, it is known clinically that arresting nerve metabolism (for example, by hypothermia) can help to limit the spread of CNS damage after injury⁵². Some years ago, we reported that anti-MBP T cells could reversibly inhibit nerve conduction *in vitro*⁵³. In support of this finding, we further showed that the anti-MBP T-cell line indeed produced a transient but significant inhibition of electrophysiological activity in the injured nerve, and that this inhibition of nerve conduction coincided with the peak of T-cell accumulation at the injury site¹⁴. There is evidence that cytokines can affect the electrophysiological functions of neurons and glial cells directly⁵⁴. Thus, cytokines secreted by anti-MBP T cells at the injury site might induce a transient reduction in neuronal excitability, for example, by

increasing inactivation of the Na⁺ current⁵⁴. These findings suggest that the anti-MBP T cells might reduce injury-induced secondary damage by inducing a transient resting state in the damaged nerve, thereby reducing its energy demands and enhancing its ability to cope with the stress that results from the injury. At this stage of study, we do not know whether the neuroprotection mediated by passive transfer of autoimmune T cells occurs directly or whether it is an indirect effect that involves other cells, such as macrophages.

Autoimmunity in the CNS

T cells that react specifically to CNS-myelin antigens have justifiably earned a bad reputation. Such autoimmune T cells cause the potentially lethal disease EAE in animals^{55,56} and are associated with multiple sclerosis in humans⁵⁷. Nevertheless, despite the classical teaching that potentially pathogenic T cells should not exist in healthy individuals⁵⁸, it is experimentally evident that MBP-responsive T cells can be isolated from healthy individuals and not only from patients suffering from multiple sclerosis^{59–61}. Natural autoimmunity to specific dominant self-antigens such as MBP was proposed to represent the immune system's positive picture of the individual self, the 'immunological homunculus'⁶². Indeed, components of myelin appear to be prominent among the limited set of self-antigens to which autoimmunity naturally exists. Moreover, CNS trauma was found to elicit an autoimmune response against a component of CNS myelin. Spinal-cord contusion was shown to cause direct sensitization of the host immune system to MBP and, indeed, when injected intravenously into naïve rats, systemic T cells isolated from spinal-cord-injured rats caused neurological deficits that were similar to EAE (Ref. 63). Thus, it seems that autoimmunity is awakened in response to CNS injury. It is conceivable that the endogenous T cells that accumulate spontaneously at sites of CNS injury arise from an injury-triggered autoimmune response⁶⁴. It might be beneficial but too weak and in need of boosting, or inappropriate and in need of modification. The results presented above suggest that, under certain circumstances, autoimmunity might be beneficial in CNS maintenance. We infer that the spontaneous autoimmune response is not optimal with respect to what is needed to prevent secondary damage.

Recent evidence suggests that inflammation in the CNS is associated with an altered presentation of endogenous MBP, which results in activation of T cells that are specific for cryptic epitopes possibly hidden in intact nerves⁶⁵. Epitopes that are not accessible in the intact CNS might become sufficiently accessible after injury to be seen by receptor-bearing T cells. This might explain the similarity in the neuroprotective effects induced by the anti-p51–70 T cells and the anti-MBP T cells, despite their differing effects in the intact CNS. Accordingly, it might be worthwhile seeking ways to augment a beneficial autoimmune response therapeutically without triggering a persisting autoimmune disease. Such augmentation might be achieved, for example, by employing T cells that are specific to the self-antigenic epitopes normally sequestered in the intact CNS. These autoimmune T cells would not accumulate or interact with undamaged areas and, thus, would not induce disease, yet they might be able to assist in the repair of injured CNS tissue if the injury should expose the covert epitope.

Concluding remarks

The results presented in this article suggest that activated, anti-CNS T cells (which confer adaptive autoimmunity), as well as activated macrophages (which represent innate immunity), can help to sustain the injured CNS. Figure 2 summarizes how activated macrophages and autoimmune T cells might promote re-growth and protection from secondary degeneration in the CNS following white-matter injury.

Over the years, immune privilege in the CNS has been interpreted in contradictory terms. It was first viewed as a life protector; the organism was seen to be so dependent on the integrity of the CNS that any form of immunological intervention could only be life threatening. Subsequent theories suggested that immune privilege in the CNS had evolved to save the specialized and intricate neural networks from modifications that might be caused by immune cells or molecules; loss of a specific function would be preferable to marred recovery. Our present theory is that immune privilege is an optimal solution for ongoing maintenance of the healthy and intact CNS, but becomes disadvantageous once the CNS has suffered injury. Furthermore, intensive care and life-support systems were not available during most of vertebrate evolution. It is only through the cultural evolution of the human species that we now find ourselves able to contemplate the potential for CNS repair. It is possible that the inability of the CNS to recover after injury is the price that the CNS pays for being an immune-privileged site. The challenge, then, is to learn how to manipulate immune privilege medicinally and how to supply the immune agents needed to reinstate the maintenance of CNS tissue. Future research should aim to exploit the biology of immune maintenance in order to improve the outcome of CNS trauma. Although still in its infancy, the idea that innate and adaptive immune responses have a potential role in CNS rescue and repair is leading to new ways of considering the dialog between the immune system and the CNS.

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