

## Neuroinflammation: Friend or Foe, It's a Matter of Time?

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### Mini Review

Inflammatory cascade was seen historically as detrimental CNS responses to injury that should be suppressed, however it is essential for tissue repair. Intraspinal inflammation caused by trauma persists indefinitely, becoming chronic. Chronic inflammation is detrimental for tissue regeneration. Treatments for spinal cord injury should resolve or modulate neuroinflammation at the appropriate time rather than suppress it completely.

Spinal cord injury (SCI) usually leads to devastating deficits that produce a strong impact on patients, their families and their communities. Neural damage may cause loss of sensory and motor capabilities (paraplegia or tetraplegia), infections, loss of bladder and bowel control, cardiac, sexual and respiratory dysfunctions and the development of neuropathic pain [1-2]. After SCI, primary mechanical insult is followed by the activation of a secondary cascade of events that ultimately causes progressive degeneration of the neural tissue. These secondary events include transient permeability of the blood brain barrier (BBB), neuronal and oligodendrocyte death, astrocyte and microglial reactivity, axonal loss, and a robust inflammatory response [3-5]. In this regard, astrocytes, microglial and infiltrating leukocytes (macrophages, neutrophils and lymphocytes) release cytokines, nitric oxide, superoxide anion, eicosanoids and proteases causing neuronal and glial toxicity [6-8]. Free radicals, TNF $\alpha$  and IL1 $\beta$  induce apoptosis in neurons and oligodendrocytes [9-13]. A feed-forward cascade is set in motion whereby these secretory products continue to enhance glial activation and leukocyte migration from the circulation into the CNS. Together, these changes exacerbate neuroinflammation and neurodegeneration. Traditionally inflammation has been considered the primary cause of post-traumatic secondary injury [14-17].

Therefore a number of therapeutic strategies were orientated to suppress inflammation and microglial activation in acute and sub-acute phase after SCI (ibuprofen, minocycline, methylprednisolone) [18-21]. However, methylprednisolone, a glucocorticoid derivative, reached an extended clinical practice, but re-evaluation and the accumulated expertise have raised serious concerns about its real effectiveness and safety [22,23] and the use of this compound is being reduced in some countries [24]. Thus, generic immune suppressive therapies have been

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largely unsuccessful, mostly because inflammation and immunity exert both beneficial and detrimental effects and these functions change over time. Indeed, controlled acute inflammation and immune invasion are fundamental processes characterizing any wound healing pathway. Neutrophils, have been shown to support recovery [25] by reducing oxidized proteins [26], promoting astrocyte activation and facilitating early production of growth factors [25]. Macrophages, and microglial cells support axonal regeneration [27,28] by clearing growth-inhibitory myelin debris [29], neurotrophic synthesis [30,31], supporting blood vessel formation/ maintenance, and resolving scar deposition [32]. Mononuclear phagocytes and astrocytes, as part of tissue regeneration, also support oligodendrocyte remyelination, as well as oligodendrocyte progenitor cell proliferation (OPC) and differentiation [33-35]. Recently, a pivotal role for recovery was attributed to monocytes that infiltrate the damaged spinal cord due to their nonclassical anti-inflammatory/resolving properties [36,37]. These cells enter the traumatized spinal cord through the brain-ventricular choroid plexus, acquire an anti-inflammatory profile, produce the anti-inflammatory cytokine, interleukin 10 (IL-10) and finally terminate the local microglial response [32,38]. Several groups have confirmed the therapeutic potential of activated microglia and monocyte derived macrophages in the injured spinal cord [39-41]. Two studies revealed that microglial transplants placed into lesioned spinal cord promoted neurite growth [42]. 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 [41]. Macrophages, activated microglia, and reactive astrocytes within the CNS lesion have a pivotal role in

the transition between the post injury phase of cleaning the lesion and its preparation for subsequent remodeling, supporting tissue regeneration and extracellular matrix modulation [38]. Therefore, it is essential that inflammation develops in the acute phase of CNS lesion. However it must be controlled by active regulatory mechanisms that lead to the resolution of the inflammatory cascade. The severity of the lesion in part defines the chronicity of the response. The force of the stimuli determines whether inflammation resolves or becomes chronic, also classified as non-resolving inflammation. In this regard, moderate CNS damage evokes protection by microglia and their regulated activation and proper termination might help in tissue preservation, repair, and renewal [43-45]. Conversely intensive acute (SCI) or chronic activation (neurodegenerative diseases) becomes microglial cells neurotoxic and may result in irreversible tissue loss [43,46-48]. Chronic inflammation is a maladaptive response of CNS to the injury and is associated with impaired tissue remodeling [49].

SCI is an intensive acute injury that develops to a chronic wound. Indeed, intraspinal inflammation caused by trauma persists indefinitely and includes a non self-limiting inflammatory cascade [50-52]. The mechanisms underlying sustained inflammation are not known, but might be due to the inefficient clearance of debris and the failure of BBB repair [38,53]. Consequently, effective repair and wound healing require coordinated inflammation with timely resolution [54].

Since emerge of chordates evolution, bone structures (vertebra column and skull) were selected for CNS protection. Mammal CNS is highly protected and has a low incidence of injuries in nature, thus there was not a strong selection pressure to recovery of severe injuries. On the other hand, if an animal suffer a severe injury the possibility of leaving offspring is minimal. In this evolutionary context there were not several chances to generate an immune system adapted to resolve this kind of severe lesion to the CNS. This coincides with the observation of an immune response that is operative for minor injuries but in the case of major damage seems deregulated generating a chronic inflammation that often increases the damage of the original injury. Inspired by knowledge of natural selection and evolution, we thus suggest that the price of "building a protective wall" was

to reduce the probabilities of selecting an immune system which can repair and resolve severe injuries.

Therefore, new therapeutic strategies should be developed based on inflammatory resolution or immunomodulation rather than complete abolishment of inflammation. On one way, scientists should search new resolution agonist, identify anit-resolution factors and develop pro-resolution treatments. In the other way, molecules that moderate inflammation emerges as a good candidates for SCI treatments, because immune responses in the CNS can have dual effects and global immune suppression is unlikely to yield benefits. In this regard, progesterone, which is widely known by its role in reproduction, emerges as promising candidate for SCI because the steroid down regulates but not abolish the inflammatory response. Recently we have demonstrated that progesterone treatment after SCI decrease the expression of pro-inflammatory cytokines (TNF $\alpha$ , IL1 $\beta$ , IL6), the pro-inflammatory enzymes (iNOS and COX-2) and reactive gliosis by a 50% compare to injured rats [55] In addition, progesterone after SCI reduces the extension of secondary injury [56], promotes the differentiation of oligodendrocytes precursor cells into mature oligodendrocytes [57] and improves functional recovery after moderate/severe contusion injury, demonstrated by the improved motor outcome in the Basso-Bresnahan-Beattie scale for locomotion and CatWalk gait analysis [56]. Progesterone beneficial effects on remyelination was observed 30 days after injury and effects on functional recovery were observed 14 days after injury and were maintained for the duration of the assessment period (60 days), showing long-term benefits. Apparently the merits of progesterone through their immunomodulatory properties lies in turning a "histologically" severe injury into a mild injury, where remyelination and functional recovery are possible.

In conclusion, inflammation is necessary for tissue repair, however if it becomes chronic, regeneration is impaired. Indeed, there is no context in which chronic inflammation is beneficial. Thus treatments for SCI should help to resolve or modulate neuroinflammation at the appropriate time before its turns detrimental. Thus, everything is a matter of time.

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