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Decoding IL-6-Driven Neuroimmune Dynamics in Spinal Cord Injury: Integration of JAK/STAT Signaling, PANoptosis, Oxidative Stress, and Neuroregenerative Responses

Alper DEMİREZEN
Kocaeli University, Medical Biology&Tübitak Marmara Teknopark, Kocaeli/Gebze, Türkiye
https://orcid.org/0000-0002-7305-8882

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Corresponding Author:
Alper DEMİREZEN
https://orcid.org/0000-0002-7305-8882

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ABSTRACT

Loss of motor, sensory, and autonomic abilities is a serious neurological disorder known as spinal cord injury (SCI), which frequently results in permanent disability and a substantial economical burden. Secondary damage processes, including neuroinflammation, are crucial in determining disease progression and functional consequences after the original mechanical trauma. Interleukin-6 (IL-6), a pleiotropic cytokine of the gp130 family, has become one of the main mediators of this process and a critical regulator of inflammatory responses following injury. After SCI, the blood-spinal cord barrier (BSCB) is disrupted, allowing peripheral immune cells such as neutrophils, monocytes/macrophages, and lymphocytes to infiltrate while local microglia and astrocytes are quickly activated. Alongside this intricate cellular interaction is a dynamic cytokine milieu where IL-6 signaling plays a role in both harmful and healing processes. IL-6 exacerbates neuronal loss and demyelination by promoting astrocyte reactivity, glial scar formation, and persistent neuroinflammation through activation of the JAK/STAT3 pathway. Simultaneously, IL-6 signaling integrates inflammatory, apoptotic, and survival signals by interacting with important molecular pathways as NF-κB, MAPK, and PI3K/Akt. According to recent research, the post-SCI microenvironment is shaped by oxidative stress regulators like Nrf2 and new types of inflammatory cell death including PANoptosis. Furthermore, the temporal and context-dependent character of inflammation highlights a dual role: whereas later immune regulation may aid in debris removal and tissue healing, early pro-inflammatory responses contribute to tissue damage. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs), biomaterial-based therapies, antioxidants, and therapeutic methods that target IL-6 signaling have demonstrated promise in reducing neuroinflammation and promoting regeneration. In summary, IL-6 is a crucial node in the intricate neuroimmune network of SCI, connecting cellular death pathways, inflammatory signals, and regeneration processes. In order to design targeted and temporally optimized therapeutic approaches for spinal cord injury, a greater comprehension of IL-6-mediated signaling dynamics may offer new insights.

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INTRODUCTION

Spinal cord injury (SCI) is a structural and functional defect of the spinal cord that can result from trauma and leads to the loss or reduction of motor, sensory, and autonomic functions below the level of the injury. This damage can result in permanent disability or even death. As such, it constitutes a neurological and public health issue with far-reaching consequences for individuals, families, and healthcare institutions.[1-5] The prognosis and treatment of SCI are generally determined by the level of the injury (e.g., cervical, thoracic) and its completeness (e.g., AIS grades). Epidemiological studies consistently highlight the significant long-term disability and the ongoing need for medical, rehabilitation, and social support, underscoring the lifelong impact of this condition.[6,7]

Some studies have been able to capture the economic and social impacts of SCI. Systematic reviews demonstrate a wide range of direct and indirect costs, significant lifelong care needs, and high societal costs; these costs vary depending on the region and the severity of the injury. Case mix, differences in how health systems operate, and lifelong deprivation of physical activity can lead to significant economic impacts at the country level. Region-specific data (e.g., the Middle East, Africa, Asia) highlight heterogeneity in terms of prevalence, causes, access to care, and financial burden, reinforcing the need for context-specific prevention and rehabilitation strategies.[8]

When examining the relationship between SCI and its distribution, regional differences in safety, transportation, workplace accidents, and public health interventions may be reflected. Age, gender, and activity level influence risk: Working-age men are disproportionately affected in many cohorts, but patterns may vary by region and over time as safety measures, urbanization, and demographic structures evolve.[9]

When considering the impact of SCI on individuals, it leads to lifelong disabilities, the inability to engage in physical activities, dependence on others for care, and a decline in quality of life. These outcomes affect and hinder mental health, employment, and an individual's independence in terms of physical activity.[9] Medical costs (acute care, surgery, rehabilitation) and long-term care costs, combined with lost productivity and the burden on caregivers, represent a significant economic burden for individuals, families, and health systems. Systematic reviews and economic analyses consistently identify spinal cord injury as a high-cost condition with sustainable economic impacts across countries and healthcare systems, despite wide variations in costs.[5]

Post-SCI Pathophysiology and Inflammation

Following a spinal cord injury, the activation of local microglia and astrocytes, the influx of neutrophils, monocytes/macrophages, and lymphocytes, as well as a complex cytokine and chemokine environment, contribute to neuroinflammation. Depending on the context and timing, this inflammatory environment can exacerbate glial scarring, neuronal loss, and demyelination, but it can also aid in the clearance of debris and support healing processes. During the acute injury phase, early inflammatory mediators, including TNF-α and IL-1β, are frequently reported as central signals contributing to changes in the blood-brain barrier and neuronal susceptibility. When downstream signaling is altered, particularly IL-1β, it has been associated with acute lesion site inflammation and holds promise as a therapeutic target. Cytokines of the gp130 family, such as IL-6, LIF, and IL-11, play a role in the inflammatory environment following spinal cord injury (SCI). For example, studies have been conducted to determine the overall effect of IL-11 signaling on neutrophil recruitment and locomotor outcomes; evidence suggests that this pathway may have a limited effect on motor outcomes in some mouse models, necessitating the targeting of other inflammatory pathways for future treatments. The Nrf2 pathway regulates inflammatory signals and is a key regulator of antioxidant responses. Following SCI, Nrf2 activation may reduce oxidative damage and influence inflammatory pathways. It is a therapeutic axis that interacts with autophagy, ferroptosis, oxidative stress, and inflammation. In preclinical models, pharmacological or genetic approaches that increase Nrf2 activity have demonstrated neuroprotective effects by reducing inflammation and preserving tissue integrity. According to recent research, PANoptosis—which combines pyroptosis, apoptosis, and necroptosis—is a major inflammatory cell death mechanism in spinal cord injuries (SCI). The pathogenesis of SCI has been linked to PANoptosis-related genes and models of immune cell infiltration; this points to new molecular targets for controlling inflammatory cell death and immunological responses in SCI.[10-13]

In the early phase following spinal cord injury, vascular damage and disruption of the blood-brain barrier (BBB) lead to edema, hemorrhage, and the influx of peripheral immune cells. When the BBB is disrupted, inflammatory damage intensifies and secondary damage is prolonged. This process is best illustrated by ET-1-mediated barrier disruption and the subsequent inflammatory cascades. In the subacute phase, angiogenesis and vascular remodeling occur; these can influence recovery by altering immune cell trafficking and perfusion. Anti-inflammatory approaches, when used in conjunction with therapeutic strategies that stabilize the BBB and promote normal vascular restoration, can improve outcomes.[14]

Following a spinal cord injury, microglia and astrocytes become activated, and cytokines produced by microglia contribute to the inflammatory environment. The balance of these effects depends on the extent of the injury and microenvironmental signals. Reactive astrogliosis and glial scar formation can hinder regeneration, but astrocyte-mediated responses can support barrier maintenance and repair signaling. During the acute phase, neutrophils rapidly infiltrate the lesion, releasing inflammatory mediators that can damage tissue while also aiding in the removal of initial debris. Over time, monocytes and macrophages

become polarized; M1-like phenotypes are often associated with pro-inflammatory activities, while M2-like phenotypes are linked to healing processes. The temporal evolution of these populations influences the dynamics of secondary injuries.[15]

Major signaling pathways such as NF-κB, MAPK, JAK/STAT, and PI3K/Akt are activated by inflammation. It is known that the expression of pro-inflammatory genes is regulated by NF-κB activation, and research has been conducted to prevent secondary damage by modulating this axis. HGF-PI3K/Akt signaling has been associated with inflammation and apoptosis in spinal cord injury models, and the PI3K/Akt pathway also interacts with cell survival and inflammation regulation. Following spinal cord injury, TGF-β signaling regulates glial responses and inflammation. The regulatory function of TGF-β may inhibit inflammatory damage and influence glial scar dynamics and brain regeneration, suggesting a potential therapeutic intervention axis. However, due to its pleiotropic effects, an approach targeting TGF-β signaling requires careful consideration of timing and context.[16]

Extracellular vesicles derived from mesenchymal stem cells (MSC-EVs) can deliver neurotrophic factors and anti-inflammatory signals to damaged tissue. Their cargo, which also includes microRNAs, enables the regulation of apoptosis and inflammation. Although MSC-EVs face challenges in standardization and targeted delivery, they provide a cell-free method for reducing inflammation and promoting regeneration. In experimental spinal cord injuries, antioxidants, polyphenols, and hormonal/neuroprotective agents (such as melatonin) have demonstrated anti-inflammatory and antioxidant effects. When administered at the right time and dose, these agents can potentially improve functional outcomes by reducing oxidative damage and inflammatory cytokines. The aim of glial scar modification and tissue engineering techniques (such as cell-injected or growth factor-loaded scaffolds) is to provide a suitable substrate for axonal development while reducing the inflammatory barrier to regeneration.[17]

Following a spinal cord injury, the inflammatory response is not always harmful; there is a complex, time-dependent balance between harmful early inflammation and subsequent immune responses that aid in repair. Translational interventions aimed at temporarily limiting inflammation rather than altering immune phenotypes or completely eliminating inflammation reflect this duality. IL-11 signaling provides a useful example of context-dependent outcomes: functional loss studies in mice have shown no significant differences in motor outcomes despite transient upregulation following spinal cord injury; suggesting the presence of redundancy or compensatory pathways in gp130 cytokine signaling and advising caution when focusing on a single cytokine axis. Observed inflammatory patterns and therapeutic responses are influenced by the variability of spinal cord injury models (contusion, compression, transection, distraction).[18]

Therapeutic Targeting of IL-6 in Spinal Cord Injury: Current Molecular Mechanisms and Treatment Approaches

In the context of spinal cord injury (SCI), IL-6 plays a complex pro-inflammatory/anti-inflammatory role. Activation of the IL-6/JAK-STAT axis, microglial/astrocytic responses, and interactions with other signaling pathways like JAK/STAT, NF-κB, and MAPK may be crucial in the secondary damage processes of SCI.[19] In this review, we will synthesize the role of IL-6 in spinal and spinal cord tissues, as well as current mechanisms and treatment strategies related to the JAK/STAT and associated pathways; we will also discuss inconsistencies in the existing literature and responses in different cell types.

Current molecular mechanisms: IL-6, JAK/STAT, and cross-talk signaling networks

Inflammation and neuroprotection mechanisms after SCI are significantly influenced by IL-6/JAK/STAT regulation. Through gp130 on the membrane IL-6R, IL-6 activates JAK kinases, which control gene expression by phosphorylating, dimerizing, and nuclear translocating STAT3. In some situations, this pathway may be influenced by anti-inflammatory reactions (e.g., via STAT3/STAT6 through IL-10), but it can also initiate a proinflammatory phenotype linked to microglial/astrocytic activation and astrogliosis. Additionally, the IL-6/JAK/STAT pathway interacts with the NF-κB and MAPK pathways, and these interactions may play a decisive role in the function of microglia and astrocytes. IL-6, along with cytokines such as IL-1β and TNF-α, contributes to the pro-inflammatory program by acting on common targets through pathways including NF-κB, MAPK (ERK, p38, JNK), and PI3K/Akt/mTOR. Interactions among these pathways direct the glial response following SCI and may therefore play a decisive role in the pathophysiology associated with pain and neurodegenerative processes. Microglia polarization: The M2/M1 balance is determined primarily through the IL-6/JAK/STAT pathway, particularly via STAT3, and through inhibition/positive feedback mechanisms involving the SOCS family. SOCS3 negatively regulates STAT3 signaling and can modulate NF-κB, p38 MAPK, and JNK activation; therefore, the effects of IL-6 may vary depending on the cellular context.[20-22] TREM families and TLR-NF-κB interactions: In the context of SCI, reciprocal regulatory networks may be established between IL-6 and the NF-κB and JAK/STAT pathways; Additionally, surface receptors such as TREM-1/TREM-2 can interact with TLR4 to modulate NF-κB and MAPK pathways, which may influence IL-6 production and microglial/axonal responses.[23]

TYPES OF CELLS

Mikroglia

JAK/STAT3 is activated via IL-6; STAT3 is associated with astrogliosis in certain cases; the negative regulation of SOCS3 may influence the activation of NF-κB and MAPK.[20]

Astrocyts

NF-κB and JAK/STAT (particularly STAT3) are key regulators; they link IL-6 production to glial scar formation; the dynamics of SOCS and IL-6 signaling, which modulate the astrocyte-neuron relationship, are a subject of debate in the literature.[24]

Oligodendroglia neurons

JAK/STAT and NF-κB interactions following SCI may influence neurological repair and permeability; in some studies, the IL-6/JAK/STAT6/STAT3 pathway may affect oligodendrocyte function.[25]

Therapeutic and response aspects: Strategies targeting IL-6

JAK/STAT inhibitors

Agents targeting STAT3 may reduce IL-6-mediated inflammation, suppress the pro-inflammatory response of microglia, and support neuroprotection through astrogliosis. However, caution is warranted regarding clinical applicability and safety; some studies have shown that JAK/STAT blockade may promote microglial phenotypic conversion in the early stages and may even enhance neurological recovery.[26]

Modulation of the NF-κB pathway

While NF-κB's interactions with IL-6 can increase IL-6 production in some cases, in other contexts it indirectly regulates IL-6 signaling. Therefore, NF-κB-targeted therapies may be beneficial or risky depending on the context and timing.[27]

MAPK pathways

P38/JNK/ERK inhibitors show potential for reducing the IL-6-associated inflammatory response; since MAPK pathways interact with the IL-6/JAK/STAT pathway, combined targeting may be advantageous.[19]

Innovative Treatment Approaches

IVD scaffolds containing HMW hyaluronic acid/genipin-crosslinked fibrin may play a role in maintaining ECM homeostasis by suppressing IL-6/TNF-α signaling; furthermore, hybrid systems containing enzymes designed to reduce the acidic environment at the nucleus pulposus may reduce IL-6 amplification. It has been demonstrated that hypoxic three-dimensional culture or MSCs pre-conditioned with IL-1β/TNF-α can enhance anti-inflammatory responses; this may support tissue healing by indirectly influencing IL-6-related networks. In IL-6/JAK/STAT-dependent contexts, these receptors and related pathways can modulate inflammation; certain G-protein-coupled receptors and TRP channels interact with NF-κB, MAPK, and JAK/STAT, thereby indirectly influencing IL-6 responses.[28]

In conclusion, the IL-6/JAK/STAT axis emerges as a key mechanism underlying inflammation and secondary damage following SCI; however, the effect of IL-6 is shaped by SOCS regulation, NF-κB/MAPK interactions, and microglia-astrocyte crosstalk. Therefore, therapeutic strategies targeting IL-6 require timing and tissue-specific, differentiated responses. While the MAPK and NF-κB pathways amplify the pro-inflammatory output of IL-6 signaling, they also participate in anti-inflammatory regulation and the regulation of MSI/astrogliosis in certain contexts; consequently, combination therapies or multi-pathway targets may be more effective than single-pathway therapies. Multilayered strategies involving scaffolds, MSC preconditioning, GPR55/TRP/TREM modulators, and SOCS regulation hold promise for targeting IL-6-associated inflammation; however, additional data are required regarding safety, long-term effects, and clinical translation.

The role of IL-6 following SCI is described as "pleiotropic"; while some studies show that IL-6/JAK/STAT3 activation leads to pro-inflammatory outcomes, others report that this pathway has anti-inflammatory or neurogenic effects that promote recovery. To explain this contradiction, one must consider the timing (early/late phase), the cell type receiving the signal (microglia/astrocytes/neurons), and the status of SOCS regulators. In clinical practice, the target must be clarified for JAK/STAT3 inhibitors or NF-κB pathway modulation to be safe and effective; dual-target or time-controlled therapies may offer potential advantages. Multimodal treatment combinations targeting the IL-6-associated inflammatory network (e.g., JAK/STAT3 inhibitor + NOS/microglia cross-talk modulators + glial scar-reducing agents) may improve long-term functional outcomes in SCI. This approach reflects the qualitative benefits of multi-pathway-targeted strategies proposed in the literature.

IL-6 is a key cytokine that drives secondary damage in SCI and operates within a complex network involving the JAK/STAT, NF-κB, MAPK, and SOCS pathways. These pathways determine the responses of microglia and astrocytes; they also play a role in pain and neuroprotection processes. Therapeutic strategies targeting IL-6 have the potential to reduce inflammation and support functional recovery; however, they require careful design regarding timing, target tissue, and patient population to ensure efficacy and safety. Multimodal approaches (combinations targeting cross-pathway interactions) currently appear the most promising based on existing evidence and may become a priority for future clinical translation.

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