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## Function of microglia and macrophages in secondary damage after spinal cord injury

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### Abstract

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Spinal cord injury (SCI) is a devastating type of neurological trauma with limited therapeutic opportunities. The pathophysiology of SCI involves primary and secondary mechanisms of injury. Among all the secondary injury mechanisms, the inflammatory response is the major contributor and results in expansion of the lesion and further loss of neurologic function. Meanwhile, the inflammation directly and indirectly dominates the outcomes of SCI, including not only pain and motor dysfunction, but also preventing neuronal regeneration. Microglia and macrophages play very important roles in secondary injury. Microglia reside in spinal parenchyma and survey the microenvironment through the signals of injury or infection. Macrophages are derived from monocytes recruited to injured sites from the peripheral circulation. Activated resident microglia and monocyte-derived macrophages induce and magnify immune and inflammatory responses not only by means of their secretory molecules and phagocytosis, but also through their influence on astrocytes, oligodendrocytes and demyelination. In this review, we focus on the roles of microglia and macrophages in secondary injury and how they contribute to the sequelae of SCI.

**Keywords:** *astrocytes, cytokines, chemokines, demyelination, inflammation, oligodendrocytes, M1/M2 activation, macrophages, microglia, secondary damage, spinal cord injury*

### Introduction

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Spinal cord injury (SCI) is associated with devastating neurological outcomes and limited therapeutic opportunities. It has three phases: acute, secondary and chronic (Oyinbo, 2011). The outcomes of SCI are mainly influenced by the secondary phase. SCI causes inflammatory responses through the activation of innate immune responses that contribute to secondary injury (Fehlings and Nguyen, 2010). Macrophages accumulated within the epicenter and the hematoma of the injured spinal cord play a significant role in this inflammation (Zhang et al., 2013). Microglia/macrophages associated inflammation appears to be a significant mechanism related to neuronal degeneration and regeneration.

Macrophages in the central nervous system (CNS) derived from blood monocytes and resident microglia, are pervasive in the injured spinal cord and change their phenotypes and functions in response to signals in the lesion environment.

In this review, we discuss the behavior and influence of microglia/macrophages during secondary damage from following perspectives: (1) the pathophysiology of spinal cord injury, and (2) how microglia and macrophages affect secondary injury, and the subsets of microglia/macrophages and their interrelationships in secondary injury mechanisms.

## Characteristics and stages/phases of SCI

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SCI, which is characterized by primary physical damage and secondary damage, results in severe sequelae such as paralysis, intense pain, and progressive neurological damage. The primary injury is typically restricted to the specific area of vertebral fracture and is characterized by acute hemorrhage and ischemia, which serve as the foci from which secondary mechanisms of injury are induced (Ray et al., 2002; Simon et al., 2009). The secondary injury, which is characterized by further destruction of neuronal and glial cells, leads to a significant expansion of the injury site, and allows paralysis to extend to adjacent spinal cord segments.

SCI has different characteristics. From the aspect of morphology, primary mechanical damage to SCI is characterized by direct destruction of spinal tissues, including the blood-spinal cord barrier, while secondary damage is characterized by inflammation that may cause reactive gliosis, edema, and cavitation of spinal parenchyma (Fleming et al., 2006). From the aspect of biological response, SCI can be divided into three phases: (1) acute (seconds to minutes after the injury), (2) secondary (minutes to weeks after the injury), and (3) chronic (months to years after the injury) (Oyinbo, 2011) ([Table 1](#)). Based on some previous SCI studies (Dumont et al., 2001; Rossignol et al., 2007; Fehlings and Nguyen, 2010; Oyinbo, 2011; Shin et al., 2013), SCI can be divided into four processes: (1) a primary mechanical insult, characterized by vasospasm and cell death from direct impact; (2) spreading of the injury, owing to vascular insults such as hemorrhage and ischemia-reperfusion; (3) immune/inflammatory reactions, characterized by apoptosis, demyelination of surviving axons and immune-mediated cell death; (4) stabilization, characterized by central cavitation and chronic scar formation.

[Table 1](#)

The phases of spinal cord injury

## Secondary damage following SCI

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As summarized from some previous SCI research (Dumont et al., 2001; Ramer et al., 2005; Liu et al., 2006; Tanhoffer et al., 2007; Fehlings and Nguyen, 2010; Varnum and Ikezu, 2012; Zhang et al., 2012), secondary damage/injury after SCI has the following aspects: (1) timing: secondary damage mechanisms initiate within minutes after injury and last for weeks or months; (2) location: secondary damage is not only restricted to the area of the vertebral fracture, but also extends to adjacent segments and even influences the whole body; (3) mechanisms of damage: secondary injury following spinal cord trauma is multifactorial (McCormick, 1998; Ramer et al., 2005) ([Table 1](#)); (4) morphology: secondary damage after SCI is characterized by hematoma, edema, glial/axon scarring, and central cavitation; (5) cytokine secretion: pro-inflammatory cytokines and chemokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-23, leukemia inhibitory factors (LIF) and inducible nitric oxide synthase (iNOS); and anti-inflammatory cytokines such as IL-10, IL-4, IL-13, and transforming growth factor  $\beta$  (TGF- $\beta$ ).

Among all the mechanisms of secondary damage, inflammation is the most important, and directly or indirectly controls the sequelae after SCI. The inflammatory responses can be spatially and temporally subdivided into several phases: immediate neutrophil invasion and activation of resident microglia at 0–2 days, recruitment of blood monocytes to the lesion at 3–7 days, and resolution of the scar by anti-inflammatory macrophages and axonal regrowth from day 7 onward (Sroga et al., 2003; Fleming et al., 2006; Kigerl et al., 2009; Jiang et al., 2013). The release of inflammatory cytokines and chemokines from spinal cord cells in or near the lesion starts the inflammatory responses (Carlson et al., 1998; Donnelly and Popovich, 2008; Popovich and Longbrake, 2008). These mediators lead to the sequentially orchestrated activation and migration of microglia towards the lesion and recruitment of circulating leukocytes to the injury (Carlson et al., 1998; Taoka and Okajima, 2000).

The potential benefits and the tissue-damaging consequences of the inflammatory response after central nervous system injury have long been disputed. But now, there is a consensus that inflammation has both beneficial and tissue-damaging effects. Obviously, inflammation causes destructive activities such as widespread cell damage and deterioration of the extracellular matrix (Gutteridge and Halliwell, 1989; Pratico et al., 2001; Pratico and Sung, 2004; Sinescu et al., 2010). These early inflammatory events in the first week after SCI also create a hostile microenvironment for various SCI treatments, thus creating obstacles for transplantation-based therapies (Okano et al., 2003; Coyne et al., 2006). Local and systematic inflammatory responses not only result in the pathogenesis of neurodegenerative events during acute and chronic phases of SCI, but also subsequently lead to the death of glia and neurons, forming glial scar and a cavity in the spinal parenchyma (Fleming et al., 2006; Kigerl et al., 2009). Recent studies have shown that inflammation benefits neuronal regeneration and functional recovery. Activated macrophages play an important role in this period. The inflammation mediated by activated microglia/macrophages plays an important role in clearance of damaged and degenerating tissues (Greenhalgh and David, 2014). As summarized by Ren and Young, abrogating the pro-inflammatory environment in the injured spinal cord has therefore become a major therapeutic target to reduce secondary cell death and promote neuronal regeneration (Gensel et al., 2011; Ren and Young, 2013).

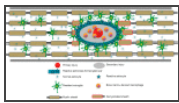
## **Microglia and macrophages in secondary injury**

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As a hallmark of SCI pathology and a pivotal inflammatory cell in the central nervous system, the macrophage has become a topic of intense research interest (Fleming et al., 2006; Donnelly and Popovich, 2008). Two macrophage populations, namely resident microglia and monocyte-derived macrophages, participate in and respond to degeneration and regeneration of spinal tissues after SCI (Beuche and Friede, 1984; Heumann et al., 1987; Perry et al., 1987; Stoll and Muller, 1999; Horie et al., 2004). Resident microglia are located in the immune-privileged CNS tissues, including the brain, the eye, and the spinal cord, which are secluded from the peripheral circulation by a complex of barriers (Hanisch and Kettenmann, 2007; Ransohoff and Perry, 2009; Rivest, 2009; Graeber, 2010; Ransohoff and Cardona, 2010; David and Kroner, 2011; Prinz et al., 2011; Saijo and Glass, 2011).

Macrophages/microglia were once thought to play a negative role in secondary tissue damage following CNS injury (Bracken et al., 1990). Popovich et al. (1999) showed that reducing the infiltration of macrophages could diminish secondary tissue damage. However, because there are no reliable morphological or specific antigenic markers that can differentiate between the resident microglia and bone marrow derived macrophages, it is difficult to clarify the respective roles of these two macrophage populations. By taking advantage of bone marrow chimeras, infiltrating bone marrow derived macrophages can be distinguished from resident microglia (Hickey and Kimura, 1988; Mueller et al., 2003). Shechter et al. (2009) showed that monocyte-derived macrophages are often localized mainly in the margins of the lesion site following SCI, while the resident microglia are distributed in the lesion core and its margins (Rolls et al., 2008; Shechter et al., 2009). However, our unpublished data have

suggested that macrophages and microglia cells have unique phenotypes and locations. Residential microglia can be distinguished from recently recruited bone marrow derived macrophages based on the expression of Mac-2 (galactin-3). After injury, infiltrating bone marrow-derived macrophages (CX3CR1<sup>low</sup>/Mac-2<sup>high</sup>) migrate to the epicenter of injury, while microglia (CX3CR1<sup>high</sup>/Mac-2<sup>low</sup>) localize to the edges of lesion (**Figure 1**). In other words, a vast majority of macrophages in the lesion site are circulating bone marrow cells rather than locally activated microglia cells after 4 weeks. These two populations of macrophages may have different functions. Residential microglial cells form a border that seems to seal the lesion and block the spread of damage (Hines et al., 2009). In contrast, bone marrow derived macrophages (BMDMs) enter the epicenter of injured spinal cord and phagocytize apoptotic and necrotic cells and clear tissue debris such as myelin debris (David and Kroner, 2011). Greenhalgh and David (2014) recently showed that microglia play a major role to clear damaged and degenerate tissues at 3 days after injury and BMDMs predominantly contribute to the phagocytosis, which persists for up to 42 days.



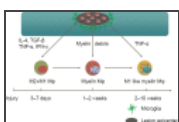
**Figure 1**

After primary injury, the nearby astrocytes and resident microglia are activated and migrate towards the injury site.

### Subsets of microglia/macrophages

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Several macrophage subsets have been classified based on the expression of cell surface markers, intracellular enzymes, and secreted molecules, including M1 (classical activation), M2 (alternative activation), regulatory macrophages, tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), and so forth (Classen et al., 2009; Menzies et al., 2010; Cassetta et al., 2011; Murray and Wynn, 2011; Vereyken et al., 2011; Comalada et al., 2012; Shechter and Schwartz, 2013). M1 and M2 are often seen as the two primary subsets of macrophages at the injured site. Depending on the phenotypes and activation status of macrophages, they may not only initiate secondary damage, but also initiate repair. The phenotypes and functions of macrophages in the injured spinal cord are dynamic and can change according to the microenvironment in the spinal lesion (Stout and Suttles, 2004; Menzies et al., 2010). As reported, M1 (CD86-positive) and M2 (arginase-1-positive) macrophages coexist at the lesion epicenter during the first week after SCI, but only M1 macrophages persist until day 28 post-injury in mice (Kigerl et al., 2009). Our unpublished data showed that macrophages phagocytosis of myelin debris are detected in injury site from 1–2 weeks after SCI. These myelin-laden macrophages exhibit M1 like phenotype and persist for long period of time (**Figure 2**). It was also reported that M1 microglia appear immediately after injury and secrete pro-inflammatory cytokines and chemokines that both lead to further damage following primary mechanical injury (Nakajima et al., 2012). The appearance of M2 macrophages and secreted anti-inflammatory cytokines and chemokines lead to the suppression of excessive inflammatory responses around the injured spinal cord and regeneration of injured spinal tissues (Gratchev et al., 2008; Varnum and Ikezu, 2012; Shechter and Schwartz, 2013; Weisser et al., 2013). In addition, a switch from M1 to M2 in the injured spinal cord, induced by transplantation of stem cells (neural and other), prevents axonal damage and improves locomotor function (Busch et al., 2011; Cusimano et al., 2012).



**Figure 2**

Bone-marrow derived macrophages (BMDMs) are recruited to lesion epicenter at 3–7 days after injury.

However, it is not clear which factors in the injured spinal cord result in a phenotype switch of macrophages. Although the expression of cytokines is a major determinant of macrophage activation

(Gordon and Taylor, 2005; Mosser and Edwards, 2008), this can be driven by lesion-related factors as well because rapid increases in pro-inflammatory cytokines are only detected before macrophages influx (Pineau and Lacroix, 2007; David and Kroner, 2011). Kroner et al. (2014) demonstrated that iron accumulated in macrophages in SCI increases TNF- $\alpha$  expression that prevents myelin phagocytosis-mediated conversion from M1 to M2. Our unpublished data demonstrated that myelin debris is one of lesion-associated factors altering the M2 phenotype. To clearly illustrate the role of macrophages in secondary damage after SCI, the differences between M1 and M2 macrophages during secondary injury is detailed in [Table 2](#).

[Table 2](#)

Classification of macrophages

### **Classically activated microglia/macrophages (M1)**

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Classical activation involves the induction of M1 macrophages by Th1 cell-derived cytokines. Generally, the properties of M1 macrophages in inflammation during secondary damage are neurotoxic and growth inhibitory. Because of these properties, M1 macrophages contribute to the formation of axonal growth-inhibitory glial scar and production of pro-inflammatory radicals/mediators, leading to a hostile environment at the lesion site, which results in the limited regenerative nature of the injured spinal cord (Shechter and Schwartz, 2013). Markers for M1 macrophages in the inflammation phase of secondary damage include NOX, NOS2, CD16/32 and CD86 (Gutteridge and Halliwell, 1989; Brown, 2007; Kigerl et al., 2009) ([Table 2](#)). Activated M1 macrophages produce a high level of pro-inflammatory molecules such as IL-1 $\beta$ , IL-6, IL-12, IL-23, TNF- $\alpha$ , IFN- $\gamma$ , chemokine (C-C motif) ligand 5 (CCL5), nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, inducible nitric oxide synthase (iNOS), toxic intermediates, and opsonic receptors such as immunoglobulin Fc $\gamma$  receptors (Unkeless et al., 1988; Gutteridge and Halliwell, 1989; Ravetch and Kinet, 1991; Heinrich et al., 1998; Akiyama et al., 2000; Pratico et al., 2001; Gordon and Taylor, 2005; Patel et al., 2005; Brown, 2007; Bellora et al., 2010). Classical activation also causes the release of proteolytic enzymes that can lead to deterioration of the extracellular matrix, such as metalloproteinases, collagenases, and furin, thus degrading cellular integrity and leading to easier destruction of the cell (Chandler et al., 1995; Maeda and Sobel, 1996; Rosenberg et al., 2001; Rosenberg, 2009; Shiryayev et al., 2009). Meanwhile, these cells secrete low levels of anti-inflammatory mediators (Kigerl et al., 2009; Shechter et al., 2013). M1-polarized macrophages show the ability to induce neuron death directly through iNOS activity and the capacity to obliquely contribute to secondary degradation (Kigerl et al., 2009).

### **Alternatively activated macrophages (M2)**

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Some researchers believe that M2 macrophages are generated from the phenotypic switch of M1 macrophages/activated microglia for inflammation resolution, but the detailed conditions and the timing of this generation are still unknown (Gratchev et al., 2008; Varnum and Ikezu, 2012; Weisser et al., 2013). We do know that M2 macrophages in SCI play an important role in resolving pro-inflammatory milieu produced by M1 macrophages and some CNS glia (both resident microglia and astrocytes), thereby supporting neuroprotection and regeneration of spinal tissues, and promoting renewal of damaged cells from progenitors. The properties of M2 macrophages are resolving/anti-inflammatory function, neuro/axonal-trophic support and scar-degrading capacities (Shechter and Schwartz, 2013). Markers for M2 macrophages are arginase-1, Ym1, found in inflammatory zone 1 (FIZZ1), CD206, CD209, CD163, and mannose receptor (MR) and IL-1 receptor antagonist (IL-1Ra) ([Table 2](#)) (Simmons and Seed, 1988; Ezekowitz et al., 1990; Law et al., 1993; Relloso et al., 2002; Menzies et al., 2010; Komori et al., 2011; Andrade et al., 2012; Rodriguez Guerrero et al., 2012; Varnum and Ikezu,



2012). Kigerl et al. (2009) showed a comparatively smaller and transient M2 macrophage response in SCI, which probably explains the prolonged pro-inflammatory response, with detrimental effects on tissue viability if not terminated on time (Shechter and Schwartz, 2013). Importantly, a deregulated M2 response might be detrimental as well when its timing, dosing or location is not optimally controlled.

Alternative activation of macrophages is induced by Th2 cell-derived cytokine activation. M2 macrophages can be further divided into three subsets: M2a, M2b, and M2c. The three subsets all play important roles in anti-inflammation and repair of a spinal lesion during secondary damage. M2a macrophages promoted by IL-4, IL-13, and arginase-1 mainly participate in reducing inflammation, enhancing phagocytosis and differentiation of neural stem cells (NSCs) (Varnum and Ikezu, 2012). Arginase-1 antagonizes iNOS and contributes to the anti-inflammatory response (Ahn et al., 2012). As an essential cytokine for M2a skewing (Maher et al., 2005; Nolan et al., 2005; Lyons et al., 2007) and a ligand of M2a, IL-4 has many functions during secondary inflammation. Through stimulating microglia/macrophages, IL-4 could up-regulate IGF-1 to induce neurogenesis, or down-regulate TNF- $\alpha$  and enhance neural differentiation (Butovsky et al., 2005; Butovsky et al., 2006; Kiyota et al., 2010). An *in vivo* study shows that gene delivery of IL-4 can directly enhance neurogenesis and restore impaired motor function (Kiyota et al., 2010). M2b macrophages contribute to the clearance of reactive nitrogen and oxygen species released during M1 activation, and take part in the production of CCL1 and IL-10. Immune complexes and TLR or IL-1R agonists are responsible for M2b skewing (Mantovani et al., 2004). The phenotype of M2c macrophages is deactivation/wound healing. These cells enhance proliferation of NSCs and deactivation of glial inflammation (Maher et al., 2005; Kiyota et al., 2010) through expressing CCR2, CCR5, chemokine (C-X-C motif) ligand 13 (CXCL13), and CCL16, CCL17, and CCL18 (Mantovani et al., 2004). IL-10 is a M2c ligand (Ekdahl et al., 2003) and an important cytokine for M2c skewing (Mantovani et al., 2004). Through stimulating microglia, IL-10 could enhance proliferation but not differentiation of NSCs (Kiyota et al., 2010), and promote anti-inflammatory responses including reducing pro-inflammatory cytokines and preventing glial activity (Plunkett et al., 2001) ([Table 2](#)).

It has been shown that administration of M2 macrophages is beneficial to noninfectious CNS inflammation including SCI (Weber et al., 2007; Shechter and Schwartz, 2013). As summarized by Shin et al. (2013), alternatively activated M2 macrophages over the M1 phenotype is a common phenomenon associated with functional recovery of SCI regardless of treatment regimens. Importantly, apart from the functions of M2 macrophages, the therapies summarized by Shin et al. are all associated with reduction of pro-inflammatory molecules and increase of anti-inflammatory molecules (Shin et al., 2013). These data suggest that some therapies to improve recovery from SCI may rely on the anti-inflammatory of M2 macrophages.

As mentioned above, the function of microglia/macrophages in SCI cannot be regarded as a simple dichotomy of bad–good or M1–M2; a much more complex scenario should be considered. To solve this problem, some researchers point out that we should classify macrophage phenotypes in another way. With this idea, macrophages are classified into six subsets according to their activities: inflammation, phagocytosis, vascular remodeling, matrix rebuilding, regeneration, and immune regulation (Hanahan and Weinberg, 2000; Condeelis and Pollard, 2006).

### **Microglia/macrophages and glial scar comprised of astrocytes**

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The formation of a glial scar is mainly mediated by activated astrocytes and other glia (Schwab and Bartholdi, 1996). A glial scar builds a barrier around the lesion epicenter ([Figure 1](#)). The infiltration of macrophages contributes to axonal diebacks, which represent the phenomenon where axons retract from a spinal lesion. A study utilizing a model of glial scar has demonstrated that macrophages are associated with unhealthy axons and directly lead to long-distance retraction of axons (Horn et al., 2008; Busch et

al., 2009). Activation of astrocytes follows and is promoted by the microglial response (Kreutzberg, 1996; Popovich et al., 1997). Inhibition of microglia has been shown to reduce damage to oligodendrocytes, inhibit axonal dieback, change the formation of glial scar, and improve recovery of locomotive function (Stirling et al., 2004; Festoff et al., 2006; Yune et al., 2007).

### **Microglia/macrophages and oligodendrocytes**

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During secondary damage after SCI, the oligodendrocytes not only influence signaling efficiency and conductance of axons, but also contribute to neuronal survival and preservation of axonal structural integrity (McTigue et al., 2006). Oligodendrocytes are injured by macrophages at the lesion epicenter after the injury and continue to undergo apoptosis in the spinal parenchyma for many weeks after SCI (Classen et al., 2009; Comalada et al., 2012). Oligodendrocytes are responsible for the myelination of multiple axons. The results of the loss of oligodendrocytes are the demyelination of many spared axons and the loss of conduction of action potential by ascending and descending lateral axons (Hains et al., 2003). As axons provide essential connections between brain and caudal spinal neurons, damage to spinal axons can cause many clinical problems (McTigue, 2008). Activated and resting macrophages and microglia secrete molecules such as IL-1 $\beta$ , glutamate, NOS and TNF- $\alpha$  which all contribute to secondary death of oligodendrocyte cells (Streit et al., 1998; Merrill and Scolding, 1999; Rosenberg et al., 1999).

### **Microglia/macrophages and demyelination**

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Astrogliosis is a pervasive response to different insults to the adult CNS, including trauma, toxicity, and genetic and degenerative diseases (Norton et al., 1992; Eddleston and Mucke, 1993; Sofroniew and Vinters, 2010). Astrogliosis is responsible for the failure of remyelination in many experimental models of demyelination and demyelinating pathologies (Sergott et al., 1985; Bunge et al., 1993; Butt and Berry, 2000; Holley et al., 2003; Keirstead et al., 2005; Frohman et al., 2006). The pathological process of demyelination due to the loss of oligodendrocytes is particularly active during the sub-acute (secondary) and chronic phase of SCI (Guest et al., 2005; Joy, 2005). Recent studies suggested that immunological demyelination is accompanied by a robust activation of macrophage/microglial cells without an astrogliosis response (Cloutier et al., 2013). The activities of macrophages and microglia following SCI are maximal between 3 and 7 days post-injury. Notably, activated macrophages and microglia were reported to exclusively locate to regions of immunological demyelination, with only a few of them outside of the region. In spinal lesions during secondary injury after SCI, the activities of microglia and macrophages were significantly higher within regions of immunological demyelination (Cloutier et al., 2013). Immunological demyelination creates a unique environment in which astrocytes do not form a glial scar and provides a unique model to understand the putative interaction between astrocytes and activated macrophage/microglial cells. However, during the process of demyelination, axons are directly exposed to damaging effects such as inflammatory cytokines and free radicals, leading to neuronal loss. As a result, demyelination leads to conduction delays and conduction block (McTigue, 2008; Hall and Traystman, 2009).

### **Conclusion**

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This review has explored the relationship between microglia/macrophages and the secondary damage that develops after SCI. By understanding how macrophages either promote or prevent secondary damage in spinal cord inflammation, we may be able to deduce new approaches for mitigating the currently poor outcomes after SCI and promoting the recovery of motor function in affected patients. Meanwhile, it is critically important to understand how current or planned therapies influence and/or interact with macrophages, even if macrophages are not the designated therapeutic target.

## Footnotes

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