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Review Article

The Role of TGF-Beta in Glial Scar after Spinal Cord Injury

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Abstract

The transforming growth factor-beta (TGF-beta) plays a pivotal role in the pathophysiology of spinal cord injury (SCI) through its involvement in the formation of the glial scar. SCI triggers a cascade of cellular and molecular responses, where TGF-beta is upregulated and contributes to the activation and proliferation of astrocytes and other glial cells, leading to scar formation. This glial scar serves as both a physical and biochemical barrier to axonal regeneration, which complicates the recovery process. The dual role of TGF-beta in neuroprotection and inhibition of axonal growth presents a challenge for therapeutic strategies aimed at improving spinal cord repair. Various experimental approaches explored to modulate TGF-beta signaling in order to reduce glial scar formation while promoting neuronal regeneration. These include the use of TGF-beta inhibitors, gene therapy, and stem cell-based interventions. Despite significant advances, a comprehensive understanding which TGF-beta influences glial scar formation and SCI recovery is still evolving. This review aims to provide an in-depth analysis of the current research on TGF-beta's role in SCI, with a focus on its impact on glial scar formation and potential therapeutic approaches to mitigate its effects.

INTRODUCTION

Spinal cord injury (SCI) is a devastating condition that results from damage to the spinal cord, leading to a loss of mobility or sensation [1]. The severity of the injury often depends on the location and extent of the damage. SCI involves two phases: the primary injury and the secondary injury. The primary injury is the initial mechanical damage that occurs at the moment of trauma, causing immediate disruption of neural and vascular structures. This is followed by the secondary injury phase, which involves a cascade of biochemical and cellular that aggravate the initial damage [2]. The secondary injury can lead to further neuronal cell death, demyelination, and glial scar formation, which impede the regeneration of axons and functional recovery [3].

Recent advancements in SCI research have highlighted the importance of targeting molecular pathways involved in the injury and repair processes [4]. Among these, the transforming growth factor-beta (TGF-beta) signaling pathway has emerged as a significant player in the regulation of inflammation, glial scar formation, and cellular responses post-injury [5-7]. Understanding the role of TGF-beta in SCI could open new avenues for therapeutic interventions aimed at enhancing neural repair and functional recovery.

Characteristics and Function of the Glial Scar

The glial scar is a complex structure that forms in response to spinal cord injury (SCI) [8]. It is primarily composed of reactive astrocytes, microglia, and extracellular matrix (ECM) components such as chondroitin sulfate proteoglycans (CSPGs) [9]. The formation of the glial scar involves several cellular and molecular mechanisms aimed at isolating the injury site and facilitating tissue repair.

Reactive astrocytes are the main cellular of the glial scar [10]. After SCI, astrocytes undergo hypertrophy and proliferate, a process known as astrogliosis. These cells migrate to the lesion site, where they secrete ECM proteins and CSPGs [11]. The latter are known to inhibit axonal growth by creating a physical and biochemical barrier. Despite this inhibitory role, reactive astrocytes also contribute positively by stabilizing the extracellular environment, limiting the spread of inflammation, and promoting tissue repair [12]. Astrocytes secrete neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), which support neuron survival and regeneration [13].

Microglia, the resident immune cells of the central nervous system, also play a crucial role in glial scar formation [14]. Upon

SCI, microglia are rapidly activated and migrate to the injury site, where they proliferate and release pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) [15]. These cytokines contribute to the recruitment of peripheral immune cells, exacerbating inflammation. However, microglia also exhibit a reparative phenotype, releasing anti-inflammatory cytokines like IL-10 and transforming growth factor-beta (TGF-β), which help in resolving inflammation and promoting tissue repair [16].

The ECM is another critical component of the glial scar [17]. The deposition of ECM proteins and CSPGs forms a dense network that encapsulates the lesion site. This matrix serves as a scaffold for cellular components of the scar and provides structural support. However, the presence of CSPGs is a major impediment to axonal regeneration. These molecules bind to receptors on the surface of axons, activating intracellular signaling pathways that lead to growth cone collapse and axonal retraction [18]. Enzymatic degradation of CSPGs using chondroitinase ABC has been shown to enhance axonal regrowth and functional recovery in experimental models of SCI, highlighting the dual role of the ECM in glial scar function [19].

The glial scar is a multifaceted structure that plays both protective and inhibitory roles in SCI [20]. While it provides critical support for tissue repair and limits secondary damage, its inhibitory effects on axonal regeneration pose significant challenges for long-term functional recovery [21]. Understanding the complex interplay between the cellular and molecular components of the glial scar is essential for developing therapeutic strategies that can modulate its formation and function to enhance recovery after SCI.

TGF-beta's Role in Astrocyte and Microglia Activation

Transforming growth factor-beta (TGF-beta) plays a pivotal role in the central nervous system (CNS) response to spinal cord injury (SCI). Upon SCI, TGF-beta is rapidly upregulated and orchestrates a series of cellular and molecular events that contribute to the activation of astrocytes and microglia, the primary glial cell types involved in the formation of the glial scar [22].

TGF-beta has been shown to be a key regulator of astrocyte activation. Studies indicate that TGF-beta signaling through the Smad2/3 pathway promotes the expression of GFAP and other extracellular matrix (ECM) components, such as chondroitin sulfate proteoglycans (CSPGs) [23]. These ECM molecules contribute to the formation of a dense and inhibitory scar matrix that can impede axonal regeneration. In addition to its role in ECM production, TGF-beta also enhances the production of cytokines and chemokines by astrocytes, further modulating the local inflammatory environment [24].

Microglia are also activated in response to SCI. TGF-beta influences microglial activation states and functions. TGF-beta can induce a transition from a pro-inflammatory phenotype (often referred to as M1) to an anti-inflammatory or neuroprotective phenotype (M2) [25]. This shift is crucial as M1 microglia produce pro-inflammatory cytokines, reactive oxygen species, and nitric oxide, which can exacerbate secondary injury [26]. Conversely, M2 microglia secrete anti-inflammatory cytokines, growth factors, and neurotrophic factors that support tissue repair and neuronal survival [27]. Experimental evidence suggests that TGF-beta modulates microglial activity through the Smad2/3 and non-Smad pathways, influencing the expression of genes involved in inflammation and tissue remodeling [28].

Furthermore, TGF-beta signaling in astrocytes and microglia is not isolated but rather part of a complex network of interactions with other cells and signaling molecules [29]. For instance, TGF-beta can interact with other cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), which are also upregulated following SCI [30]. These interactions can amplify or attenuate the activation responses of astrocytes and microglia, adding another layer of regulation to the glial scar formation process.

Through its regulation of reactive astrogliosis, ECM production, and inflammatory responses, TGF-beta contributes to both the protective and inhibitory aspects of the glial scar [31]. Understanding the precise mechanisms by which TGF-beta influences glial cell activation is essential for developing therapeutic strategies aimed at modulating the glial scar to promote axonal regeneration and functional recovery after SCI.

TGF-beta's Role in Axonal Regeneration and Neuroprotection

Transforming growth factor-beta (TGF-beta) is a critical cytokine that significantly influences the formation and function of the glial scar [32]. The dual role of TGF-beta in promoting neuroprotection while inhibiting axonal regeneration underscores the complexity of its implications in SCI.

TGF-beta is upregulated following SCI and contributes to the activation of astrocytes and microglia, leading to the formation of the glial scar which can isolate the injured area, thereby minimizing the spread of inflammation and further tissue damage [33]. The anti-inflammatory properties of TGF-beta help to mitigate secondary injury processes, which can exacerbate neuronal loss and dysfunction. For instance, TGF-beta can reduce the release of pro-inflammatory cytokines and chemokines, potentially preserving the surrounding neural tissue from further degradation [34].

However, the glial scar also presents a formidable barrier to axonal regeneration. The extracellular matrix components deposited by reactive astrocytes, such as chondroitin sulfate proteoglycans (CSPGs), inhibit axonal growth and prevent the re-establishment of neural connections [35]. TGF-beta contributes to the upregulation of these inhibitory molecules, thereby limiting the regenerative capacity of injured axons. Studies have shown that neutralizing TGF-beta or its downstream signaling pathways can reduce the expression of CSPGs and promote axonal sprouting and growth across the injury site [36].

In preclinical models, modulating TGF-beta signaling has yielded mixed results. For example, some studies have demonstrated that blocking TGF-beta can enhance axonal regeneration and functional recovery, while others have reported exacerbated tissue damage and worsened outcomes due to increased inflammation [37,38]. These findings highlight the need for a balanced approach to targeting TGF-beta, where the goal is to preserve its neuroprotective effects while mitigating its inhibitory impact on axonal regeneration.

Strategies to Modulate TGF-beta Signaling

Modulating TGF-beta signaling presents a promising therapeutic avenue for addressing spinal cord injury (SCI)-induced glial scar formation and its consequent inhibitory effects on axonal regeneration [39]. Various strategies have been explored to achieve this modulation, each with its own set of advantages and challenges.

One approach involves the use of small molecule inhibitors that specifically target the TGF-beta receptors [40]. These inhibitors can block the phosphorylation of Smad proteins, which are critical intracellular effectors of TGF-beta signaling [41]. SB-431542 is a well-documented inhibitor that has shown efficacy in reducing TGF-beta-mediated signaling pathways [42]. In rodent models of SCI, administration of SB-431542 has been reported to attenuate glial scar formation, promote axonal growth, and improve functional recovery [43]. Some studys utilized contusive SCI to investigate the effects of TGF-beta inhibition on glial scar formation and functional recovery [44,45]. Researchers administered a TGF-beta receptor antagonist immediately after injury and observed a reduction in glial scar density and an increase in axonal regeneration [46]. Functional assessments, including the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale, showed significant improvements in motor function in treated rats compared to controls [46]. Using transgenic mice with conditional knockout of TGF-beta receptors in microglia, the researchers found that the absence of TGF-beta signaling led to reduced microglial activation and decreased expression of pro-inflammatory cytokines [47]. These mice demonstrated better preservation of spinal cord tissue and improved locomotor function, suggesting that TGF-beta may exacerbate inflammation and secondary injury post-SCI [47].

Another strategy focuses on the use of neutralizing antibodies against TGF-beta ligands [48]. These antibodies can sequester TGF-beta in the extracellular space, preventing it from binding to its receptors and initiating downstream signaling. Fresolimumab, a pan-neutralizing antibody against all three isoforms of TGF-beta, has demonstrated potential in preclinical models [49]. When applied to spinal cord injury sites, it resulted in reduced fibrosis and enhanced neuroprotection [50,51].

Gene therapy presents an innovative approach by delivering genetic constructs that either downregulate TGF-beta expression or enhance the expression of its natural antagonists [52]. Viral vectors encoding short hairpin RNAs (shRNAs) targeting TGF-beta mRNA can effectively decrease TGF-beta production [53]. Alternatively, overexpression of Smad7, an inhibitory Smad that can bind to activated TGF-beta receptors and prevent Smad2/3 phosphorylation, has been explored [54]. These genetic interventions offer the advantage of sustained modulation of TGF-beta signaling but come with challenges related to delivery and potential off-target effects. In addition to pharmacological and genetic approaches, gene therapy has been explored as a method to modulate TGF-beta signaling [55]. One innovative approach involved the use of adeno-associated virus (AAV) vectors to deliver TGF-beta decoy receptors to the injury site [56]. This strategy successfully sequestered endogenous TGF-beta, mitigating its effects on glial scar formation. Treated animals exhibited enhanced axonal sprouting and synaptic plasticity, translating to improved sensorimotor outcomes [57-59].

Small interfering RNA (siRNA) technology also holds promise in this domain [60]. siRNAs designed to silence TGF-beta mRNA can be delivered to the injury site using nanoparticles or liposomes [61]. This method allows for targeted suppression of TGF-beta expression, and preliminary studies have shown encouraging results in terms of reduced glial scar formation and improved axonal regeneration [62].

Pharmacological agents that upregulate the expression of TGF-beta pathway inhibitors represent another viable strategy [63]. Synthetic compounds that induce the expression of decorin, a proteoglycan known to inhibit TGF-beta activity, have shown potential in reducing scar formation and promoting tissue repair [64]. These agents can be administered systemically or locally at the site of injury.

Combining multiple strategies to achieve a synergistic effect is also being explored. The simultaneous use of TGF-beta receptor inhibitors and gene therapy approaches could provide a more comprehensive blockade of TGF-beta signaling [65,66]. Combining TGF-beta receptor blockade with chondroitinase ABC, an enzyme that degrades inhibitory extracelluar matrix components, demonstrated synergistic effects in promoting axonal regeneration [67, 68]. This combination therapy resulted in more robust axonal growth and greater functional recovery than either treatment alone, highlighting the potential for multi-targeted approaches in SCI therapy. Additionally, the timing and dosing of these interventions are critical parameters that need optimization to maximize therapeutic outcomes while minimizing adverse effects.

CONCLUSION

In conclusion, various strategies to modulate TGF-beta signaling offer significant promise in the context of spinal cord injury. These approaches, ranging from small molecule inhibitors and neutralizing antibodies to gene therapy and siRNA, each bring unique benefits and challenges. Continued research and refinement of these strategies are essential to develop effective therapies that can improve recovery and quality of life for individuals with spinal cord injuries.

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