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Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury

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Abstract

Trauma to the central nervous system (CNS) triggers intraparenchymal inflammation and activation of systemic immunity with the capacity to exacerbate neuropathology and stimulate mechanisms of tissue repair. Despite our incomplete understanding of the mechanisms that control these divergent functions, immune-based therapies are becoming a therapeutic focus. This review will address the complexities and controversies of post-traumatic neuroinflammation, particularly in spinal cord. In addition, current therapies designed to target neuroinflammatory cascades will be discussed.

Keywords

macrophages; lymphocytes; neuroinflammation; spinal cord injury; traumatic brain injury; blood-brain barrier

Introduction

Central nervous system (CNS) trauma, either in the form of traumatic brain injury (TBI) or spinal cord injury (SCI), causes marked neuropathology and limited functional recovery. While mechanical trauma rapidly kills neurons and glia, an insidious and delayed secondary pathology follows. The latter may be amenable to therapy and is characterized by neuronal and glial apoptosis, increased blood-CNS barrier permeability and a complex and poorly understood neuroinflammatory response that can persist for months or years after the initial trauma (44;122;140).

The role of neuroinflammation is controversial. Both beneficial and detrimental effects have been ascribed to microglia/macrophages (CNS macrophages), lymphocytes, antibodies and cytokines. The goal of this review is to address the complexities and controversies of this response with an emphasis on SCI. In addition, we will discuss pre-clinical and clinical therapies that target neuroinflammation, addressing those that suppress or enhance the immune response.

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Traumatically-injured brain and spinal cord elicit distinct neuroinflammatory reactions

Although inflammation is a ubiquitous consequence of CNS trauma, the temporal sequence, composition and magnitude of this response in brain are distinct from spinal cord. Schnell and colleagues proved this point by comparing the inflammatory responses elicited by identical injuries delivered to mouse brain and spinal cord (147). Following a parasagittal incision to the cortex or a similar incision to the dorsal spinal cord, marked differences in cellular inflammation were observed. In the brain, neutrophil infiltration was minimal and was restricted to the lesion site. In contrast, twice as many neutrophils infiltrated the spinal cord lesion within 24 hours with large numbers of cells infiltrating into the surrounding parenchyma. Similarly, activation and recruitment of CNS macrophages was attenuated and restricted in distribution after brain injury relative to SCI. Lymphocyte numbers also were 2–3 times greater in the spinal cord with increased infiltration into surrounding tissue.

Similar changes were noted when neuroinflammation was elicited by non-traumatic microinjection of IL-1β or TNFα (148). In response to these cytokines, the recruitment of neutrophils and CNS macrophages was always greater in spinal cord. Following IL-1β microinjection, lymphocytes infiltrated the spinal cord but never the brain. TNFα microinjections into brain elicited a response comprised only of CNS macrophages while identical injections into spinal cord elicited neutrophils and macrophages. Molecular and anatomical differences between brain and spinal cord may explain the regional differences in leukocyte recruitment (170;171). Microvascular injury and serum extravasation in the inflamed spinal cord is increased in magnitude and duration relative to the brain (54;147) and is more susceptible to the permeabilizing effects of cytokines (148). Unique patterns of chemokine expression may also explain differential leukocyte recruitment. Specifically, neutrophil-attracting chemokines (e.g., CINC) are up-regulated to a greater extent in the injured spinal cord than in the brain (27).

There is a tendency for researchers to categorically lump mechanisms of brain and spinal cord neuroinflammation together; however, it is becoming clear that the spinal cord should not be considered simply an extension of the brain. Given the pivotal role played by immune cells in orchestrating cellular and molecular cascades of tissue injury and repair, future studies should explore the extent to which brain and spinal cord inflammation differ and define the mechanisms responsible for these differences. By doing so, novel site-specific therapies should be possible.

Species and strain-dependent differences in the neuroinflammatory response to spinal cord injury

Neuroinflammatory responses to SCI vary between species and strains of a given species. These differences are unlikely to be due to variable degrees of primary trauma between small and large animals. Spinal contusion and compression injury cause acute central hemorrhagic necrosis in all mammals and are accompanied by prominent glial activation and leukocyte infiltration (see Fig. 1B) (44;63;136;159). However, the onset, duration and composition of infiltrating leukocytes is distinct between humans and rodents, between rodent species (rat vs. mouse) and between different rat and mouse strains (44;81;136;159).

In all species, neutrophils accumulate within the lesion over the course of hours to days then, in most species, are rapidly cleared during the first week post-injury. In mice, elevated numbers of neutrophils persist in the lesion for months (81). In rats, lymphocytes infiltrate the lesion with monocytes 3–7 days post-injury. In contrast, lymphocyte entry is delayed in humans and mice with peak numbers evident after a delay of months post-injury (81;159). Unique to mice

is the formation of a dense connective tissue matrix in the lesion in parallel with lymphocyte accumulation (44;81;136;159).

It is clear that genetics are an important determinant of post-traumatic neuroinflammation. After SCI, the MRL and 129X1/SvJ mouse strains mount a diminutive neuroinflammatory response that is associated with enhanced tissue repair and endogenous axonal plasticity (34; 99). In contrast, dense fibrosis accompanies a robust inflammatory response in C57BL/6 mice but without significant axonal growth (81;99). A detailed comparative analysis in four common strains of mice after SCI failed to reveal a strict correlation between neuroinflammation, functional recovery and lesion pathology (81). Strain differences also extend to SCI rats, with increased numbers of leukocytes found in Lewis rats compared to Sprague-Dawley rats (136). The extended time course of macrophage accumulation in Lewis rats has also been described after optic nerve crush injury (154). These strain differences underscore the fact that within a genetically heterogeneous human population, attempts to manipulate inflammation to promote repair or minimize secondary injury will undoubtedly yield variable results. As diverse strains and species will continue to be used to extrapolate the human condition, future studies need to define how leukocyte populations vary between strains/species in the context of outcomes that are relevant to CNS repair. For example, do macrophages from C57BL/6 and MRL mouse strains release similar quantities of axon growth promoting proteins? Should the inflammatory contributions to remyelination be studied in BALB/c mice where post-injury inflammation is minimal relative to most other strains?

Changes in microvascular permeability after CNS injury: relationship to intraparenchymal inflammation

A prelude to the inflammatory response elicited by CNS trauma, and perhaps a consequence of this response at later times post-injury, is an increase in blood-brain barrier permeability (see Fig. 1E) (54;106;120;133;136;147;179). Using a rat model of spinal contusion injury, Noble and Wrathall initially described injury-induced changes in permeability to horseradish peroxidase (HRP) (120). They found that HRP extravasation correlated with injury severity; mild injury resulted in focal extravasation in spinal gray matter while severe injury involved gray and white matter. HRP extravasation was maximal within 1 day, with closure of the barrier by 14 days. Whetstone *et al.* described similar changes in acute permeability in SCI mice with a secondary rise in permeability 3–7 days post-injury (179). Interestingly, this secondary change parallels a time when blood monocytes infiltrate the injured spinal cord. A correlation between microglia activation and changes in microvascular permeability has been described in spinal cord white matter in SCI rats (133). While mechanical forces contribute to initial disruption of the blood-brain barrier, inflammatory mediators undoubtedly influence later changes in endothelial function, including maintenance of blood-to-tissue transfer.

The proinflammatory cytokines TNFα and IL-1β, which are up-regulated immediately after injury (see below and Fig. 1C), can enhance vascular permeability (148). A number of other vasoactive substances released by glia and leukocytes, including reactive oxygen species, kinins, histamines, nitric oxide and elastase, may also play a role (4;25;28;40;113;146;172). Furthermore, matrix metalloproteinase (MMP)-9, which is produced by neutrophils and endothelia, facilitates leukocyte diapedesis and may be a vascular permeabilizing factor (106). These data indicate that pathological alterations in blood-brain barrier function may be regulated by manipulating inflammatory cells and their release products. Alternatively, if properly controlled, these vasoactive properties of neuroinflammation could be harnessed to facilitate delivery of drugs to the chronically injured brain or spinal cord.

Immune-mediated injury in the traumatically injured CNS

Neutrophils and macrophages

Via the release of cytokines, free radicals, eicosanoids and proteases, activated neutrophils and macrophages can cause neuronal and glial toxicity (see Fig. 1A) (9;22;29;31;97;109;117; 155). This toxic potential has been demonstrated repeatedly in various models of SCI. Protocols to deplete or neutralize neutrophils and macrophages or inhibit their functions, have provided consistent neuroprotection and improved neurological recovery (15;19;41;49;50;52;119;131; 166).

Neurons and glia synthesize pro-inflammatory cytokines (e.g., TNFα and IL-1β) as part of normal intercellular communication (69;139). However, sustained elevations of TNFα and IL-1β evoke inflammation and dysregulate cytokine release causing neuron and oligodendrocyte death (see Fig. 1C) (26;66;91;98;155). Blocking TNFα or IL-1β confers neuroprotection in models of SCI, TBI and stroke (48;116;145;156). IL-6 and LIF also have been implicated in secondary neurodegeneration after CNS injury (see Fig. 1C) (77;89;100; 124). Over-expression of IL-6 or LIF in spinal cord enhances leukocyte infiltration, decreases axonal growth and impairs locomotor recovery (89). Clearly, cytokines are important for maintaining homeostasis in the CNS but after injury they can become pathological.

Oxidative stress, caused by ischemia-reperfusion and inflammatory byproducts, contributes to cell death cascades after traumatic and ischemic CNS injury (5;57;94;157;180;183). Neutrophils, microglia and macrophages produce superoxide anion and nitric oxide which combine to form the highly reactive and toxic compound peroxynitrite (32;36;96;102;177; 180). Free radicals produced during these processes induce apoptosis in neurons and glia via the irreversible oxidation of proteins, lipids and nucleic acids (42;92;95;109;180).

Glutamate is the chief excitatory neurotransmitter in the CNS; however, excess glutamate causes excitotoxicity in gray and white matter (33;93;107;123). Normally, glutamate is cleared from the extracellular space by astrocytes and to a limited degree by microglia (105;144; 174). After injury, glutamate metabolism by astrocytes is impaired and clearance is inhibited further by TNFα and IL-1β (30;130;164), reactive oxygen species (128;175) and arachidonic acid (187). Activated microglia and macrophages are also likely to increase glutamate levels in the extracellular cleft (121;126;127). These latter changes in glutamate may be undetectable via conventional detection systems (e.g., microdialysis) but could still sensitize neurons to the effects of other substances in the microenvironment. Indeed, a feed-forward mechanism of glutamate excitotoxicity is feasible given that pro-inflammatory cytokines (e.g., TNFα) modulate the expression of synaptic AMPA and GABA receptors rendering neurons more susceptible to excitotoxicity (13;160).

Activated neutrophils and macrophages also produce neurotoxic enzymes. Phospholipase A2, a key enzyme in eicosanoid synthesis, is up-regulated in microglia, neurons and oligodendrocytes (97). Arachidonic acid and eicosanoids can be neurotoxic due to their ability to promote cyclooxygenase and free radical synthesis and by enhancing vascular permeability and leukocyte influx (3;38;76;88;103;173). Extracellular matrix-degrading enzymes (e.g., MMPs) produced by neutrophils, macrophages and endothelia also have been implicated in secondary injury (44;119;178;186).

Lymphocytes

Like microglia and macrophages, activated lymphocytes have conflicting effects on the injured CNS. Decades of experimental and clinical research in multiple sclerosis have shown the pathological potential of neuroantigen-reactive T and B lymphocytes, mostly those that recognize and mount reactions against myelin proteins (e.g., myelin basic protein; MBP)

(47;55;65;68;161;176). These autoimmune responses amplify CNS macrophage effector functions resulting in blood-brain barrier injury and toxicity to oligodendrocytes and neurons (14;149;158). The result is widespread edema, axonal injury and loss of function (see Fig. 1A). The notion that traumatic or ischemic CNS injury can trigger pathological autoimmunity is a relatively new concept (1;135). Still, a growing body of evidence in animal models and human SCI has confirmed this potential (43;51;74;82). Using transgenic mice and rats vaccinated to expand MBP-reactive T cells, we have shown that autoimmune reactions exacerbate demyelination and axonal pathology, effectively increasing the size of the contusion lesion and causing loss of supraspinal neurons (73;74). This destructive potential is not restricted to MBP-reactive cells or SCI as T cells reactive with myelin oligodendrocyte glycoprotein (MOG) or ovalbumin (OVA; a non-CNS protein) exacerbate neuron loss in a model of peripheral nerve injury (2). The fact that OVA immunizations increased neuropathology indicates that T cells need not be myelin-reactive to contribute to secondary neurodegeneration. Indeed, mice and rats without T-lymphocytes (RAG knockout and athymic nude rats) have attenuated neuropathology after TBI and SCI (43;137). Also, antibody-mediated blockade of lymphocyte chemokines inhibits T cell infiltration and attenuates secondary injury after SCI (51).

Implicit to most T cell reactions is parallel activation of B cells and antibody secretion. Evidence that B cells are activated after SCI is implied from clinical data showing elevated levels of CNS autoantibodies in the serum of individuals with chronic SCI (64). We recently confirmed this potential in a mouse model of spinal contusion injury showing that SCI induces the production of autoantibodies directed against CNS proteins and systemic antigens including DNA (1). Interestingly, anti-DNA antibodies can cross-react with glutamate receptors (37). If these cross-reactive anti-DNA antibodies are pathological, then B cell-mediated pathology may transcend the spinal cord. Indeed, in systemic lupus erythematosus, anti-DNA antibodies cause cognitive deficits and widespread organ pathology. These latter parameters are not usually considered in paraplegic or quadriplegic individuals; however, SCI autoantibodies injected into intact hippocampi induced neuroinflammation and neuronal apoptosis (1).

Immune cell-mediated neuroprotection and regeneration

Neutrophils and macrophages

Given their primary function as bactericidal cells, it is doubtful that neutrophils exert neuroprotection in the CNS. This is not true for CNS macrophages. Despite being adept killers of neurons and glia, microglia may be intrinsically neuroprotective; they regularly survey the CNS and provide trophic support to neurons and glia (6;87;118). Indeed, it makes little sense to have evolved a homogeneously distributed network of cells capable of destroying the CNS from within. Instead, both microglia and macrophages derived from infiltrating monocytes produce neuroprotective cytokines and growth factors (see Fig. 1D). For example, TGFβ1 produced by macrophages after injury (90;108) has beneficial effects on neurons (79) and limits oligodendrocyte toxicity (110). Classical neurotrophic factors including CNTF, IGF, HGF, PDGF, NGF, BDNF, GDNF and NT-3 also are synthesized and released by activated CNS macrophages (39;60;78;83;114;115).

CNS macrophages may protect and repair the injured CNS by modulating glutamate excitotoxicity and by promoting the growth of injured axons (see Fig. 1A). Better known for their ability to release glutamate, microglia and macrophages increase transporters that are able to take up extracellular glutamate (144;174). Several lines of evidence suggest that CNS macrophages can promote axon growth and perhaps long-distance regeneration. Arguably the most convincing of the recent data illustrating this potential was described in a model of optic nerve injury. In that study, a novel protein called oncomodulin (OM), released by activated macrophages, was shown to be responsible for promoting regeneration of injured retinal ganglion cells (185). Interestingly, the same mode of macrophage activation that produces OM,

causes the release of neurotoxic molecules (184). Thus, even though macrophages can promote axon regeneration, the potential for causing simultaneous injury exists. This will make it difficult to exploit CNS macrophage functions as a therapy in any form of CNS injury. Still, the rapid and enduring turnover of CNS macrophages from bone marrow makes it hard to ignore the possibility that these cells could be genetically-modified *ex vivo* and act as vehicles for drug delivery (17).

Lymphocytes

Although there is overwhelming evidence that lymphocytes can initiate and exacerbate injury to neurons and glia, recent data show that B and T cells may be an important and perhaps necessary component of CNS repair. Indeed, B and T cells can secrete a bioactive form of the neurotrophin BDNF (78). Moreover, Schwartz and colleagues have championed the idea of "protective autoimmunity" stating that autoreactive T cells, specifically those responding to myelin proteins, are an advantageous but inefficient response to CNS injury (151;152). As a result, they propose therapeutic vaccines to treat neurological disorders including SCI, TBI, glaucoma, and amyotrophic lateral sclerosis (150). Although this notion is in conflict with the prevailing dogma that autoreactive T cells are neurodestructive, the Schwartz laboratory has shown that passive or active MBP immunization limits secondary neurodegeneration in injured spinal cord and optic nerve (45;61;111). This neuroprotection is attributed to the expression of neurotrophins and antithrombin III by MBP-specific T cells (see Fig. 1D) (45). Because these protective effects are not evident in all rat or mouse strains, the application of therapeutic vaccines in humans will require a better understanding of how genetics influences autoimmunity (62;85). B cells also can exert beneficial effects in the traumatized CNS. In addition to providing neurotrophic factors, autoantibodies specific for myelin protein can promote axon regeneration and improve locomotor recovery after SCI (70).

Protective autoimmunity, as defined by Schwartz et al., requires proinflammatory myelin-reactive T cells (84). However, other investigators have suggested that neuroprotection is conferred by T cells that are not CNS-reactive after central and peripheral nerve injury (58; 75;153). Importantly, these latter cells are activated along with T cells specific for MBP (112). Clearly, our understanding of lymphocyte functions in the injured nervous system is incomplete.

Immunomodulatory and cell-specific therapies for SCI

Methylprednisolone (MP), a potent immunosuppressive glucocorticoid, can successfully suppress various indices of neuroinflammation in experimental SCI models (10;46;181;182). Although MP is the current standard of care for human SCI, the effectiveness and safety of this drug have recently been questioned (35;71;141). Because immune responses in the CNS can have dual effects, global immune suppression is unlikely to yield long-term benefits. Instead, optimal treatments should be tailored to augment the beneficial functions of neuroinflammation while simultaneously minimizing those that cause injury. Currently, an immunomodulatory therapy of this type does not exist. However, a number of promising pre-clinical studies and clinical trials have been completed illustrating the therapeutic potential of cell-specific therapies after SCI.

Several groups have confirmed the therapeutic potential of activated microglia and monocyte-derived macrophages in the injured spinal cord (21;138;142;143). Two studies revealed that microglial transplants placed into lesioned spinal cord promoted neurite growth (138;142). Although functional recovery was not documented in these latter reports, partial recovery was provided by transplanting activated monocytes into the caudal stump of transected rat spinal cord (143). The success of these pre-clinical models prompted a Phase I clinical trial. This trial was completed without any adverse effects associated with macrophage transplantation (86).

For more information about this trial and its implications, readers are directed to a recent review (80).

Other studies have illustrated the neuroprotective capacity of acute macrophage depletion. Indeed, studies in various species and models of SCI have independently verified that secondary loss of neurons (axons) and myelin is reduced after inhibition of monocyte, and in some cases, neutrophil, infiltration. This has been accomplished using macrophage-specific toxins (19;131), antibody-mediated blockade of integrins (7;8;52;101), chemokine antagonists (41) and pharmacological agents that inhibit microglia and/or monocyte migration and secretion (20;49). More importantly, these anatomical indices of recovery were paralleled by significant but variable improvements in motor, sensory and autonomic function.

Despite the pre-clinical success of therapeutic CNS vaccines, the safety of intentionally expanding autoreactive lymphocytes to repair the injured spinal cord remains questionable (134). Although, this type of therapy has been applied in humans with Alzheimer's disease with some evidence of efficacy (12;53;104;168), Phase II trials were suspended due to the onset of autoimmune meningoencephalitis in a small cohort of patients (18;125).

In addition to cell-specific therapies, a number of pharmacotherapies that target the immune-CNS axis have been investigated. Systemic treatment with the anti-inflammatory cytokine IL-10 limits secondary neurodegeneration and improves locomotor recovery in some but not all SCI rodents (16;23;165). Similarly, the antibiotic minocycline, known for its ability to inhibit microglia and macrophages, has been shown to be neuroprotective and reduce neuropathic pain in rat and mouse models of SCI (56;162;167).

Conclusions

Despite extensive experimental data implicating inflammation as a pathogenic component of SCI, inflammation also appears to be pivotal for tissue repair. A challenge for researchers is to learn how to control cross-talk between the nervous and immune systems to minimize delayed neurodegeneration while promoting axonal plasticity and regeneration. Moreover, a greater appreciation for how SCI influences leukocyte development, activation and mobilization within and from peripheral lymphoid tissues is needed. Armed with this new knowledge, more effective and safer immune-based strategies will become available to treat spinal cord trauma and other CNS injuries.

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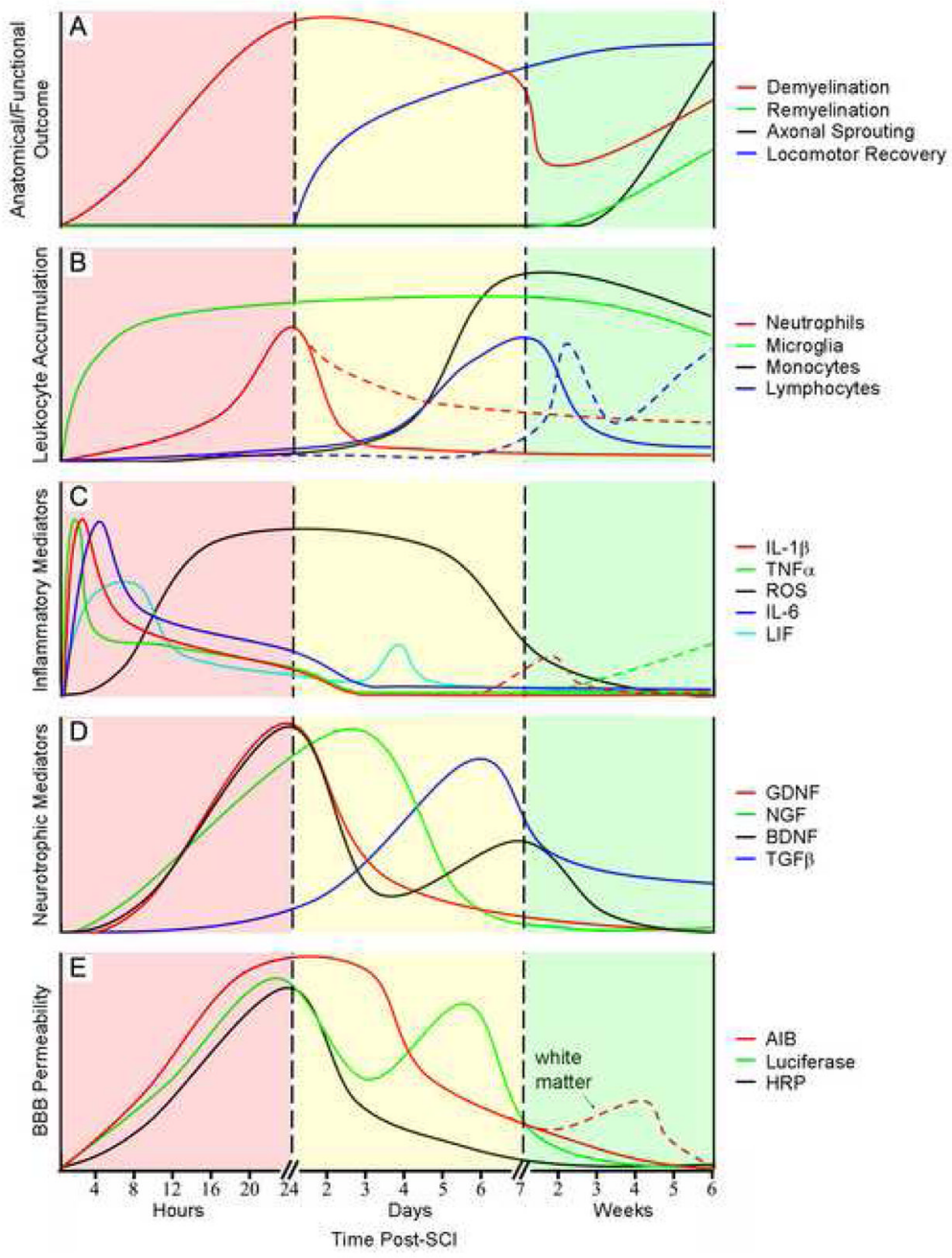

Figure 1.

Temporal correlation between inflammatory cascades, secondary neurodegenerative events and functional recovery in SCI rodents. **A)** Anatomical and functional outcomes, including de- and remyelination, axonal sprouting/plasticity and locomotor recovery. **B)** Activation of resident microglia and intraspinal accumulation of circulating leukocytes. Dashed lines departing from solid curves depict data from SCI mice whereas continuing solid curves indicate data from SCI rats. Solid curves before these break points are from both species. **C)** Expression of proinflammatory cytokines and reactive oxygen species (ROS). **D)** Expression of neurotrophic cytokines. **E)** Blood-brain barrier permeability to α-aminoisobutyric acid (AIB; 104 Da), horseradish peroxidase (HRP; 44000 Da), and luciferase (61000 Da). All AIB and

HRP data were obtained from rat SCI models while luciferase data was from mice. Dashed curve departing from AIB solid curve indicates secondary rise in AIB permeability in white matter whereas continuing solid curve indicates permeability in gray matter. Solid curve before this break point represents permeability in both white and gray matter. Values on the vertical axis represent relative changes and are not to scale. Curves were generated using data from the following references: A) (11;67;169); B) (81;132;136;159;188): C) (129;163;180); D) (24; 59;72;108); E) (120;133;179).