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REVIEW

# The Microanatomy of Spinal Cord Injury: A Review

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Spinal cord injury is a highly prevalent condition associated with significant morbidity and mortality. The pathophysiology underlying it is extraordinarily complex and still not completely understood. We performed a comprehensive literature review of the pathophysiologic processes underlying spinal cord injury. The mechanisms underlying primary and secondary spinal cord injury are distinguished based on a number of factors and include the initial mechanical injury force, the vascular supply of the spinal cord which is associated with spinal cord perfusion, spinal cord autoregulation, and post-traumatic ischemia, and a complex inflammatory cascade involving local and infiltrating immunomodulating cells. This review illustrates the current literature regarding the pathophysiology behind spinal cord injury and outlines potential therapeutic options for reversing these mechanisms. Clin. Anat. 00:000–000, 2014. © 2014 Wiley Periodicals, Inc.

**Key words: spinal cord; injury; mechanisms; vascular; compromise; therapy; inflammation**

## INTRODUCTION

Spinal cord injury (SCI) is one of the most prevalent and disabling conditions in the world. In the United States, its incidence has been estimated around 12,000 new cases a year, most are young and otherwise healthy patients. The mortality rate in injured patients ranges between 750 and 1,000 per year, mainly owing to septicemia and pneumonia (Center, June 15, 2011). SCI can be classified into four groups based on the gross findings: (1) solid cord injury, the least common type, is associated with normal appearance of the spinal cord after injury; (2) contusion/cavity, the most common type, is associated with the areas of hemorrhage and expanding necrosis and cavitation, but with no disruption of the surface of the spinal cord; (3) laceration, where is a clear-cut disruption of the surface anatomy; and (4) massive compression, where the cord is macerated or pulpified to varying degrees (Norenberg et al., 2004). However, in most instances, the anatomic degree of spinal cord disruption does not correlate with the degree of functional loss. This disparity is owing to the different phases of SCI and progressively deteriorating neuronal function. SCI can be divided into two, partially overlapping, phases: primary and secondary. Injury in the primary, or acute, phase occurs owing to the traumatic effect of the insult on the spinal cord. During and after this phase, the more insidious and deleterious secondary, or subacute, phase begins. This phase is associated with disruption to vascular supply of the spinal cord and inflammatory changes with consequent ischemia, cellular necrosis and apoptosis, scar formation, and prolonged Wallerian degeneration (WD) (Norenberg et al., 2004). The major challenge lies within the very limited regenerative capacity of the neural tissues through the central nervous system (CNS) tissue. Thus, in most cases, a

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permanent loss of motor, sensory, and autonomic function is inevitable. Nevertheless, improvements in understanding the pathological changes during and after the mechanical insult have resulted in the identification of targets for treatment. Herein, we will discuss the processes underlying vascular and inflammatory changes that govern the pathological process of SCI and their implications for treatment. Targets of inflammatory response and their corresponsive medical therapy have been reviewed recently (Mitchell and Lee, 2008; David et al., 2012; Singh et al., 2012) and go beyond the scope of this article.

## The Duration and Force of Mechanical SCI

In 1957, Tarlov described a series of experiments in dogs in which he described an approximate maximal duration and force of a compression that could give permanent SCI, both with acute and with subacute compression (Tarlov, 1957). In acute compression, he showed that no recovery could be seen if large balloon compression lasted at 5 min, medium balloon compression lasted at least 1 hr, and the small balloon compression lasted at least 3 hr. With the same force but shorter compression times, recovery could be achieved. When the compressive force increased slowly and steadily up to the maximal force, the chance of recovery was inversely proportional to the length of the speed and length of the force. Later, Carlson et al. (2003) came to the same conclusion in dogs, verifying that recovery is probably dependent on the duration of ischemia. Similar results have also been found in rats (Ducker et al., 1978; Dolan et al., 1980a; Delamarter et al., 1995).

## SCI and Perfusion

Neurological compromise in SCI has been, at least, partially attributed to diminished spinal cord perfusion. Carlson et al. showed a direct correlation between spinal cord blood flow and neurologic recovery measured with evoked potentials. Another study by the same group found that spinal cord compression for a short (5 min) and a long (3 hrs) duration resulted in diminished perfusion and neurologic compromise in terms of decreased evoked potentials. Decompression restituted perfusion and evoked potentials only if performed early (Carlson et al., 1997). Spinal cord perfusion was measured by the injection of fluorescent microspheres into the left ventricle of the heart. The microspheres lodge into the tissue microvasculature of various tissues in direct proportion to the cardiac output the tissue receives. Blood for the arterial reference sample is drawn. The number of microspheres in the tissue (in our case, spinal cord) and blood is compared by the mathematic formula: $Q_{SC} = (C_{SC} \times Q_R)/C_R$. $Q_{SC}$ is the spinal blood flow (mL/min/g), $C_{SC}$ is the microsphere count per gram of tissue, $Q_R$ is the withdrawal rate of the reference blood sample (mL/min), and $C_R$ is the microsphere count in the reference blood sample.

Other means of measuring spinal cord perfusion are the hydrogen electrode technique and the C14-antipyrine autoradiographic technique (Tator, 1991). However, these techniques are complicated and time consuming. Other ways of measuring spinal cord perfusion have been suggested by measuring the intrathecal oxygen, which has been shown being proportional to intramedullary oxygen (Ishizaki et al., 1997). One study in cats in which mannitol was given after a T5–6 crush injury clear and significant angiographic evidence of increased flow to the cord was demonstrated although this was not followed by neurologic recovery measured electrophysiologically (Reed et al., 1979).

In the injured spinal cord with disturbed autoregulation, the arterioles are maximally dilated owing to local acidosis and perfusion of the spinal cord becomes directly proportional to the systemic blood pressure. With use of systemic vasodilating agents or an increase in $pCO_2$, systemic vasodilatation may cause decreased systemic pressure, as well as dilatation of neighboring undilated arterioles and stealing of blood from the injured spinal cord where the arterioles are already maximally dilated. Thus, the collateral circulation of the spinal cord is of great importance. A more moderate trauma may leave the collaterals intact with some collateral circulation, limiting the impact of the main circulatory compromise to the spinal cord, whereas a severe and extended trauma, also compromising the collateral circulation, leaves no circulation to the injured spinal cord (Jellinger, 1972). Initially, vasopressors alone have not shown an increase in spinal cord blood flow by increasing the mean arterial pressure. However, a later study showed that when a vasopressor (epinephrine) and a calcium channel blocker (nimodipine) were systemically administered, local perfusion increased significantly after SCI. This study showed that solely maintaining a sufficient mean arterial pressure could not restore blood flow, but probably local effects, in terms of the presumptive arterial tone relaxation effects, of nimodipine played an important role (Dolan et al., 1980b). The findings also put the importance of the "steal-phenomenon" in question.

In an animal study, low-pressure reperfusion of the spinal cord after 25 min of ischemia showed significantly decreased neurological impairment compared to normotensive reperfusion (Shi et al., 2007). However, a different study showed that reperfusion of the cord after a compressive insult is not accompanied by the recovery of evoked potentials (Hitchon et al., 1990). Furthermore, the spinal venous system appears to have an impact on spinal cord perfusion and it is as well as shown in compression experiments (Jellinger, 1972; Griessenauer et al., 2014).

## SCI and Autoregulation

Intracranial pressure, systemic arterial pressure, and cerebral perfusion pressure are closely related to the brain and there is a reason to believe that a comparable system may exist in the spinal cord. The literature on this topic, however, is extremely sparse.

In the brain, perfusion pressure has been grossly calculated as the difference between the systemic

arterial pressure and the cortical venous pressure. As the cerebrospinal (colony-stimulating factor, CSF) pressure differs very little from the cortical venous pressure and the former is easier to measure, CSF pressure has been measured instead of cortical venous pressure. In a study performed on dogs, it has been shown that increasing CSF pressure through CSF infusion leads to decreased perfusion pressure, and is counteracted with arterial vasodilatation by decreasing vascular resistance to maintain steady blood flow (Haggendal et al., 1970). Therefore, it is reasonable to assume that the vascular tone is partly involved in autoregulation. On the other hand, the level of the autoregulatory cutoff has been shown to be affected by the sympathetic nervous system (Fitch et al., 1975). Furthermore, a human study has shown that preganglionic sympathectomy by complete cervical SCI impairs autoregulation during the first month after the injury although this impairment slowly regresses long term (Yamamoto et al., 1980).

In regard to autoregulation, the effects of CSF pressure on spinal cord blood flow, measured by the hydrogen clearance technique, were studied in dogs. CSF pressure was altered by the infusion of mock CSF into the lumbar subarachnoid space. Occluding snares at T13 limited the effect of raised pressure on the brain. As the spinal cord perfusion pressure was reduced when the CSF pressure was increased, flow remained constant down to a perfusion pressure of approximately 50 mm Hg. Below this value, flow decreased with decreasing spinal cord perfusion pressure. Normal flow values could be re-established even at a raised CSF pressure by raising systemic arterial pressure, and thus increasing the spinal cord perfusion pressure. Rapid reduction of CSF pressure was accompanied by reactive hyperemia. The autoregulation of flow down to a perfusion pressure of 50 mm Hg was postulated as being owing to a progressive decrease in vascular resistance. $CO_2$-responsiveness of the vessels was markedly decreased as the spinal cord perfusion pressure was reduced (Griffiths et al., 1978).

In another study in cats, autoregulation of the spinal cord showed a temporal relationship to SCI. It indicated that there was intact autoregulation during the initial 90 min after the cord injury and impairment coincided with the onset of ischemia (Senter and Venes, 1979). In a human study, 25 patients who underwent elective surgeries that required aortic crossclamping were studied prospectively. CSF drainage was applied both to measure CSF pressure and to have possibility to drain CSF. This study showed that the minimum spinal cord perfusion pressure needed in humans was 40 mm Hg as two patients with spinal cord perfusion pressures of 32 and 35 mm Hg had paraplegia. This study also showed that CSF drainage altering the balance toward keeping the spinal cord perfusion pressure more than 40 mm Hg was beneficial for preventing ischemia (Maeda et al., 1989) although other authors have suggested a distal aortic pressure of 60–70 mm Hg (Laschinger et al., 1983), without making mention of the spinal cord perfusion pressure itself.

## Peritraumatic Ischemia

Cord ischemia in experimental models parallels the severity of the clinical insult (Sandler and Tator, 1976b; Dolan et al., 1980b; Tator and Fehlings, 1991; Young, 1993) and is more pronounced in gray matter (Sandler and Tator, 1976a,b; Dolan et al., 1980b; Tator and Fehlings, 1991; Amar and Levy, 1999). Ischemia per se causes metabolic acidosis owing to the relative anaerobic metabolism, with a resulting decrease in pH, followed by reactive hyperemia (Sandler and Tator, 1976b) and reperfusion that may promote influx of toxic byproducts including free radicals, and therefore, cause cell damage (Lipton and Rosenberg, 1994). The traumatic force itself and intravascular coagulation owing to platelet thrombi and fibrin cause rupture of sulcal arterioles or postcapillary venules with resulting petechial hemorrhages within the spinal cord, which in turn, cause venous stasis and distension (Sandler and Tator, 1976a; Young, 1993; Chapman and Anderson, 1994; Tator and Koyanagi, 1997; Amar and Levy, 1999;). This causes leakage of proteinaceous fluid from the vascular bed into the extracellular space, leading to edema (Sandler and Tator, 1976a,b). As the pia is relatively firm, the edema causes increased interstitial pressure with resulting ischemia (Schwab and Bartholdi, 1996). Different substances released by the injured cells, including vasoactive substances such as endothelin, released from injured capillaries, may play a role in impairing spinal cord perfusion (Sandler and Tator, 1976a,b; Koyanagi et al., 1993; Tator and Koyanagi, 1997; Amar and Levy, 1999). Focal narrowing, aneurysmal dilatation, and occlusion of sulcal arterioles and intramedullary capillaries have all been demonstrated earlier (Koyanagi et al., 1993; Tator and Koyanagi, 1997). Ischemia in turn causes depletion of ATP which in turn leads to dysfunction of energy-dependent processes such as the sodium–potassium pump that preserves the cellular polarization. Once this process fails, the passive ionic gradients prevail, with influx of sodium and calcium into the cell, and efflux of potassium from the intracellular space, causing acute cellular swelling and worsening the pre-existing edema and cell dysfunction.

One important component of this dysfunctional process is a depolarization-dependent release of excitatory amino acids (EAAs) from the synaptic vesicles. As the uptake of the EAA is also ATP dependent and therefore inactivated by ATP depletion after ischemia, their extracellular concentration rises dramatically. For instance, the intracellular concentration of glutamate in the brain is approximately 10 mmol/L compared to its extracellular concentration of 0.6 μmol/L. Although its exact level in the spinal cord is less clear, it is reasonable to consider that the levels in the spinal cord approximate those in the brain. The cell disintegration by the primary mechanical injury itself and free radical action on cell membrane disintegration also cause efflux of the intracellular EAA to the extracellular compartment. Thus, the progressive increase of extracellular EAA secondary to three mechanisms relies on three mechanisms namely cell damage, Ca-dependent release of the EAA-containing intracellular vesicles,

and ischemic and Ca-dependent decrease in ATP-dependent EAA reuptake. It has been shown that the extracellular concentration of EAA increases dramatically to approximately eightfold of the normal (Rothman and Olney, 1986; Choi, 1988; Greenamyre and Porter, 1994). Extracellular EAA concentrations within the spinal cord have been shown to reach toxic levels within 15 min after experimental SCI (Wrathall et al., 1996). The increase in EAA is transient and probably lasts for about 2 hr after SCI (Farooque et al., 1996).

EAAs affect their surrounding mostly through a ligand–receptor reaction. Glutamate, for instance, may act on several receptor families (Greenamyre and Porter, 1994; Lipton and Rosenberg, 1994; Tymianski and Tator, 1996). There are two types of receptors: ionotropic and metabotropic. Ionotropic receptors are those that comprise ligand-gated ion channels. Metabotropic receptors comprise transmembrane proteins coupled with changes in the concentration of intracellular second messengers such as phosphoinositol and cyclic nucleotides.

Among ionotropic receptors are α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate receptors, and *N*-methyl-D-aspartate (NMDA) receptor. These receptors result in influx of sodium from the extracellular space although some subtypes may also be permeable to calcium. Metabotrophic receptors are more complex and have a binding site for glycine, an obligate coagonist. At resting membrane potential, the inward current is blocked by magnesium. The degree of the magnesium blockade is reduced as the neuron becomes depolarized. Therefore, additional depolarization of the cell, for instance influx of sodium by AMPA/kainite/NMDA receptors, or dysfunction of the ATP-dependent Na/K-pump, decreases magnesium's effect on the metabotrophic receptors and thus causes influx of calcium into the intracellular space (Choi, 1988; Siesjo, 1988; Greenamyre and Porter, 1994; Lipton and Rosenberg, 1994; Tymianski and Tator, 1996). The metabotropic receptors' activation leads to metabolism of inositol phospholipids and mobilization of intracellular calcium stores as well as inactivation of energy-dependent calcium transporters that pump cytosolic calcium across the cell membrane or store them within the mitochondria and the endoplasmic reticulum (Choi, 1988; Siesjo, 1988; Greenamyre and Porter, 1994; Lipton and Rosenberg, 1994; Tymianski and Tator, 1996).

Most of these models have been studied in the gray matter and most studies have failed to demonstrate that axons, myelin, oligodendrocytes, and astrocytes are equipped with NMDA receptors or they are vulnerable to glutamate administration (Greenamyre and Porter, 1994). Some studies, however, have suggested that periaxonal astrocytes may express certain subtypes of the AMPA and kainate receptors on their surface, and thus implicating these cells in glutaminergic white-matter injury (Tymianski and Tator, 1996).

In summary, malfunction of the ATP-dependent sodium/potassium pump with secondary increase of calcium leads to extracellular release and decrease in reuptake of EAA. This leads to further increase in intracellular calcium by their action on both NMDA and non-NMDA receptors which in turn causes more action on the EAA system and leads to a circle of progressively increasing intracellular calcium. Increased intracellular calcium also triggers several calcium-dependent processes, including generation of free radicals, further depletion of ATP through activation of calcium-dependent ATPase, activation of phospholipase A2, resulting in liberation of idonic acid from membrane phospholipids, mobilization of free fatty acids from the cell membrane, synthesis of toxic eicosanoids (Bethea and Dietrich, 2002; Jakovcevic and Harder, 2007), modification of the microtubular and neurofilament components of the cytoskeleton, impairment of mitochondrial oxidative phosphorylation, activation of lytic enzymes such as phosphatases, proteases and endonucleases, and axonal degeneration (Hall and Wolf, 1986; Choi, 1988; Lipton and Rosenberg, 1994; Tymianski and Tator, 1996).

The sustained elevation of cytosolic calcium is postulated as being the final common pathway mediating cell death in various tissue types (Hall and Wolf, 1986; Choi, 1988; Choi et al., 1988; Siesjo, 1988; Choi and Rothman, 1990; Lipton and Rosenberg, 1994; Tymianski and Tator, 1996).

Metabolites of arachidonic acid, discussed more in detail in the following paragraphs, are implicated in inflammation, immunity, act as messengers in the brain, and exert thrombogenic activity (Bethea and Dietrich, 2002; Jakovcevic and Harder, 2007). Arachidonic acid is metabolized by cyclooxygenase to prostaglandins, prostacyclines, thromboxanes, and a generator of free radicals.

## SCI and Mannitol

The recent literature on the role of mannitol in SCI is sparse. A recent study performed on rats demonstrated that the administration of 2 g/kg of 20% of mannitol showed significant improvement in the neural structures and protects the spinal cord after injury (Baysefer et al., 2003). In an older study, mannitol showed clear positive effects on promoting spinal cord perfusion in cats although no neuroprotection was seen here (Reed et al., 1979). As there is early edema and vascular compromise after SCI, beneficial effects of mannitol may be expected analogous to its effects in brain trauma. Its role and especially the timing of its administration in spinal cord trauma warrant further investigation.

## Inflammatory Cascade

**Cellular response and proinflammatory cytokines.** The most rapid cellular response after SCI is mounted by cells inherent to the spinal cord including microglia, astrocytes, oligodendrocytes, neurons, and endothelial cells. At 12-hr postinjury, microglia is seen in the lesion with a peak on 3–7 days throughout the gray and white matter at the epicenter of the lesion in rat spinal cord (Sroga et al., 2003). Both endothelial cells and microglia function as antigen-presenting cells (Popovich et al., 1997). These cells also express proinflammatory cytokines that are able to induce inflammatory response and recruit systemic immune

cells to the site of injury (David et al., 2012). These factors include interleukin (IL)-α (Pan et al., 2002), IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α) (Yang et al., 2004), macrophage colony-stimulating factor (M-CSF) (Streit et al., 1998), and leukemia inhibitory factor (Pineau and Lacroix, 2007). In a study on human patients, these factors were expressed by local neurons at 30 min and by neurons and microglia at 5 hr postinjury. However, this expression sharply declined to baseline 2 days postinjury (Yang et al., 2004). In mice and rats, these factors are expressed at 1 hr by the local neurons and at 6 hr by neurons and microglia, and declined to baseline after 1 day of injury (Streit et al., 1998; Pan et al., 2002; Yang et al., 2005; Pineau and Lacroix, 2007; Rice et al., 2007). In another study on mice, IL-1β and TNF-α were detected 5–15 min postinjury and expressed mainly by the microglia and astrocytes. Peak expression was at 12 hr for IL-1β and at 1 hr for TNF-α (Pineau and Lacroix, 2007). Another study first recorded their expression by microglia and endothelial cells at 30 min, whereas expression by neurons was evident at 24 hr (Bethea et al., 1998). Besides orchestrating the inflammatory reaction at the site of injury these factors may be involved in neuronal survival, neuronal myelination and myelin phagocytosis are associated with WD, regulation of astrocytic migration, proliferation, and consequent glial scar formation. The expression of IL-1β and TNF-α peaks again at 14 days after injury, before returning to control level again at day 28. This peak coincides with the T-lymphocyte infiltration at the site on injury (Pineau and Lacroix, 2007). The level of mRNA expression of these factors is dependent on the degree of injury, with less significant increases noticed in mild injury (Yang et al., 2005). After their early release, IL-1β and TNF-α will further activate other local cells, peripheral immune cells, and vasculoendothelial cells to secret cytokines, chemokines, and express cellular adherent molecules (CAMs) such as intracellular CAM-1, endothelial CAM-1, and E-selectin (Pineau and Lacroix, 2007). They may also have positive feedback effect on their secreting cells (Pan et al., 2002; Basu et al., 2004).

Chemokines, including CCL2 (monocyte chemoattractant protein-1 [MCP-1]), CCL3 (macrophage inflammatory protein-1 [MIP-1]), CCL4 (macrophage inflammatory protein-1A [MIP-1A]), CXCL2/3 (macrophage inflammatory protein-2 [MIP-2]), and CXCL10 (interferon-inducible protein of 10 kDa [IP-10]), are expressed by local cells at 30 min and peak at 6 hr after injury (Rice et al., 2007). In contrast to the cytokines, chemokines are still present at 24 hr after injury although at lower levels (Rice et al., 2007). Adherent molecules and chemokines represent the earliest method by which leukocytes are attracted to the site of injury. As the level of the early cytokines decreases after the first day, many systemic leukocytes have already infiltrated the site of injury and produce inflammatory cytokines, free radicals, and perform phagocytosis (Rice et al., 2007).

Regarding the peripheral immune cells, neutrophils are among the first cells coming to the injury site, being activated by IL1, IL2, and especially by IL6 (Taoka et al., 1997). They reach a peak level at 24 hr after injury and are markedly decreased at 3 days (Norenberg et al., 2004; Yang et al., 2005; Fleming et al., 2006; Donnelly and Popovich, 2008), and they represent 90% of the infiltrating cells 12 hr after the injury (Stirling and Yong, 2008). These are followed by the entry of the peripheral monocytes and macrophages, which occurs around 3–4 days postinjury. Their recruitment, as in the case of neutrophils, might be mainly related to the CCL2, CXCL1, and CXCL2 chemokines (Pineau et al., 2010). Once at the site of injury, these cells assume a phagocytic function and are hardly differentiated from the local microglia based on their morphology or antigenic profile alone, and thus collectively referred to as macrophages/microglia (also known as CNS macrophages) (Rice et al., 2007; Stirling and Yong, 2008). Macrophages play a critical role in phagocytosis of denatured dendrites (Wu et al., 2005). The level of these cells peak is at 7–10 days and may persist until weeks or months after injury (Donnelly and Popovich, 2008).

In humans, SCI infiltration with T-lymphocytes might be detected months after injury, and no B-lymphocytes are usually found (Fleming et al., 2006). This contrast mice models where both cells types can be found at 1 week after SCI, reaching their peak at 42 days, and contribute to secondary SCI (see below) (Ankeny et al., 2006; Ankeny and Popovich, 2009). The fact that reroutes the T cells and their subtypes to the lesion site has been extensively studied without final conclusions. However, it appears as if dendritic cells (DCs), as well as endothelial and the inherent microglia, contribute (Banati et al., 1993; Sroga et al., 2003). Interactions between subgroups of DCs and T-cell differentiation are described below. There have been three subsets of T-helper cells (Th1, Th2, and Th17) and at least two subsets of DCs (myeloid and plasmocytic) have been identified. The myeloid DC usually directs the immature T cells toward the Th1 subtype which is more active against intracellular pathogens. Meanwhile, the plasmocytic DC predominantly steers T cells toward the Th2 subtype that is mostly involved in the extracellular response including antigen-related responses. The role of the more recently identified Th17 is under investigation. No specific T-helper has been specifically associated with SCI, yet understanding of T-cell differentiation and DC interactions may be of importance in this entity as well. For instance, one study showed significant recovery when myelin-activated bone marrow-derived DCs were injected either locally into the lesion or systemically (Hauben et al., 2003).

The rerouted T cells, in turn, excrete cytokines, controlling subgroups of T cells as well as monocytes toward the lesion site. T-cell vaccination of mice with a myelin-derived peptide, when combined with neural precursor cell (also known as stem cell) transplantation into the cerebrospinal fluid, synergistically promoted functional recovery (Ziv et al., 2006). Monocytes leaving the vascular bed and into the lesion site, being activated macrophages, increase in number, and are the predominant inflammatory cell in the gray matter within the first week. Microglia are also transformed into intrinsic macrophages and appear to be under strict control (Banati et al., 1993).

The entry of the peripheral immune cells is facilitated by increased vascular permeability and the disruption of the blood–brain barrier. This is induced by the initial mechanical force and inflammatory mediators (Donnelly and Popovich, 2008). The latter include the early inflammatory cytokines, TNF-$\alpha$ and IL-1$\beta$, and may also include reactive oxygen species, kinins, histamines, nitric oxide, elastase, and matrix metalloproteinase-9 (Donnelly and Popovich, 2008). The permeability peaks increased during the first day after injury (Noble and Wrathall, 1989) and also at 3–7 days (Whetstone et al., 2003) before significantly decreasing at 14 days (Noble and Wrathall, 1989). The secondary peak correlates with monocytes and macrophage infiltration.

Complement activation is also a part of these inflammatory reactions. Cleavage of C3 by the enzyme C3 convertase ultimately leads to the formation of the terminal proinflammatory and cytolytic membrane attack complex. There are studies suggesting complement proteins being deposited in neurons and oligodendrocytes at the site of the SCI for a sustained period of time after injury in rats (Anderson et al., 2004). Mice deficient in C3, and wild-type mice treated with CR2-cry, a complement inhibitor, have improved functional outcomes (Qiao et al., 2006).

Oligodendrocytes assume a maturation process that eventually results in remyelination above the lesion. Below the lesion, this process is prematurely interrupted; however, intact oligodendrocytes persist even below the lesion where they constitute a source for remyelination of regenerating or implanted axons (Morin-Richaud et al., 1998).

**Secondary injury and neuroprotection induced by inflammatory cells.** The inflammatory reactions put the surrounding viable cells and tracts at risk for more damage, leading to secondary injury or apoptosis (Schwab and Caroni, 1988). Thus, the terminal SCI usually is potentially greater than the initial SCI depending on the detrimental effects of ischemia and inflammatory processes. However, although a subset of inflammatory processes are detrimental, other components of the inflammatory system, for instance macrophages and some subsets of T cells, are important for regeneration (David et al., 1990; Kawaja and Gage, 1991).

As described above, during the inflammatory cascade after the initial SCI and ischemia, mechanical stimulation or mobilization of calcium results in liberation of arachidonic acid from the membrane phospholipids (Hsu et al., 1985; Tymianski and Tator, 1996). The excitotoxic effect of the extracellular glutamate is further accentuated by reduced uptake by astrocytes and migroglia triggered by arachidonic acid (Zerangue et al., 1995), TNF-$\alpha$ and IL-1$\beta$ (Pitt et al., 2003; Takahashi et al., 2003), and reactive oxygen species (Piani et al., 1993; Volterra et al., 1994). Although the extracellular glutamate level might be chemically undetectable, it has induced apoptosis in neurons and oligodendrocytes (Donnelly and Popovich, 2008).

The arachidonic acid metabolites prostacycline and thromboxanes have opposite effects on microcirculation. Thromboxane stimulates vasoconstriction, platelet adherence to the endothelium, intravascular platelet aggregation, microvascular occlusion, microvascular thromboembolism, and vascular stasis. In SCI, the prostacycline–thromboxane balance shifts toward thromboxane, resulting in a thromboembolic environment and further ischemia (Hsu et al., 1985; Tymianski and Tator, 1996).

In addition, peroxidases interact with polyunsaturated fatty acid components of the cell membrane to cause phospholipid peroxidation that compromises the structural and functional integrity of the cell membrane and ultimately leads to cell death (Hall, 1993; Tymianski and Tator, 1996). Peroxidation of arachidonic acid metabolites is an important source of free radicals. Peroxidases and free radicals may also directly damage cell proteins and nucleic acids, as well as the vascular structures. Other source of oxygen-derived free radicals is the xanthine oxidase-dependent system located primarily in the endothelial cells. These oxygen-derived free radicals acting primarily at the capillary level, therefore, alter the vascular permeability and cause further edema (Kinuta et al., 1989; Wrathall et al., 1996). They also induce apoptosis in neurons and glia via the irreversible oxidation of proteins, lipids, and nucleic acids (Donnelly and Popovich, 2008). Reactive iron in hemoglobin and active inflammatory cells comprise other sources of free radical formation (Schwab and Bartholdi, 1996; Lewen et al., 2000). The body's own scavenger system consisting of superoxide dismutases, catalyases, glutathione, and ascorbic acid may become overwhelmed with the dramatic production of these free radicals (Katoh et al., 1996; Ilhan et al., 2004; Fan et al., 2006).

Local and infiltrating inflammatory cells also play a prominent role in secondary injury. The determination of whether these cells also contribute to neuroprotection and repair is still controversial. Local injection of ex vivo activated peripheral macrophages at the site of SCI showed promising results in improving functional recovery (Bomstein et al., 2003; Schwartz and Yoles, 2006). More recently, a subset of infiltrating monocyte-derived macrophages that are recruited at the margins of the injury site were seen to contribute to recovery after SCI by mediating an immunoregulatory role via the anti-inflammatory cytokine IL-10 (Shechter et al., 2009). These microphages are sometimes referred to as alternatively activated "M2" phenotype and distinguished from the proinflammatory classically activated "M1" macrophages. They are mainly activated by cytokines IL-4 and IL-13 and they downregulate inflammation, facilitate wound healing, and improve recovery (Shechter et al., 2009). This was further proven by augmenting the monocytes pool by either adoptive transfer or CNS-specific vaccination which resulted in improved recovery, and also with monocytes transfer in monocyte-depleted rodents (Shechter et al., 2009). The number of these spontaneously recruited protective cells, however, may be insufficient within the critical therapeutic time frame (Kigerl et al., 2009; Shechter et al., 2009). The effect of these cells is more prominent in the first week of injury and transplantation or monocyte augmentation after this period of time is mostly ineffective. Monocyte-derived microglia and macrophages

may induce regeneration via neurotrophic growth factors secretion, mainly transforming growth factor-β1 (Merrill and Zimmerman, 1991; McTigue et al., 2000; Lagord et al., 2002; Donnelly and Popovich, 2008). The ability of these cells to take up extracellular glutamate may also play a role in functional recovery (Rimaniol et al., 2000; van Landeghem et al., 2001).

The contribution of the lymphocytes to SCI and associated post-traumatic autoimmunity is still controversial. In animal (Popovich et al., 1996) and human (Kil et al., 1999) studies, SCI could induce sensitization of the host immune system to certain myelin components, mainly myelin basic protein (MBP), which is considered to be highly immunogenic and encephalitogenic in its ability to elicit T-cell responses to myelin and to induce inflammation in the CNS. These antigens are expressed by local and infiltrating antigen-presenting cells and cause activation to the CD-4 helper T-lymphocytes. Based on their subtype, these T cells may secrete four types of cytokines including TNF-α, γ-interferon, IL-4, and IL-10. The former two cytokine, secreted by Th1, are the main inducers of local inflammation and neuronal damage (Kil et al., 1999). The studies using T-cell receptor transgenic mice in which the majority of the lymphocytes are reactive with the immunodominant epitope of MBP have demonstrated extensive axonal loss and demyelination with consequent functional impairment as compared to control group (Jones et al., 2002). Activated T cell may be able to directly influence macrophage function, the integrity of microvascular endothelia, axonal conduction, and antibody production by B-lymphocytes (Popovich et al., 1996). This results in more extensive damage to the neurons and oligodendrocytes (Schroeter and Jander, 2005) and damage and loss of integrity of the BBB with consequent widespread edema (Donnelly and Popovich, 2008).

Other studies have shown that autoreactive T cells also contribute to long-term recovery and neuroprotection after SCI (Cohen and Schwartz, 1999; Schwartz et al., 1999; Hauben et al., 2000a,b). This role was supported by functional recovery via injection of MBP-reactive T-cell lines or immunization with MBP after injury. However, this might be related to accumulation of nonmyelin reactive T cells (Jones et al., 2002) or the expression of neurotrophins and antithrombin III by MBP-reactive T cells (Friedmann et al., 2001). Other authors support a bimodal role of the autoreactive cells in CNS injury (Fee et al., 2003).

Infiltrating B-lymphocytes were detected at sites of acute and chronic SCI in animal models (Ankeny et al., 2006). Although their presence in traumatized spinal cords of human patients is still a matter of debate, autoantibodies specific for GM1 ganglioside (anti-GM1) and myelin-associated glycoprotein (anti-MAG) were detected in most of these patients in acute and chronic phases (Mizrachi et al., 1983; Hayes et al., 2002). One study reported the presence of autoantibodies that bind neuronal nuclear antigens including DNA and RNA, suggesting probable damage in a similar fashion to systemic lupus erythematosus (Ankeny et al., 2006). Despite the strong activation of MBP-autoreactive T cells which play the most prominent role in B-cell activation, no anti-MBP antibodies could be detected in animal-based studies (Ibarra et al., 2000; Ankeny et al., 2006). In addition to their role in inflammation, autoantibodies specific for myelin protein can also promote axon regeneration and improve locomotor recovery after SCI (Donnelly and Popovich, 2008).

## CONCLUSIONS

Regeneration of the injured spinal cord continues to be among the most difficult tasks that neuroscience has to face. Not too long ago, this issue was considered an impossible task. Owing to the diligent works performed over the last 20 years and providing us with an understanding of the basics of the injury down to the molecular level, it is no longer considered impossible. Future treatments will most likely use a multimodal approach using medical as well as surgical knowledge to improve the outcome in patient after SCI.

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