Chapter

Cytokines in Scar Glial Formation after an Acute and Chronic Spinal Cord Injury

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Abstract

The inflammatory response after a spinal cord injury (SCI) is a secondary mechanism of damage, this involves alterations at the local and systemic level, and it is mediated by cytokine participation that takes part actively. The excessive inflammatory response causes an autoreactive response that targets against components of the nervous tissue; this response lengthens the inflammatory process initiated during the acute phase. The participation of immune cells in acute phases is characterized by the arrival of neutrophils, macrophages, and microglia, as well as T lymphocytes, which express their peaks on different days post-injury (1st, 3rd, and 11th respectively). The chronic phase of the injury begins 14 days after it occurred, reaching its highest point at 60 days, and can still be detected the following 180 days. One of the outcomes of the inflammatory process and cytokine synthesis is the generation of glial scar. In this chapter, we will review the different cytokine mechanisms involved in the formation of glial scar in acute and chronic phases, as well as the modulating treatments of glial scar.

Keywords: spinal cord injury, immune cells, scar glial, modulating treatments

1. Introduction

Spinal cord injury (SCI) causes catastrophic damaged to patients, and the incidence is getting higher each year. Most of them are occasioned by physical trauma from sports injuries, car accidents, falls, and more [1, 2]. This life-changing neurological condition also comes with socioeconomic implications for patients and their caregivers, besides the functional and sensitive consequences that are largely determined by the level and completeness of the injury [1, 3].

After SCI, the acute and focal inflammation triggers a multicellular and multifunctional complex response which induces resident and infiltrating cells to form the glial scar (GS) at the site of the lesion [3]. The GS is a complicated phenomenon which has been considered as one of the main causes of limited regenerative capacity by inhibiting axonal regeneration and preventing functional recovery [4]. It has been proven that the GS creates both a physical barrier for neural repair as well as a chemical inhibition by the secretion of inhibitory extracellular matrix

molecules [5]. At the present time, finding an effective treatment has shown to be challenging due to the lack of complete understanding about the multifactorial pathophysiology of SCI. Current medical treatment is confined to surgical procedures and anti-inflammatory drugs which aim to reduce the damage caused by the continuous inflammatory reactions and therefore increase the locomotor recovery. More importantly, recent studies have demonstrated that the GS can be both favorable or prejudicial depending on the evolution time of the SCI, being able to participate in tissue repair and functional recovery during the acute phase but later on establishing a recovery plateau due to the inhibition of axonal regeneration during the chronic phase [6, 7]. Therefore, in recent years there has been an increasing interest in developing new therapies that can modulate the immunological responses involved in the GS formation. Although there are many drugs that have been identified as potential treatments for SCI, there is currently no therapy that can effectively restore the neural function that is lost during this pathology. The purpose of this chapter is to describe the importance of cytokines in the immunological processes of GS formation as well novel therapies that could serve as potential treatments of SCI.

2. Inflammation in traumatic central nervous system

Disorders in the homeostasis of the central nervous system (CNS) just as infection, trauma, ischemia, neurodegenerative diseases, and disturbances in general induce the beginning of neuroinflammatory responses that can be considered to consist principally of innate immune mechanisms [8, 9].

Inflammation is the way the human body acts in response to situations such as injury and infection. This mechanism involves several processes of the somatosensory, autonomic, immune, and vascular systems and more [10].

The immune and nervous system are capable of regulating physiological homeostasis and defending against infection and injury through inflammation. Both systems have improved many features for the recognition of alterations in the changing microenvironment to facilitate the protective responses. Although cells in each system (neurons and immune cells) have many differences, they can interact and communicate together to make a functional cooperation for the integral homeostasis [11].

Neuroinflammation is a localized inflammation in both CNS and peripheral nervous system (PNS), despite being distinct from the inflammation in peripheral tissues. There is also upregulation of several pro-inflammatory cytokines like IL-1β, IL-6, TNFα, and chemokines that affect the integrity of the blood brain barrier (BBB) resulting in local and systemic immune responses [9, 10, 12].

During these events, neural control plays an important role due to the fact that many immune molecules are detected by sensory neurons, which lead the system to generate immunoregulatory responses [13]. In general, the nervous system integrates biological functions to restore homeostatic function with the use of neurotransmitters and other regulatory molecules [11].

On the other hand, there are other cell types involved in the response, such as microglial and astrocytes. Microglial cells are made to deal with the harmful effects involving the activation of astrocytes, which are capable of modulating the activity of other immunocompetent cells in the site of the injury and also have an active role in the synaptic elimination, regeneration, cell elongation, and repair [8, 14, 15]. Many studies have reported that astrocytes participate in axonal regeneration by providing growth substrates and guidance structures [16]. They are also required in CNS repair, especially in the acute phase after injury but not

in the chronic phase, reducing GS formation and exacerbating the magnitude and duration of inflammatory activation [17, 18].

Nevertheless, it has been confirmed that inflammatory mechanisms contribute both to cell damage and tissue remodeling [12]. They are involved in reactive plasticity modulation of neuronal populations in different types of brain injuries, as well as in microglial cells and astrocytes, since they can activate and promote recovery and repair the neural circuits [8].

Owing to the events explained before, neuroinflammation is taken into account as an important manipulable aspect of injury in animal and human studies to develop immunomodulatory therapies because it can be detrimental or beneficial; however, it is necessary to understand the processes in a better way [19].

2.1 Inflammatory response after spinal cord injury

In the SCI there are two phases of the pathology: the primary one which consists in the initial accident-induced damage that can result from the compression of the spinal cord (SC), stretching of the nervous tissue, or disruption of local blood supply and the secondary one, which is characterized by the damage caused by inflammation and other biological mechanisms. These events can start at the moment of the injury and go on for days, and even weeks, after the event [2, 20] (see **Figure 1**).

Inflammatory microenvironment after SCI involves activated microglia, astrocytes, and infiltrating macrophages that play a role in the development of the secondary injury, and it is the major target to combat SCI [1, 2]. Then, this environment following SCI is mediated by the activation of microglia and astrocytes and infiltrating macrophages that greatly contribute to the progression of secondary injury that is a compilation of complex events derived from the initial trauma. Some of the mechanisms in its pathogenesis includes neurodegeneration, gliosis, and apoptosis in nearby intact neural tissues [21–25]. Effective restraint of secondary injury is essential to minimize neurodegeneration and to improve significantly functional recovery [1].

It is important to know that a traumatic injury in the CNS begins with the disruption of the BBB and blood-spinal barrier (BSB), followed by the arrival of several cells and molecules of the immune system with the possibility of aggravating the situation, affecting subsequent events such as repair and regeneration [26].

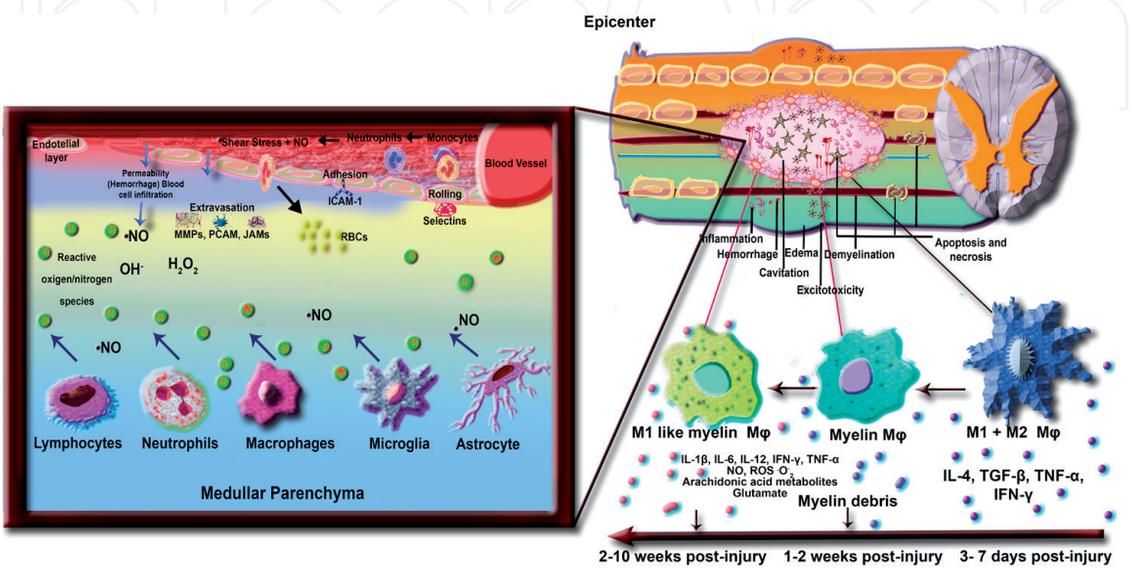

Figure 1.
Inflammatory response after spinal cord injury.

The inflammatory microenvironment after SCI involves activated microglia, astrocytes, and infiltrating macrophages that play a role in the development of the secondary injury, and it is the major target to combat SCI.

It has been demonstrated that there is a multiphasic response during the inflammation processes after SCI and a huge interaction between central and peripheral cellular and soluble components, which are influenced by some factors like patient age, sex, mechanism and degree of injury, therapeutic interventions, and genetic variability [9, 26].

In a study made by Beck et al. [26], they established two types of cellular inflammation phases. The early phase includes principally the infiltration of neutrophils which are polymorphonuclear leucocytes (PMNs), macrophages, and microglia, which inhibit recovery of the brain and SCI after the traumatic event. It was discovered that neutrophils are peaking 1 day of post-injury, macrophages/microglia 7 days of post-injury, and T cells 9 days of post-injury. The late phase was detected after 14 days of post-injury with its peak after 60 days of post-injury, and it also remained detectable throughout the 180 days of post-injury for all three cell types mentioned before. Moreover, the inhibition of the C5a-mediated inflammation after 14 days of injury reduced the locomotor recovery and myelination of the SC in the damaged site, suggesting that the late phase involves a restorative function [26].

Following this line, after the damage to the microvasculature, the presence of progressive edema and proapoptotic signaling begins. All of these events promote thrombosis and microvessel spasms causing hypoxia. Therefore, a relevant aspect to mention is that astrocytes are the first to act in the injury site, contributing to the formation of the GS, as well as preventing neurons to grow and heal [1, 20]. In the same way, neutrophils and macrophages are recruited from the periphery to the injured area, and, together with reactive astrocytes, microglia/macrophages will also contribute to the formation of a regeneration-inhibiting GS [27].

3. Cytokines and acute glial scar formation after spinal cord injury

In the early phase, the formation of GS has a protective function, isolating potentially dangerous molecules of the rest of healthy tissue and controlling the spread of damage [28]. Accordingly with this, GS is considered as a mechanism of protection, developed by the organism against injuries that affect the CNS.

Overall, the GS is composed of two parts, the fibrotic and the glial. The fibrotic scar occupies the core of the injury with deposits of collagen matrix and is mainly composed of invading fibroblasts derived from meningeal and perivascular cells [29, 30]. The GS occupies the peripheral zone of the lesion and is composed mainly of astrocytes due to its evolution from a dynamic process known as reactive astrogliosis [30]. The glial limiting membrane is a specialized structure that is located close to the outer layer of the fibrotic scar and marks the division between these two parts [31]. Besides fibroblasts and astrocytes, the GS is also formed by NG2 + oligodendrocyte precursor cells (OPCs), microglia, pericytes, and ependymal cells [32].

A phenomenon that occurs simultaneously with the destruction of neuronal components is the activation of an inflammatory response characterized at first moment by the release of chemokines by endothelial cells and microglia cells [33]. These chemokines induce the migration of peripheral immunological cells to the affected tissue and promote the posterior establishment of inflammatory response [34]. The migration of macrophages and lymphocytes besides the activation of microglial cells is joined to the deficiency to control an inflammatory process in the CNS, thereby contributing with a destructive immunological response [35]. Both resident and

infiltrating cells contribute to the GS formation, and the main characteristic of the inflammatory response at this time point is the sustained production of free radicals due to the continuous synthesis of pro-inflammatory cytokines like TNF-α, IL-1β, INF-γ, and enzymes that activate glial cells or disrupt the BSB [34, 36]. Moreover, activated macrophages produce and secrete matrix metalloproteinases (MMPs) to furtherly disrupt the BSB and increase vascular permeability [37].

Another phenomenon observed is the activation of inflammasome. The damage of cell membranes permits the release of molecules of ATP and the efflux of K^+, stimulating the activation of the inflammasome and inducing the production of the pro-inflammatory cytokines, IL-1β and IL-18, which these cytokines have been related with neurodegenerative process [38]. Furthermore, studies in vitro have shown the direct relation of IL-1β with the overexpression of glial fibrillary acidic protein (GFAP) on astrocytes; for this reason the activation of inflammasome is a key factor involved in the formation and maturation of GS [39].

Astrocyte is a specific cell residing only in the CNS that maintains the homeostasis, conforms the BBB, and keeps the concentration of ions and neurotransmitters to regulate the activity in neuronal synapsis [40].

Reactive astrocytes (RAs) possess surface receptors for different cytokines just like the cells of the immune system, making them a target for products derived from the inflammatory environment. The pro-inflammatory cytokines induce the upregulation of inflammatory genes on astrocytes and the posterior secretion of various chemokines, including CXCL1, CCL2, CCL3, CCL4, and CXCL12, and cytokines like IL-1, transforming growth factor β (TGFβ), TNF-α, and INFγ. For example, INFγ interacts to modulate several facets of the gliotic response, and such interactions with growth factors may be important in creating the biochemical and physical properties of the GS; for this reason this cytokine is responsible for failed neuronal regeneration after SCI [41]. In this way, the astrocytes can contribute with the presence of a constant inflammatory response, affecting themselves and influencing other cell populations related with the formation of GS [41, 42].

Fibroblasts secrete extracellular matrix (ECM) components which include the chondroitin sulfate proteoglycans (CSPGs) family (neurocan, versican, brevican, phosphocan, and NG2) which is mainly secreted by astrocytes as well as fibronectin, collagen, and laminin which are produced by fibroblasts [36, 43]. Altogether, they contribute to the formation of GS and participate in developing its characteristic impermeability and the expression of molecules that impede the anatomical and functional restoration after the lesion [32, 44]. Fibroblasts also possess cytokine receptors on their surface which respond to high concentrations of pro-inflammatory cytokines and stimulate the activation of enzymatic machinery synthesized ECM protein. The inhibition of pericytes and fibroblasts by the application of different therapeutical strategies reduce the size and consolidation of GS, showing the importance of these types of cells in the GS formation. Of great importance is the presence of specific receptor for TGFβ on fibroblasts; the stimulation with this molecule facilitates the synthesis and release of collagen type IV [45].

Generally speaking, after an injury to the CNS, there is a sequential phenotypic change in astrocytes called reactive astrogliosis, where naïve astrocytes (NAs) are transformed to RAs which eventually become scar-forming astrocytes (SAs) that can inhibit axonal regeneration and functional recovery [7]. Astrocytes are the most abundant glial cells within the CNS, and although they are not part of the immune system, they play a crucial role in the pathophysiology of the GS formation [36].

Furthermore, RAs substantially upregulate their expression of GFAP, intermediate filaments, nestin, and vimentin and mobilize to the center of the injury

to form a mesh-like structure of interlaced filamentous structures [46]. A high concentration of pro-inflammatory cytokines induces upregulation of GFAP on astrocytes and the development of hypertrophic prolongation. A certain study showed that genetically modified mice with deficiency of vimentin and GFAP produced a less dense GS which frequently conducted to constant bleeding, suggesting that vimentin and GFAP are part of the main cytoskeletal intermediate filaments that form the GS [47].

This astrocytic migration secludes inflammatory cells from the surrounding intact tissues and minimize the extension of secondary damage after CNS injury leading to tissue repair and functional improvement during the acute phase of GS formation [7, 48, 49]. In addition, the hemorrhagic flow into the CNS due to the rupture of the BBB exposes scar-forming cells to factors in plasma such as fibrinogen which has been proven to induce the expression of CSPGs in astrocytes through TGFβ/Smad2 signaling pathway [50].

Besides, in the acute phase of the GS formation, the overexpression of CSPGs (neurocan, versican, brevican, phosphocan, and NG2+) plays a beneficial role by modulating the inflammatory activity of resident microglia as well as the infiltration of monocytes through the CD44 receptor [51].

Moreover, to the featured RAs, the GS formation also requires the activation of ependymal cells, NG2+-expressing glia (including OPCs), meningeal- and vascular-derived fibroblasts, pericytes, and macrophages surrounding the injury area [52]. More importantly, some of these previously mentioned cells have the capacity to switch their phenotypes and become RAs to furtherly contribute in the GS formation [53]. Furthermore, there are several molecular mechanisms that contribute to the formation of the GS such as the upregulation of bone morphogenetic proteins (BMPs), MMPs, epidermal growth factor receptor (EGFR), eph/ephrins, TGFβ, and signal transducer and activator of transcription and interleukin (STAT/IL) family (STAT3) [30, 54, 55]. The upregulation of BMP-4 has shown to promote astrocyte differentiation and to inhibit the production of oligodendrocytes and neurons [56]. In addition, the MMP family is involved in the ECM remodeling, and therefore, they are structurally and temporally involved in the GS formation [57]. The limitation of the extent of the GS was seen with the suppression of MMP-2 in mice, and MMP-9 has proven to be involved in the augmented migration of RAs to the injury site, therefore facilitating GS formation [58]. EGFR is upregulated in astrocytes following damage to the SC, leading to the activation of the Rheb-mToR signaling pathway which induces astrocytes to migrate and suffer hypertrophy to furtherly form the GS [59]. Moreover, EGFR ligands, such as transforming growth factor-alpha (TGF-alpha) and EGF, contribute to the formation of the GS by inducing astrocytes to secrete CSGPs [60]. In addition, TGFβ expression is upregulated immediately after SCI. It promotes the formation of the GS by simultaneously stimulating monocyte and lymphocyte activity as well as inducing the production and deposition of new ECM proteins (collagen, fibronectin, and proteoglycans) [61, 62]. The manipulation of TGFβ signaling in the injured CNS modulates the formation of the fibrotic scar in the lesion site. The administration of TGFβ1 to the injured CNS increases the deposition of ECMs in the lesion site [63, 64], while antibodies to TGFβ1 and TGFβ2 and the endogenous TGFβ inhibitor decorin, a small leucine-rich CSPG, conversely reduce the size of GS [64], which proposes the involvement of TGFβs in the formation of GS. In addition, RAs release TNF-α to inhibit oligodendrocyte progenitor cell (OPG) survival and prevent them from differentiating into mature oligodendrocytes, suggesting a mechanism for the failure of remyelination after SCI [65].

4. Modifications of the glial scar

RAs have been traditionally considered to be a unidirectional and irreversible process; however, recent studies have proven to inhibit its progress and even revert the astrocyte's phenotype according to environmental cues [48, 49]. Over the past few years, there has been an increasing interest in modulating the GS formation; nevertheless, there has been a wide spectrum of results mainly due to the fact that the GS has many components and there are many different types of therapy strategies. Inclusive, recent studies have shown that the attenuation of RAs to prevent GS formation has resulted in a worse outcome in SCI and limited functional recovery [6, 7]. In transgenic mice where STAT3 selectively suppressed RAs showed reduced migration to the lesion epicenter, leading to an extensive area of injury with uncontrolled inflammatory cell filtration and limited functional recovery [7]. Another study showed a pronounced reduction of glial scarring in animals with conditional knockdown of STAT3, suggesting that this molecule is one of the most important factors involved in the formation of the GS [62]. A wide spectrum of molecules such as type I and II interferons and cytokines, growth factors including EGF, platelet-derived growth factor, IL-6, leukemia inhibitory factor, and ciliary neurotrophic factor (CNF) is able to activate STAT3 in order to cause variations in RAs and elicit GS formation [66, 67]. Similarly, a recent study used HSV1tk/GCV (a suicide system gene) to selectively kill proliferating RAs in SCI to avoid GS formation, resulting in a widespread infiltration of inflammatory cells and continuous involvement of healthy tissue surrounding the epicenter of the lesion as well as decreased neuronal survival and decreased locomotor recovery [5]. These findings furtherly support that reactive astrogliosis in acute-subacute phases plays beneficial roles in acute wound healing, remodeling processes, and isolating the injury to prevent the spread of cytotoxic molecules and inflammatory cells into the surrounding tissue [4, 5].

Even though GS formation in acute phases has proven to have beneficial effects, its evolution and persistence in chronic stages of the injury have shown to become a strong inhibitor for SC regeneration [3]. Therefore, there has been some attempts in regulating the chronic phase of the GS to improve axonal outgrowth.

5. Cytokines and chronic glial scar formation after spinal cord injury

Through the years, it became clear that both the scar tissue and the immune system play important beneficial roles in axonal regeneration and healing of the CNS [68].

As mentioned before, SCI results in the disruption of the BBB, and the BSB increased inflammatory reactions such as the activation of the microglia and the production of various cytokines and augmented the activation of TGFβ and Smad2 signaling pathways [49]. The inflammatory microenvironment presented after the insult continues in most of the cases until the chronic phase [34].

Acute GS formation restricts inflammation and preserves neural tissue [28, 46, 69]. Nonetheless, at the chronic phase (>14 days after the injury in mice), RAs progressively transform into SAs that form astrocytic scars which compose the main impediment for axonal regeneration and functional recovery in the chronic phase of SCI [70, 71]. It has been suggested that after inflammation has resolved, chronic GS is expendable and detrimental because it continually prevents axon regeneration [6]. For this reason, it is necessary in chronic phases to inhibit, modulate, or remove the mature GS.

Certain factors present during the acute formation of the glial scar are also active during its chronic formation. The genetic suppression of BMPR1b (a subtype of the BMP type 1 receptor) resulted in the weakening of the GS in chronic stages of SCI, suggesting that BMPs play an important role in the acute formation of the GS as well as in its stabilization through the chronic stage [72].

Although the expression of CSPGs during acute glial scar formation participates in reducing the damage extent, the prolonged exposure of CSPGs is prejudicial for functional recovery for they are well-known to be the main inhibitors of GS axonal regeneration, sprouting, and remyelination during the chronic phase of SCI [3, 73]. The posterior formation of the GS traps on its core of GS, where they reside contributing with the chronic presence of an inflammatory response. The continual synthesis of pro-inflammatory cytokines like TNFα, IL1β, and INFγ promotes the aggregation of new elements and the modification of GS [74].

This is the main reason why astrogliosis may cause both beneficial and detrimental effects depending on its dynamic features and on its time course [50, 69]. Cytokines behave in a similar way. In the early stages of GS formation, pro-inflammatory cytokines such as TNF-α, IL-1β, and INF-γ help by recruiting and activating microglial cells, astrocytes, and other peripheral immunological cells to the injury site to prevent the extension of the injury [33, 35]. However, other acute-secreted cytokines such as IL-1β and IL-18 have been associated with neurodegenerative processes and activation of the inflammasome [37, 38]. On the other hand, during the chronic formation of the GS, cytokines contribute to impede axonal regeneration and functional recovery. Overall, cytokines may present both beneficial and detrimental effects depending on the stage of GS formation and depending on the process in which they are involved. Certain cytokines which are present in early stages and may present beneficial effects by increasing the production of CSPGs may become prejudicial as time progresses. Current pharmacological treatments

Cytokine	Scar glial effect	References
TGFβ	Induces the expression of CSPGs in astrocyte Facilitates the synthesis and release of collagen type IV in fibroblast Increases the deposition of ECMs in the lesion site Inhibits the generation of TGFβ1, TGFβ2, and SOX-9 and as a result there is a decreased deposition of CSPG	[60] [45] [63, 64] [28]
IL-1β	Increases overexpression of GFAP on astrocytes and maturation of GS	[39]
TNFα	RAs release TNF-α to inhibit OPCs survival and prevent them from differentiating into mature oligodendrocytes, suggesting a mechanism for the failure of remyelination after SCI Reduces the expression of GFAP through anti-inflammatory processes and helps to suppress reactive gliosis	[27]
INFγ	Promotes SG formation and modulates ECM which helps that the interactions with growth factors may be important in creating modification in the GS	[36]
IL-4 and IL13 IL-4 and IL-10	Transplantation with BMSCs was associated with significant increases in IL-4 and IL-13; these changes were associated with less scar tissue formation INDP in combination with scar removal and DPY reduces pro-inflammatory cytokines in chronic phase	[79] [78]
IL-10	Activates beneficial M2 macrophages which were found to regulate scar resolution	[18]

Table 1.
Main cytokines involve in scar glial formation.

depend on cytokines to establish their mechanism of action and should be focused to develop further pharmacological strategies.

The majority of SCI patients are those with lesions who may benefit insufficiently from therapeutic treatments designed for application in the chronic stage and focused on cytokines and other immunological processes. However, compared to treatments of acute experimental SCI, the efficacy of therapies promoting axonal regeneration seems impaired in chronic models. Therefore, GS formation can be improved if we combine treatments like stem cell transplants [75], iron chelators [76–78], and matrix biocompatible [16, 78]. **Table 1** summarizes some GS effects exerted by cytokines.

6. Modulate, inhibit, or remove glial scar as therapeutic tool

In this section we will review some modulating treatments of the GS. That should be able to counteract posttraumatic factors of inhibitory growth and promote axonal and tissue recovery.

6.1 Anti-inflammatory therapy

In contrast with the pro-inflammatory cytokines produced after the injury, the application of anti-inflammatory therapies like the treatment with doses of methylprednisolone (MP) after the injury avoids the formation of the GS. The application of MP is helpful to reduce the expression of GFAP and reduce the deposition of CSPG and avoid the formation of the GS [80].

Combination therapy using MP and tranilast after SCI in rats significantly reduced posttraumatic SC edema and neutrophil infiltration and improved functional recovery better than single individual therapies, and it also significantly reduced the amount of GFAP expression at the injury site [81].

Therapies that induce elevated concentrations of IL-10, a well-known anti-inflammatory cytokine, reduce in an important way the presence of CSPG on GS [82]. Astrocytes also express the transcription nuclear factor (NF-kB). The selective inhibition of NF-kB induces a better neurological outcome and a reduction in size of the GS. In addition, the interference of NF-kB induces the reduction of pro-inflammatory cytokines, chemokines, and secretion of CSPG [83].

Curcinum is a phytochemical compound that has an anti-inflammatory effect. This molecule inhibits pro-inflammatory cytokines (TNFα and IL-1β), which contribute to reduce the expression of GFAP through anti-inflammatory processes and help to suppress reactive gliosis [26]. Previous studies have also demonstrated to inhibit the generation of TGFβ1, TGFβ2, and SOX-9; as a result, there is a decreased deposition of CSPG, causing the inhibition of TGFβ and transcription factors. There is also evidence that curcinum reduces the amount of nestin and GFAP around de SCI, suggesting that it inhibits astrogliosis improving the microenvironment to SC repair [27].

In addition, rapamycin is an immunosuppressant that inhibits the mTor pathway selectively, and, it is considered neuroprotective because it increases the anti-inflammatory microenvironment and reduces locomotor impairment and damage in neural tissue. Other outcomes have shown that reduced infiltrations of macrophages and neutrophils at the SCI also reduce microglial activation and secretion of TNFβ; the amount of cells expressing GFAP inhibits proliferation of astrocytes and promotes angiogenesis and neuronal survival around the injury [2, 30].

Finally, TGFβ is involved in GS formation process, increasing the expression of neurocan, a CSPG that mediates GS formation and inhibits axon growth. Therefore, the use of antibodies against TGFβ1 and TGFβ2 is necessary; they mitigate the response of GFAP, causing the interruption of scar tissue and glial membrane

formation that limit the edge of the injury. Astrocytes, OPCs, and NG2+ responses are diminished. This is possible by interrupting the Smad 3 signaling pathway in conjunction with TGFβ [2, 84].

In contrast, a study carried out by Kohta and colleagues showed that the inhibition of TGFβ1 with a neutralizing antibody resulted in the suppression of the GS formation resulting in a mild improvement of growth and/or preservation of axons in the injured GS caudal to the site of contusion [31]. Furthermore, rats treated with anti-TGFβ1 increased the activation of the microglia after injury, apparently providing a beneficial environment for the restoration and healing of the neural network [31].

The macrophages are immune cells with phagocytic capabilities. There are three subgroups, but now the focus goes towards M2 macrophages. When M2 macrophages infiltrate the SC, they may also secrete protective factors, such as the anti-inflammatory cytokine IL-10, and boosting the release of protective molecules would be advantageous. In addition, when MMP-2 is upregulated, it represents a beneficial effect for SCI recovery; however, when there is a deficiency in MMP-2-expression, an exacerbated lesion expansion, scar formation, vascular instability, and locomotor deficits are present [18, 85].

6.2 Cell therapies

6.2.1 Schwann cells

The SCs are the principal glia of the peripheral nervous system (PNS) [86], and in a SCI, they have shown to promote axonal regeneration through the formation of bridges across the injury. This bridge is a multicellular structure that crosses the lesion from the rostral to caudal part, providing an environment in which axons can grow and cover the GS to suppress axonal regeneration impediment [87, 88].

SC transplant provides a neuroprotective effect, preventing neural death by continuous inflammatory reaction caused by a SCI; moreover the neural peripheral grafts promote the expression of neurotrophins like BDNF and NGF, which is key for a successful regeneration as it delays the formation of the GS [89]. It is not advisable to transplant the SCs alone, because their regenerative capacity is limited by the secretion of myelin-associated and axonal growth inhibitors (CSPGs, semaphorins, and myelin-associated proteins) by the GS. Although many types of cells have been studied for transplantation, the SCs have always been considered as one of the best proposals for this treatment; however, they need to be co-transplanted with other molecules or cells such as OECs, MSCs, and NSCs, among other cells, in order to achieve its full therapeutic potential [88, 90].

6.2.2 Bone marrow mesenchymal stem cells

Bone marrow stem cells (BMSCs) are the most abundant cells in the bone marrow; they are hematopoietic and functional support cells [91]. The implantation of BMSCs has shown to have regenerative and immunomodulative properties that help to prevent the GS formation [91]. Furthermore, these cells are able to regulate CNTF-STAT3 signal transduction which reduces tissue scarring, inflammatory responses, and apoptosis [92]. Okuda et al. reported that BMSC sheets suppress the GS and provide a positive environment for axonal regeneration, causing changes in reactive astrocyte morphology [93]. Moreover, BMSCs can secrete different trophic factors (VEGF, BDNF, NGF, and hepatocyte growth factor) which increase positive results associated with BMSC transplantation [91, 94]. In addition, the transplant of BMSCs are associated with significant increases in IL-4 and IL-13; these changes were associated with less scar tissue formation [79].

With all that said, BMSCs possess many features that make them eligible for cell culture transplantation; however there are still many knowledge gaps that need to be studied, such as their survival rate when transplanted.

6.2.3 Olfactory ensheathing cells

Olfactory ensheathing cells (OECs) form the glial component of the primary olfactory system, and they reside both on CNS and PNS [87, 95]. Recent olfactory bulb (OB) transplants have shown to be able to infiltrate the scar tissue, through the environment of astrocytes thanks to their heparin profile [87]. They also provide a scaffold that promotes neuronal growth and angiogenesis and supply a bridge through the injury site that decreases the contusion area [96, 97]. OECs promote neural regeneration by promoting cell-to-cell interaction with sensorial axons and migrate ahead to the olfactory bulb, creating a favorable environment for axonal growth where cellular debris are phagocytized to increase restoration, neuroinflammation is modulated, neuroprotection is provided, and the expression of neurotrophic factors like BNDF, GDNF, NGF, and ECM molecules is augmented to provide a substrate for newly generated axons [98, 99]. These cells inhibits pro-inflammatory cytokines and induces the activation anti-inflammatory cytokines; they can activate neurotrophic factors.

Neurotrophic factors secreted by OECs are capable of inhibiting scar formation and promote axonal regeneration, implying that they also are neuroprotective. The receptors of each neurotrophic factor are NGF/p75, BDNF/Trκβ, GDNF/GFR-1, NTN/GFR-2, and NRG-1/ErbB [43]. Also OECs reduce the expression of GFAP by an earlier shorter immune response by astrocytes and microglia, due to the attenuation of NF-κβ, which is involved in RAs [100].

6.3 Chondroitinase ABC

The chondroitinase ABC (ChABC) is a bacterial enzyme that catalyzes the removal of the CSPG and therefore digests them. The administration of ChABC has demonstrated to inhibit CSPG and deactivate their glycosaminoglycan chains, which promotes a significant regeneration of axons, and M2 macrophage phenotype activation [2, 101].

Certain studies have used ChABC in SCI models in rats to enzymatically degrade CSPGs and therefore reduce its inhibitory functions in axonal regeneration [35, 36]. The results of these experiments showed a significant improvement in locomotor and proprioceptive functions, demonstrating that the degradation of CSPGs is a promising strategy to avoid its long-term prejudicial effects in chronic SCI [36, 37]. It is also reported that the combination of glial-derived neurotrophic factor (GDNF) and transplanted SCs causes a reduction in astrogliosis (GFAP and CSPG) and is also responsible for promoting axon regeneration after SCI [102]. Another combination therapy with ChABC, acidic fibroblast growth factor (aFGF), and peripheral nerve graft bridge supports axon regeneration and functional recovery after chronic SCI like so bladder physiology outcomes associated with an invasive repair strategy. CSPG are significantly downregulated by the astroglial NF-kB inhibition [83]. Taken all together, these studies demonstrate that the degradation of CSPGs is a promising strategy to avoid its long-term prejudicial effects in chronic SCI.

6.4 Iron chelators to inhibit collagen biosynthesis

Using iron chelators to inhibit collagen biosynthesis has been demonstrated to have beneficial effects by transient suppressing fibrous scarring in an acute SCI

model [45, 77]. The iron chelation of α,α'-dipyridyl (DPY) has previously shown to decrease the collagen synthesis at a posttranscriptional level by inhibiting 4-prolyl hydroxylase, one of the key enzymes in collagen metabolism [103].

In a study with unilateral SC transection in adult and postnatal mice (14 days old) where DPY was applied at the injury site, it was observed that collagen type IV deposits and axons showed the expression of tyrosine hydroxylase and these axons extended through the site of injury by reinnervating the striatum [104]. Conversely, iron chelators suppress GS but do not degrade the existing scar, meaning that this treatment is not transferable to chronic SCI where a mature lesion scar is present, with a plethora of axon growth-inhibitory molecules attached [105, 106].

6.5 Surgical resections

Some studies have shown that the surgical removal of the GS promotes the development of axons in the injured portion of the SC, suggesting that axonal reconnection is feasible [16, 107]. Another study indicates that the use of surgical resection of the GS by itself does not offer positive results, because at the time of incising and removing the tissue healing, the same mechanisms that are activated during the acute phase are reactivated, generating a second lesion [75].

On the other hand, one study showed that careful surgical resection of the scar and filling cavity with biocompatible matrices promotes a functional improvement in a full-section model [16].

Therefore, the treatment of SCI can be improved if the behavior of the GS with the combination of transplants [75], iron chelators [45, 77], and matrices is biocompatible [16]. Furthermore, Rodriguez and colleagues explored whether INDP in combination with scar removal and DPY provided an appropriate microenvironment to promote neural restoration in chronic SCI. They found an increased activity in genes encoding for IL4, TGFβ, BDNF, IGF1, and GAP43, as well as a decreased activity in genes encoding for TNFα and IFNγ. Moreover, there was a significant increment in the number of serotonergic (5-HT-positive) and catecholaminergic (TH-positive) fibers at the caudal segment of the GS [78].

7. Conclusions

Cytokines are incredibly involved in GS formation during the acute and chronic phases of SCI, participating in either beneficial or detrimental effects. To achieve the best possible results, it is necessary to maintain the anti-inflammatory microenvironment for more extended periods of time in order to promote axonal regeneration, M2 phenotype macrophage activation, and secretion of neurotrophic factors that are capable of inhibiting the GS formation in the chronic phase. Several clinical trials have shown different therapeutic strategies to modulate the formation of GS. Although those experiments have had a significant therapeutic potential in patients with SCI, there are still enormous knowledge gaps which need further investigation in order to develop a potential cure for SCI.

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Conflict of interest

The authors declare no conflict of interest.

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