

Manipulating neuroinflammatory reactions in the injured spinal cord: back to basics

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Recruitment of inflammatory leukocytes to the injured spinal cord is a physiological response that is associated with the production of cytokines and proteinases that are involved in host defense and wound repair. Cells in the spinal cord are mainly post-mitotic and tissue regeneration is poor; thus, these inflammatory mediators can exacerbate the damage to spared tissue and thereby impair spontaneous functional recovery. Although several aspects of immune function might benefit the CNS, experimental studies indicate that acute neuroinflammation aggravates tissue injury. Until the timing and nature of the molecular signals that govern leukocyte recruitment and activation after spinal injury are defined, clinical therapies designed to boost immune cell function should be avoided.

Inflammation is an inevitable but poorly understood consequence of traumatic spinal cord injury (SCI). Debate about the beneficial versus injurious potential of inflammation is not surprising given its pivotal role in the physiology and pathology of all organ systems. Historically, clinical and experimental research in multiple sclerosis (MS) has focused on ameliorating the destructive potential of leukocytes (i.e. macrophages and lymphocytes). Recently, with the realization that leukocytes can also promote remyelination and neuronal survival, attention has shifted towards amplifying the immune response as a therapy for a variety of neurological diseases. Clinical trials are currently under way to evaluate the regenerative potential of macrophages transplanted into the acutely injured spinal cord [1,2]. Similarly, according to the concept of 'protective autoimmunity' vaccines designed to augment CNS-reactive lymphocytes could be therapeutic and clinical trials appear imminent [3]. Both approaches are predicated on the notion that the immune response to SCI is weak or ineffective and that immune-mediated healing can only be achieved by boosting the response. However, it is just as likely that the inflammatory response that accompanies SCI is potentially damaging and that boosting it will cause immune-mediated destruction of nervous tissue.

Role of innate immunity in the injured spinal cord

Mammalian immune responses require the collective actions of innate and adaptive immunity (Fig. 1). Phagocytes (i.e. neutrophils and macrophages) are the primary cellular components of the innate immune system. This system is evolutionarily conserved and non-specific for particular antigens. By contrast, adaptive immunity, which is mediated by lymphocytes, is activated in response to specific antigenic signals (Fig. 1). Historically, the CNS has been viewed as devoid of routine immune-system surveillance. This notion was perpetuated by studies showing that leukocyte recruitment to the injured brain is delayed and limited [4,5]. The rapid and vigorous inflammation that accompanies regeneration of injured peripheral nerves cemented the belief that immune responses in the CNS are weak and must be amplified to exploit the intrinsic reparative capacity of inflammation [6]. Although attractive in theory, and perhaps valid in the brain, this hypothesis is countered

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by several studies that show rapid and robust inflammation after SCI [7–10]. In fact, the infiltration kinetics and phenotype of cells that participate in inflammation in an injured spinal cord are indistinguishable from those found in injured peripheral tissues and are typical of the early phases of wound healing [11]. Later phases of wound healing, including growth factor and/or cytokine production, extracellular matrix deposition, revascularization and scarring, are also prevalent in the injured spinal cord. However, the question remains as to whether the CNS wound-healing response is conventional and, if so, whether it is advantageous [11]. Specifically, although required for cleaning and preparing the injury site for the proliferative and remodeling phases of wound repair, the physiological functions of neutrophils, macrophages and lymphocytes might be linked to CNS tissue damage.

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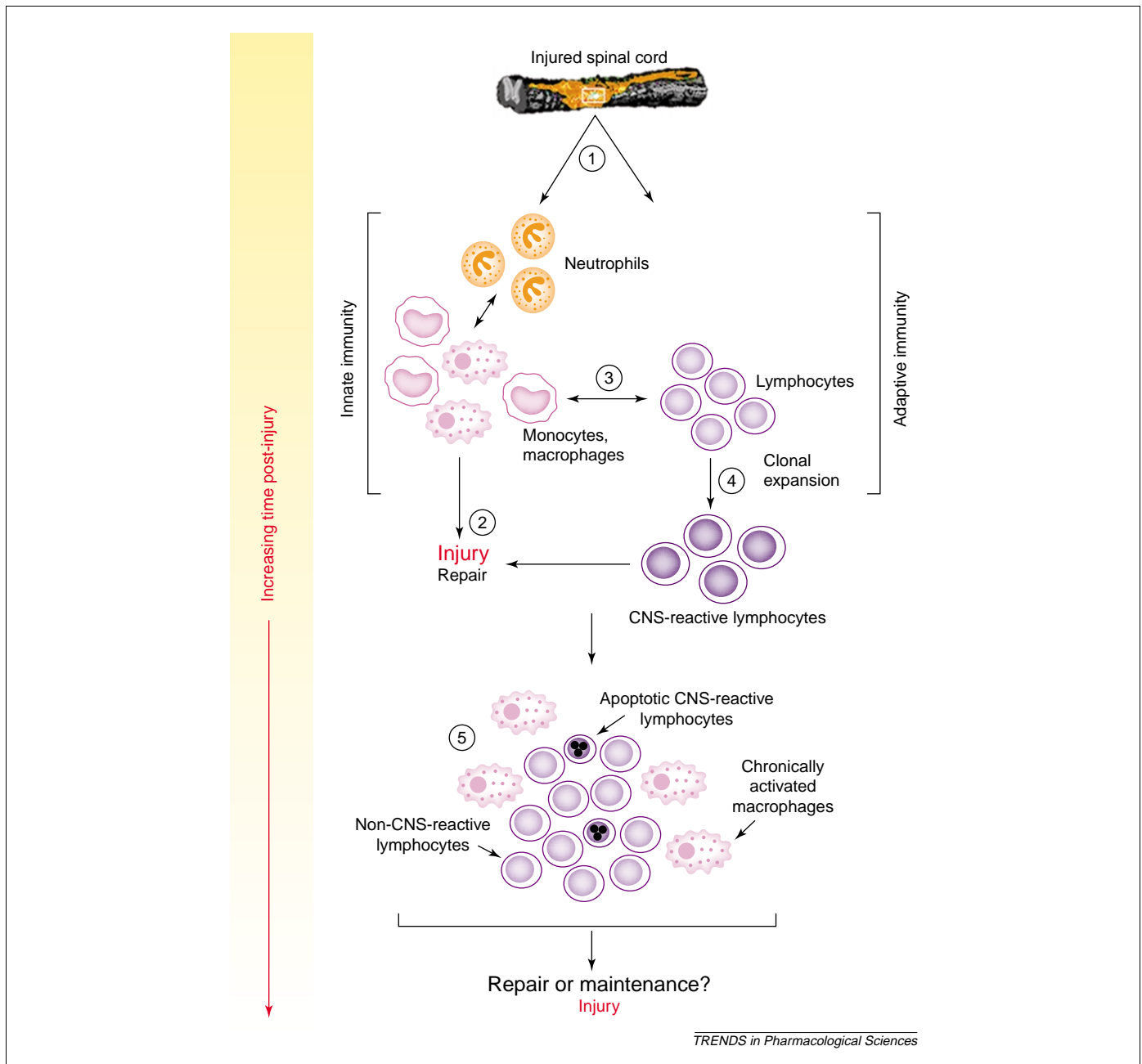


Fig. 1. Cells of the innate and adaptive immune systems are recruited to the spinal cord after injury [8]. The relative timing of leukocyte infiltration is illustrated on a continuum with early infiltrating cells pictured above later infiltrating cells (i.e. infiltration by neutrophils precedes that of monocytes, which overlap in time with lymphocytes). Uninjured spinal cord represents day 0. Double-headed arrows denote reciprocal interactions that might occur between immune cells. Leukocytes are recruited to the site of injury in the first few days after injury (1). Neutrophils infiltrate early, presumably to clear the injury site of pathogens (e.g. bacteria). Monocytes and macrophages infiltrate soon after and remove effete neutrophils. Monocytes and macrophages are crucial to virtually all forms of wound healing and remove necrotic debris while simultaneously preparing the injury site for the infiltration of new blood vessels and parenchymal cells. Macrophages also release a cadre of proteolytic enzymes (e.g. matrix metalloproteinases) that break down the extracellular matrix and are neurotoxic and gliotoxic (2). Macrophages also act as accessory cells (i.e. antigen-presenting cells) that can regulate the survival of infiltrating lymphocytes, a subset of which might be CNS reactive (3). If activated, CNS-reactive lymphocytes proliferate and undergo clonal expansion (4). Collectively, the acute host-defense activity of innate and adaptive immunity is injurious to spared CNS tissues and prevails over neuroinflammatory repair (2). However, macrophages and lymphocytes persist in the spinal cord for months and years after spinal cord injury but they are not associated with chronic neurological deterioration. Thus, it is possible that the physiological regulation of acute inflammation and trauma-induced autoimmunity, which involves the induction of regulatory immune networks and apoptosis of CNS-reactive T cells, might contribute to either repair or maintenance of the CNS (5) [29]. Interventions that boost immune function too early in the continuum run the risk of accentuating the physiological host-defense functions of the immune system, which can exacerbate neuronal and glial cell death (2). Interventions at later post-injury intervals are equally problematic because the chronic functional potential of innate and adaptive immune cells in the spinal parenchyma is unknown.

Recruitment of neutrophils and monocytes to the site of injury is a physiological response to trauma and one of the earliest phases of host defense and wound healing (Fig. 1). Regardless of whether pathogens are encountered at the injury site, the accumulation of CNS debris is probably sufficient to initiate neutrophil and macrophage

phagocytosis and release of neurotoxins. Ligation of CR3, Fc and Toll-like receptors on either neutrophils or macrophages by CNS proteins, myelin debris and other cells can trigger the release of inflammatory mediators that can cause necrotic cavitating pathology and demyelination [12–15]. However, the extent to which neutrophils

and macrophages contribute individually to this response after SCI is not clear.

Activation of neutrophils is accompanied by the release of microbicidal factors, including myeloperoxidase and elastase, which undoubtedly contribute to tissue injury after traumatic SCI (Fig. 1). Pharmacological blockade of these neutrophil products improves the anatomical and functional outcomes after SCI in rats [16,17]. Additionally, macrophage secretions are toxic to neurons and glia [18]. Not surprisingly, either attenuation or depletion of monocyte and/or macrophage activity in the acutely injured spinal cord of rats, guinea-pigs and rabbits decreases secondary demyelination and/or axon loss and improves neurological recovery [19–22].

However, signaling through the same receptors also initiates early phases of tissue repair (Fig. 1) [23]. The challenge is to define ways to selectively manipulate macrophage signaling pathways to maximize their repair potential and, simultaneously, minimize their inherent destructive capacities. Unfortunately, there is no experimental data to indicate that such an approach is feasible. Conversely, there is evidence that bulk activation of monocytes and/or macrophages early after SCI is both beneficial and detrimental. For example, blood monocytes can promote axon regeneration if they are activated *in vitro* with pre-degenerated peripheral nerve before transplantation into the spinal cord [2]. Similarly, using injections of lipopolysaccharide (LPS) to trigger cytokine production by macrophages *in vivo*, Guth and colleagues showed a modest reduction of lesion cavitation and increased neuritic sprouting after SCI in rats [24]. Together, these studies indicate that triggering macrophage activity can circumvent the deleterious effects of the endogenous inflammatory response. However, when LPS was co-administered with anti-inflammatory steroids and a cyclooxygenase inhibitor, anatomical repair was enhanced and neurological function improved [25]. These data illustrate that regardless of whether macrophage repair functions can be bolstered, several aspects of acute macrophage activation are deleterious in the CNS.

In the chronically injured spinal cord, lipid-engorged macrophages persist for months to years post-injury. What role these cells play in chronic phases of tissue injury, maintenance and repair is unknown. However, chronic activation of macrophages is consistent with the formation of a granuloma and is indicative of aberrant wound healing. Any intervention that increases the number of macrophages in the acutely injured spinal cord might exacerbate this condition and predispose the spinal cord to chronic macrophage-mediated injury. Indeed, deleterious macrophage functions could be triggered by persisting neuronal and/or glial debris (see above). Interestingly, chronic macrophage activation might also facilitate the expression of latent endogenous retroviral proteins that could trigger the onset of additional neurological complications, including autoimmune disease [26]. Until we better appreciate the ligand–receptor pathways and molecular signaling cascades that are used by macrophages after SCI and whether they can be controlled, we argue against the intentional activation and/or introduction of these cells into the injury site, which

could provoke tissue injury beyond a level sustained by trauma.

Adaptive immunity and the induction of autoimmune responses after SCI

Lymphocytes represent the adaptive cellular arm of the immune system (Fig. 1). If a lymphocyte recognizes and responds to self-protein, it is said to be 'autoreactive'. Although most autoreactive lymphocytes are eliminated in the thymus during immunological development, a small number persist throughout an individual's lifetime. Of these cells, some can react with CNS proteins [27] and activation of CNS-reactive T cells is believed to play a prominent role in the demyelinating disorder MS [28].

Previously, we demonstrated that CNS-reactive T cells are activated in SCI [29,30]. Other groups have shown activation of myelin basic protein (MBP)-reactive T cells after experimental and clinical nerve trauma [31,32]. Clinical studies that show increased frequencies of MBP-reactive T cells in SCI and stroke patients provide further evidence of an association between CNS trauma and the activation of CNS-autoreactive T cells [33–35]. The extent to which these T cells participate in tissue injury after SCI remains controversial. However, using Lewis rats and transgenic mice enriched in MBP-reactive T cells, we have demonstrated that CNS-reactive T cells can exacerbate axonal injury, demyelination and functional loss after SCI, thereby revealing their destructive potential [29,30].

Nevertheless, although these cells have the potential to contribute to neurodegeneration after SCI, a chronic, progressive, immune-mediated pathology, such as that seen in MS, is not typical after either experimental or clinical SCI [29]. Thus, it appears that T-cell reactions against CNS proteins exacerbate acute tissue damage while simultaneously triggering the induction of chronic immunoregulatory networks (Fig. 1). Previously, we suggested that destructive autoimmune reactions initiated by SCI were self-limiting and terminated by either regulatory cytokine networks or the rapid, widespread induction of apoptosis in infiltrating T cells [29,36]. Recently, Schwartz and colleagues have proposed that trauma-induced activation of myelin-reactive T cells is a physiological rather than a pathological consequence of injury and should be boosted (i.e. vaccines should be developed) to achieve neuroprotection [3]. This 'protective autoimmunity' theory is based on data that show improved histological and functional outcome from SCI in animals immunized with MBP, MBP-reactive T-cell lines and 'myelin-like' proteins [37,38]. To date, 'protective autoimmunity' has not been corroborated and there is no definitive mechanism that describes its efficacy. Potential mechanisms include the induction of 'metabolic rest' in injured neurons and improved neuronal survival as a result of either cytokine or neurotrophin production by infiltrating, autoreactive T cells [39,40].

Immune-mediated induction of metabolic rest in neurons could also be interpreted as impaired nerve conduction. Cytokines can impair axonal conduction and increases in these molecules in patients with chronic SCI might exacerbate the deficits caused by axonal injury and

demyelination [41,42]. Furthermore, although myelin-reactive T cells can produce neurotrophins *in vitro*, it is debatable whether these are produced in the injured CNS. In fact, if autoreactive lymphocytes can support neuronal survival *in vivo*, it is probably the result of autoreactive-T-cell-mediated activation of other, non-CNS-reactive T cells or B cells, resident microglia and infiltrating macrophages.

Several lines of evidence support this hypothesis. First, using transgenic mice in which virtually all T cells are MBP-reactive, we could not detect increased intraspinal production of neurotrophins (neurotrophin 3 and brain-derived neurotrophic factor) following SCI [30]. In these mice, we observed progressive demyelinating pathology and chronic functional impairment, findings that could be explained by a paucity of naturally occurring 'regulatory T cells'. Indeed, regulatory T cells can attenuate the destructive potential of autoimmunity in experimental autoimmune encephalitis (EAE) and stroke [35,43], and the usual absence of a sustained, pathogenic, CNS-reactive T-cell response after SCI could be explained by the parallel activation of regulatory T cells [3,29] (Fig. 1). Whether regulatory T cells are either involved in neurotrophin production or responsible for 'protective autoimmunity' is not known. In fact, the physiology and functional significance of these cells is ill defined [44]. Second, enhanced survival of mechanically injured spinal neurons in rats with EAE is associated with increased neurotrophin production by non-CNS-reactive T cells [45]. Third, reduced survival of facial motoneurons in immunodeficient (*scid*) mice is reversed by reconstitution with splenocytes (T cells and B cells of diverse antigen specificity) from wildtype mice [46]. Last, a recent study by Muhallab *et al.* revealed that in EAE, where MBP-reactive cells are the primary effectors of CNS inflammation, intraparenchymal neurotrophin production is associated predominantly with non-CNS-reactive T cells [47].

Based on these data, we question the safety of intentionally activating CNS-reactive T cells – a subset of which cause demyelination and axonal injury – that will non-specifically recruit other immune cells with poorly defined neuroprotective potential. Even activation of CNS-reactive T cells via 'safe' immunogens, such as altered peptide ligands (APLs) and glatiramer acetate (Cop-1) is questionable. This is especially true for APLs where two independent clinical trials in MS have been terminated following adverse immunological reactions [48,49]. Similarly, recent Phase IIA clinical trials in Alzheimer's disease were terminated after a subset of patients that received a vaccine to boost immune responses to β -amyloid in the CNS developed clinical signs of cerebral inflammation [50].

Concluding remarks

The above data illustrate the complexity of manipulating the immune system to repair CNS injuries. It is clear that most immune cells have the capacity to either repair or protect injured neurons and glia. Currently, however, we do not know whether it is possible to dissociate the beneficial aspects of inflammation from those that cause injury. Moreover, our relative ignorance of how gender and

genetics influence the immune response to CNS trauma makes developing immune-specific therapies for SCI a daunting task. In MS, polymorphisms in major histocompatibility complex (MHC) genes dramatically influence susceptibility to autoimmune disease. A similar relationship between the MHC, neuroinflammation and the outcome of SCI has not been determined. However, in individuals that are genetically predisposed to CNS autoimmune pathology autoreactive-T-cell vaccines or macrophage-augmentation therapies after SCI could either exacerbate tissue injury and loss of function or impair spontaneous recovery. Thus, immune therapies might need to be tailored to the individual. We are just beginning to appreciate that cells and mediators of the immune system can have divergent effects on neuronal and glial survival after SCI. Consequently, we must proceed with caution and acknowledge the infancy of this research area; otherwise, we risk damaging spared tissues that patients might learn to use either spontaneously or through rehabilitation therapy.

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