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DOI: 10.14670/HH-18-262
Article type: REVIEW
Accepted: 2020-10-01
Epub ahead of print: 2020-10-01
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Funding information: National Natural Science Foundation of China (NSFC) (NO.81671907 and 81871556).
Abstract

Spinal cord injury (SCI) is one of the most destructive traumatic diseases in human beings. The balance of inflammation in the microenvironment is crucial to the repair process of spinal cord injury. Inflammatory cytokines are direct mediators of local lesion inflammation and affect the prognosis of spinal cord injury to varying degrees. In spinal cord injury models, some inflammatory cytokines are beneficial for spinal cord repair, while others are harmful. A large number of animal studies have shown that local targeted administration can effectively regulate the secretion and delivery of inflammatory cytokines and promote the repair of spinal cord injury. In addition, many clinical studies have shown that drugs can promote the repair of spinal cord injury by regulating the content of inflammatory cytokines. However, topical administration affects only a small portion of inflammatory cytokines. In addition, different individuals have different inflammatory cytokine profiles during spinal cord injury. Therefore, future research should aim to develop a personalized local delivery therapeutic cocktail strategy to effectively and accurately regulate inflammation and obtain substantial functional recovery from spinal cord injury.

Keywords: Spinal cord injury; Neuroinflammation; Inflammatory cytokines
1. Introduction

The spinal cord is an important part of the central nervous system and plays a vital role in the transmission of motor and sensory information and in the regulation of most primary reflexes (Chen et al., 2016). The importance of its role makes spinal cord injury one of the worst traumatic diseases in humans (Charlifue et al., 2016). Spinal cord injury not only affects the body's sensory and motor functions, but also causes the loss of important visceral functions. Paralysis is a common clinical outcome of spinal cord injury, and severe cases directly lead to death of patients.

The incidence of spinal cord injuries ranges from 3.6 to 195.4 cases per million people worldwide. For example, in the United States, there are more than 120,000 new cases each year and more than 250,000 people suffer from spinal cord injuries (DeVivo et al., 2002). The high prevalence of spinal cord injury and the cost of rehabilitation determine the urgency of its treatment. However, there is currently no clinically effective treatment to promote functional recovery.

A series of inflammatory responses are activated, particularly the destruction of the blood spinal cord barrier (BSCB) (Bartanusz et al., 2011) after spinal cord injury (Bloom et al., 2019). During the pathological process of the destruction of the blood spinal cord barrier, various inflammatory cytokines are secreted and accumulated in the lesion microenvironment. Inflammatory cytokines are a class of soluble small molecular proteins that are widely present in the complex functional interactions and reactions of the immune system (Bloom et al., 2019). The huge impact of the blood spinal barrier (BSCB) on the role of inflammatory cytokines in the repair of spinal cord injury has been confirmed by a large number of studies (Hu et al., 2016; Yu et al., 2016). However, the special inflammatory factor has different effects at different times in the course of spinal cord injury (Badhiwala et al., 2018). Therefore, this study will review the role of inflammatory cytokines in the repair of spinal cord injury.

2. Roles of Inflammatory Cytokines in SCI Repair

Beneficial and harmful inflammatory cytokines for spinal cord repair are discussed in the review. Determining whether a certain inflammatory cytokine is beneficial or harmful is direct evidence of functional recovery in vivo.
2.1. Inflammatory Cytokines Beneficial to SCI Repair

2.1.1. Erythropoietin (EPO)

Erythropoietin (Sirén et al., 2009), known as hematopoietin, was originally discovered as a glycoprotein hormone that controls the production of red blood cells. Erythropoietin is also a cytokine, and its tissue protective activity has been extensively studied in various injury models (French, 2019), including SCI (Mammis et al., 2009; Grasso, 2018). It is reported for the first time that EPO can significantly improve the motor function of ischemic spinal cord injury models in experimental animals (Grasso, 2018), and its mechanism may be inhibition of apoptosis. EPO can inhibit the apoptosis of neurons and oligodendrocytes (Utada et al., 2015), the possible molecular mechanism is to inhibit lipid peroxidation, reduce the expression of caspase-3 and antagonize the oxidative stress (Jin et al., 2014) (such as Nrf2 signaling pathway), and down-regulate the activity of some phosphorylated proteases (Huang et al., 2009) (such as the ERK, JAK signaling pathway). In addition, erythropoietin (EPO) also limits the inflammatory response, and its role is also closely related to its molecular mechanism of anti-apoptosis (Foley et al., 2017). Erythropoietin also has other beneficial effects, such as promoting angiogenesis, and the restoration of vascular integrity may be due to its promotion of vascular endothelial growth factor (VEGF) expression (Furlani et al., 2008).

2.1.2. Interferon beta (IFN-β)

IFN-β is the only interferon that can be produced by almost all nucleated cells, and it also has antiviral, cancer suppressing and immunomodulatory effects (Borden et al., 2000). In animal experiments, IFN-β can promote the functional recovery of spinal cord injury by reducing oxidative stress, reducing infiltration of blood-derived immune cells, and inhibiting scar formation (Gok et al., 2007; Nishimura et al., 2013).

2.1.3. Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine with important immunoregulatory functions (Geng et al., 1994). It is a cytokine with potent anti-inflammatory properties, repressing the expression of inflammatory cytokines by activating macrophages. IL-10 is a pleiotropic cytokine with important
immunoregulatory functions. Its actions influence the activities of many of the cell-types in the immune system (Berkman et al., 1995). It is primarily secreted by antigen-presenting cells such as activated T-cells, monocytes, B-cells and macrophages (Berkman et al., 1995). IL-10 has been shown to promote functional recovery of SCI in animals, mainly by regulating the activation of microglia/macrophages and astrocytes (Jackson et al., 2005). In addition, IL-10 can significantly reduce the incidence of long-term complications of spinal cord injury (Lau et al., 2012).

2.1.4. Interleukin-33 (IL-33)

IL-33 is an IL-1 family protein mainly secreted by non-hematopoietic cells (fibroblasts, epithelial cells, endothelial cells, etc.) (Schmitz et al., 2005). It is a class of "orphan receptor" ST2 ligands. Through ST2, IL-33 can lead to the recruitment of intracellular MyD88 protein, which in turn leads to the activation of a variety of signals, including NF-kB and MAPK (Schmitz et al., 2005). More and more evidence shows that IL-33 has an important role in allergic reactions and Th-2 immune diseases. On the other hand, IL-33 can protect from inflammatory reactions (such as atherosclerosis, etc.). Therefore, IL-33 has dual immunomodulatory activities. Studies have confirmed that IL-33 reduces the secondary injury of spinal cord injury in mice and improves functional recovery by inducing T cells to transfer to Th2 (Pomeshchik et al., 2015). In addition, IL-33 has also been found to reduce axon demyelination and inhibit astrocyte scar formation (Pomeshchik et al., 2015).

2.1.5. Stromal Cell-Derived Factor-1 (SDF-1)

SDF-1 (Aiuti et al., 1997), also known as CXCL12, belongs to the chemokine protein family. It has two forms, SDF-1α / CXCL12a and SDF-1β / CXCL12b. SDF-1 has a strong chemotactic effect on lymphocytes and plays an important role in development. SDF-1 directs the migration of hematopoietic stem cells from fetal liver to bone marrow during embryonic development (Aiuti et al., 1997). SDF-1 knockout mice often die in the fetus or within 1 hour after birth. SDF-1α / CXCL12a has an effect on the electrophysiological conduction of neurons. SDF-1 can be expressed in many tissues including brain, thymus, heart, lung, liver, kidney, bone marrow, and spleen. SDF-1 promotes the entry of blood-derived monocyte / macrophage cell lines into injured spinal cord lesions (Zendedel et al., 2012) and reduces the expression of proinflammatory
inflammatory factors such as IL-18, IL-1β, TNF-α (Zhang et al., 2011). SDF-1 also inhibits the formation of glial cells, thereby reducing scar formation (Tysseling et al., 2011).

2.1.6. Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF is a type of cytokine that is essential for the proliferation and differentiation of mature granulocytes and macrophages (Hayashida et al., 1990). It is suitable for cancer chemotherapy and leukopenia caused by bone marrow suppression therapy. It is also suitable for treating patients with bone marrow failure. Low white blood cells can also speed up the recovery of neutropenia caused by infection (Bryson et al., 2019). GM-CSF promotes functional recovery after spinal cord injury, and its main molecular mechanism is inhibition of neuronal apoptosis (Ha et al., 2005). In addition, GM-CSF can also promote the recruitment of blood-derived macrophages, inhibit the formation of focal scars and improve the prognosis of animals after spinal cord injury (Kim et al., 2013).

2.1.7. Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF, a small molecular cytokine, has been clinically used to treat or prevent chemotherapy-induced neutropenia, bone marrow collection, and anti-infective therapy (Nagata et al., 1986). It was found that G-CSF promotes the mobilization of bone marrow stem cells and improves the recovery of motor function after spinal cord injury in rats (Urdziková et al., 2006; Koda et al., 2007). In the study of spinal cord injury in mice, G-CSF can promote the recovery of hind limb function (Koda et al., 2007). G-CSF has been found to reduce the number of neurons and protect oligodendrocytes (Nishio et al., 2007). These neuroprotective effects are mainly the promotion of angiogenesis and autophagy and the selective activation of anti-inflammatory microglia. Previous research by our research group found that administration of zinc ions after spinal cord injury can target microglia to secrete G-CSF and inhibit neuronal apoptosis (Li et al., 2019).
2.2. Inflammatory Cytokines Detrimental to SCI Repair

2.2.1. Interleukin-1 (IL-1)

The IL-1 cytokine family consists of eleven members that play important roles in regulating inflammation (Zong et al., 2012). Members include IL-1 alpha, IL-1 beta, IL-1ra, IL-18, IL-33, IL-36Ra, IL-36 alpha, IL-36 beta, IL-36 gamma, IL-37, and IL-38. IL-1 is mainly produced by macrophages; in addition, almost all nucleated cells, such as B cells, NK cells, T cells cultured in vitro, keratinocytes, dendritic cells, astrocytes, fibroblasts, and neutrophils cells, endothelial cells, and smooth muscle cells can all produce IL-1 (Dinarello, 1989). Under normal circumstances, only a certain amount of IL-1 is contained in the skin, sweat and urine, and most cells can synthesize and secrete IL-1 after being stimulated by foreign antigens or mitogens (Arend et al., 1998). IL-1 has two different molecular forms, one called IL-1α and the other called IL-1β, both of which are encoded by different genes. Although the amino acid sequence is only 26% homologous, IL-1α and IL-1β bind to the same cell surface receptor with the same affinity and play the same biological role. IL-1 receptor (IL-1R) IL-1R exists on the surface of almost all nucleated cells (Arend et al., 1998). There are two main types of IL-1R: one is IL-1R1, which has a longer peptide chain extending into the cytoplasm and plays a role in transmitting activation signals; the other is IL-1R2, in which the peptide is short and cannot effectively transmit signals. Instead, the extracellular peptide chain is released into the extracellular fluid, which binds to IL-1 in a free form and exerts feedback inhibition. GM-CSF, G-CSF and IL-1 can all increase the expression level of IL-1R in cells, while TGF and corticosteroids can reduce the expression of IL-1R (Xu, 2014; Paré et al., 2017). IL-1 receptor antagonist (IL-1ra), is a selective endogenous receptor antagonist that blocks the effects of IL-1α and IL-1β. In animal models, the application of IL-1ra promotes the recovery of spinal cord injury and inhibits apoptosis and necrosis by reducing the activation of MAPK and caspase-3 (Nesic et al., 2001; Wang et al., 2005). Numerous clinical studies have confirmed that IL-1β is highly expressed during the entire disease process of spinal cord injury.

2.2.2. Tumor Necrosis Factor-Alpha (TNF-α)

TNF-α is a pro-inflammatory cytokine mainly produced by macrophages and monocytes, and is involved in normal inflammatory and immune responses (Pandi et al., 2017). TNF-α is increased
in many pathological conditions, including sepsis, malignancy, heart failure, and chronic inflammatory diseases (Kemanetzoglou and Andreadou, 2017). TNF-α-mediated signaling is mainly carried out through two receptors with different structures: type 1 receptor (TNFR1, also known as p60, p55, CD120a) and type 2 receptor (TNFR2, also known as p80, p75, CD120b). Mice lacking the TNFR1 gene exhibit an antagonistic effect on endotoxin-induced death, while mice lacking the TNFR2 gene remain sensitive to this (Piguet et al., 1998). In the course of spinal cord injury, the increased expression of TNF-α in the lesion can promote neutrophil infiltration and inflammation (Hermann et al., 2001), and trigger neuronal apoptosis (Sharma et al., 2003). In addition, high levels of TNF-α in serum after spinal cord injury exacerbate the occurrence of neuropathic pain (Peng et al., 2006).

3. Future Direction

Current research shows that the regulation of inflammatory cytokines is the best treatment method in the repair of spinal cord injury (Chen et al., 2010; Hu et al., 2016), whether in animal models or clinical trials. However, there are two problems: one is how to make cytokine-targeted drugs exert anti-inflammatory effects while minimizing side effects. Local administration shows excellent advantages in solving the above problems. Therefore, local administration and personalized treatment of therapeutic drugs have great potential in the future. In addition, a large number of animal experiments have shown that local administration can regulate inflammatory cytokines and promote functional recovery, further indicating that local administration can promote the repair of SCI (Kim et al., 2013). Moreover, spinal cord injury can occur in any part of the spinal cord, so local administration is more accurate and economical than systemic administration.

The second is that different patients with spinal cord injuries have different inflammation profiles. One study found that the microglia / macrophages of patients with poor prognosis mainly exhibited the dominant subpopulation characteristic of M1. Their plasma levels of IL-12 and CXCL10 were higher, while patients with better prognosis showed different characteristics. M2 Dominant subgroups had higher levels of IL-10, IL-15, and IL-7 (Xu, 2014). Therefore, future research should aim to develop personalized strategies for locally delivered therapeutic cocktails to effectively and precisely regulate inflammation and obtain substantial functional recovery from SCI.
Considering the situation that inflammatory cytokines are direct mediators of inflammatory response in diseases, and which are basically not expressed under normal conditions, this review manifests that regulation of inflammatory cytokines has a positive effect on recovery from SCI.

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