Chapter 4

Role of the Neuroinflammation in the Degree of Spinal Cord Injury: New Therapeutic Strategies

Irene Paterniti, Emanuela Esposito and Salvatore Cuzzocrea

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Abstract

A case of spinal cord injury (SCI) is defined as the occurrence of an acute traumatic lesion of neural elements in the spinal canal (spinal cord and cauda equina), resulting in temporary or permanent sensory and/or motor deficit. Most studies on traumatic SCI show a bimodal age distribution, with a first peak in young adulthood and a second peak in older adults. Spinal cord trauma activates a cascade of events that exacerbates the damage such as activation of inflammatory process that determinates cytokine and chemokine production and that generates reduction in functional recovery resulting in necrosis or apoptosis of neurons. However, the precise mechanism of SCI-induced inflammatory response remains not fully understood at present. Current strategy to treat damage to the spinal cord is limited, only the treatment with methylprednisolone (MP), if administered in excessive dose during the acute phase of the damage, could ameliorate patients with severe SCI. However, associated to the beneficial effects, there are growing evidence that high-dose of MP is correlated to increased risk of infections, pneumonia and gastrointestinal bleeding. Therefore, there is a necessity to develop new therapies to treat SCI; one of these is to selectively reduce inflammation that possess unique role in the processes of injury and recovery.

Keywords: Immune response, oxidative stress, spinal cord injury, inflammation, neuroprotection

1. Inflammation response after spinal cord injury

Spinal cord injury (SCI) is damage caused to the spinal cord that compromise the major functions of the spinal cord and remains actually the most important cause of mortality in the society. In

addition to its cost to the individual, physically as well as the health care system and society financially, SCI has profound psychosocial effects that are devastating for patients, families and friends. SCI usually begins with a sudden, traumatic blow to the spine that fractures or dislocates vertebrae; long-term mechanical compression of the spinal cord gradually causes various pathologic changes in neural tissue. The pathophysiology of SCI comprises both primary and secondary mechanisms of injury; the "primary injury" refers to the forces that impart the primary mechanical insult to the spinal cord, which in its mildest form causes a cord concussion with brief transient neurologic deficits and in its most severe form causes complete and permanent paralysis. The primary damage to tissue is followed by a second phase of tissue degeneration that might occur over weeks or even months and further generate progressive destruction of the tissue surrounding the necrotic core that expands from the injury "epicenter" and is known as secondary injury, that is a persistence of some crucial events of the acute phase such as edema and apoptotic cell death as well as generation of oxidative stress, activation of immune system response and inflammation process. In particular we focus our attention on some mechanisms that occur after spinal cord injury such as on the involvement of the inflammation process and immune system response.

Inflammation is a physiological process that removes damaged stimuli and initiates the healing process; however, if it persists and if it is over-activated, then the inflammation becomes devastating; inflammation is a key element in the pathophysiology of some disorders such as chronic pain, neurodegenerative pathology, trauma and spinal cord injury [1–5]. Principal pro-inflammatory markers that are both cellular components, such as neutrophils, macrophages and T cells, and non-cellular components, such as cytokines, prostaglandins and complement, have been found in spinal cord tissue that received a mechanical insult. Following spinal cord trauma, the site of injury is penetrated by neutrophils, that determinate release of cytokines that may progressive damage local tissue and recruit other inflammatory cells [6]; moreover, monocytes/macrophages are released and locally activated in microglia, that subsequently invade the injured tissue [7]. The pro-inflammatory cytokines that are produced at the site of injury, such as tumor necrosis factor (TNF-α), interleukins and interferons, mediate the inflammatory response and can generate further tissue damage [8,9]. Furthermore, cytokines can induce the expression of cyclo-oxygenase (COX) 2 and thus promote the breakdown of arachidonic acid into pro-inflammatory prostanoids (prostaglandins, prostacyclin and thromboxanes) that mediate vascular permeability/resistance and platelet aggregation/adherance [10,11]. The involvement of the cyclo-oxygenases in the generation of these inflammatory mediators represents a potential target for intervention, because inhibitors of these enzymes are in widespread clinical use. Additionally, TNF-α contributes to the tissue injury induced by neutrophils by directly activating them [12,13] as well as by increasing the expression of such molecules as ICAM-1 and E-selectin, which cause the activated neutrophils to adhere to the surface of the endothelial cells; it has also been shown that the inhibition of neutrophil adhesion to the endothelial cell surface markedly reduces the severity of the SCI induced by compressive trauma [14]. These observations indicate that the interaction of activated neutrophils with the surface of the endothelial cells is another important mediator in the secondary tissue damage of the spinal cord.

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1.1. Cytokine responses to inflammation

Cytokines are small and non-structural proteins with no amino acid sequence motif, their biological activities allow us in turn to group them into different classes: exit 18 cytokines called interleukin (IL), some of these promote inflammation and are named pro-inflammatory cytokines such as IL1β and IL1α, IL6, IL8 and TNF-α, whereas other cytokines suppress the activity of pro-inflammatory cytokines and are called anti-inflammatory cytokines such as IL-4, IL-10, TGFβ. The hypothesis that some cytokine functions primarily induce inflammation while others suppress inflammation is essential to cytokine biology and also to clinical medicine.

Cytokines are secreted by a variety of immune cells such as T-lymphocytes and macrophages, as well as b non-immune cells such as fibroblasts; the physiological effects mediated by cytokines comprise the stimulation or inhibition of cell growth, cytotoxicity/apoptosis, antiviral activity and inflammatory responses. The main function of cytokines is the regulation of T-cell differentiation from undifferentiated cells to T-helper 1 and 2, regulatory T cells, and T-helper 17 cells [15]. These regulatory proteins include ILs, interferons (IFNs) and TNFs. Many of these cytokines have already been shown to be produced by neurons or glia in central nervous system (CNS) disorders in which they are notably increased.

The cytokine class of inflammatory mediators is secreted by microglia and astrocytes and their production is increased in inflammatory states; moreover they act by modulating the intensity and duration of the immune response. Pro-inflammatory cytokines and chemokines up-regulate microbicidal activity of neutrophils, and they can be considered as additional immunomodulatory agents to treat serious or refractory infections in humans.

Through cytokines IL-1 the immune response is initiated, having a crucial role in the onset and expansion of a complex hormonal and cellular inflammatory cascade; the IL-1 family of cytokines includes IL-1α and IL-1β, which generate cell activation upon binding with specific membrane receptors and has been documented that IL-1 plays a role in neuronal degeneration. In astrocytes, IL-1 induces IL-6 production, stimulates iNOS activity [16], enhances neuronal acetylcholinesterase activity, microglial activation and additional IL-1 production, and astrocyte activation.

Another important pro-inflammatory cytokine is the IL-6, a multifunctional cytokine that plays an important role in host defence [17] and possesses main effects during the inflammatory response [18]. IL-6 is associated to the family of neuropoietin cytokine and it possesses direct and indirect neurotrophic effects on neurons [19]; moreover, IL-6 promotes astrogliosis [20], activates microglia [21], and stimulates the release of acute phase molecules.

1.2. Inflammatory mediator: crucial role of TNF-α

Through all the cytokines involved in the secondary damage, TNF-α plays a crucial role; in fact it releases shortly after injury, it can accumulate rapidly at the site of injury, and it is produced by a number of different cell populations, such as neutrophils, macrophages and microglia, astrocytes and T cells [22]. Several cell types are able to produce TNF-α, including macrophages after its activation, dendritic cells, monocytes, NK cells, CD4+ T cells, CD8+ T

cells, microglia and astrocytes. Macrophages/monocytes are able to produce TNF-α in the acute phase of inflammation and this cytokines drives several range of signalling events within cells, leading to necrosis or apoptosis.

Several biological functions are ascribed to the TNF-α and for this reason the mechanism of action is somewhat complex; although it inhibits the growth of tumor cells and it has an enhancing effect on the proliferation of normal cells [23]. TNF-α takes part in septic shock, autoimmunity, and inflammatory disorders. The major role of TNF-α is explicated as mediator in resistance against infections; moreover, it was postulated that TNF plays a pathological role in a number of autoimmune pathology such as graft vs host rejection or rheumatoid arthritis. Moreover, TNF-α possesses potent pro-inflammatory effects that are associated to its capacity to generate endothelial cell adhesion molecules and subsequently support neutrophil adherence to vascular endothelium. Neutrophils are exquisite targets of TNF-α that is under certain conditions it strengthens their expression of adhesion molecules induces their degranulation and successive release of lysosomal enzymes, causing the production of highly reactive oxygen species. TNF-α induces the migration of neutrophils mediating the production of chemotactic factors, including IL-8; this testifies cytokine networking involvement in inflammatory cell recruitment and an active role in inflammation.

TNF-α works by binding and clustering high-affinity receptors that are present in a great numbers on most cell membranes [24], the ligand/receptor complex is easily internalised via clathrin-coated pits and ends up in secondary lysozymes where it is degraded. Interestingly, the binding of TNF-α to the 75 kDa TNFR-2 is not sufficient to reach cytotoxicity, but rather binding to the 55 kDa TNFR-1 is sufficient to reach TNF-α mediated cell killing. TNF-α exerts its effects by activating several secondary proteins that provoke a variety of responses within the cell such as activation of gene transcription and/or production of reactive oxygen or nitrogen radicals (e.g., NO). Activated proteins include Gprotein, transcription factors such as NF-κB and AP-1 and serine and cysteine proteases, known as caspases. Many members of the TNF receptor superfamily have intracellular "death domains" which represent protein interaction domains each consisting of 65–80 amino acids; these proteins participate in TNF-α mediated apoptosis process; many evidence demonstrated that TNF–TNFR interactions are implicated in the pathogenesis of CNS disorders such as EAE and MS. These interactions are able to monitor the disease outcome by modifying immune response and the interactions between CNS-resident cells and effector immune cells in the CNS.

However, recent studies showed a dual nature for TNF-α that it can be not only neurotoxic but also neuroprotective; a study conducted with transgenic mice for TNF-α receptors demonstrated that the mice lacking TNF-α showed more tissue loss and functional deficits compared to wild-type mice, implying that TNF-α mediated a neuroprotective effect [25]. The beneficial or deleterious effects of TNF-α dependent when it is being released and on cellular population that is acting on, the conflicting actions of TNF-α described above reflects a growing view of inflammation as a "dual-edged sword" having neurotoxic and neuroprotective properties [26].

Thus, comprehension of their profile, kinetics of expression and interactions between TNF-α ligands and their TNFRs on different CNS residents and infiltrating immune cells would aid

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to better design strategies to control neuroinflammation and CNS autoimmunity. Blockers of TNF-α have been acknowledged for human use in treating TNF-linked autoimmune and inflammatory disorders. Pathways downstream of receptor ligation supply critical points for interjection for planning new therapeutic strategies.

1.3. Microglia activation

Moreover, other important mediators of inflammation that respond rapidly to disturbances within the microenvironment by change in morphology are the microglia, the expression "activated microglia" is used to define cells that change their immunophenotype and their morphology after a specific stimuli; the principal role of microglia at the lesion site is a rapid phagocytosis of fragments and induction of apoptosis [27]. The different response of microglia *in vitro* suggests that these cells may elicit unique functional properties and consequently control the inflammatory response at the injury site. Microglial activation has been well-known in the spinal cord tissue that has received a trauma and has shown to occur from caudal to lumbar enlargement, based on that there are papers supporting the role of microglia in pain after injury and showing activation of microglia post-SCI.

Thus, we postulated that activated spinal microglia have a role in chronic pain after SCI.

Microglia activate the innate immune system and are key regulators of inflammatory processes in CNS pathologies such as trauma and neurodegenerative diseases participation in both acute and chronic phase of the inflammatory responses. Activated microglia secrete cytotoxic substances including various cytokines such as TNF-α, IL-1, reactive free radicals, and nitric oxide. However, the principal effects of microglia at the levels of the lesion core are probably rapid phagocytosis of debris rather than induction of apoptosis. Microglia when activated can cause neuronal and glial toxicity through the release of cytokines, free radicals, eicosanoids, activated neutrophils, and macrophages [28]. On the other hand, microglia activation leads to beneficial effects producing growth factors that are fundamental for neuronal and tissue restoration. Moreover, it has been demonstrated that transplantation of peripherally activated macrophages has beneficial effects on spinal cord regeneration.

1.4. Apoptosis

In the last decade the generation of apoptotic process after spinal cord trauma was also confirmed, apoptosis can be triggered by a variety of insults including cytokines, inflammatory injury, free radical damage, and excitotoxicity.

The apoptotic process after spinal cord trauma is activated in neurons, oligodendrocytes, microglia, and perhaps, astrocytes; apoptosis in microglia contributes to inflammatory secondary injury.

Two main pathways of apoptosis—extrinsic or receptor-dependent and intrinsic or receptor-independent—have been well characterized, and both appear to be active in SCI; the extrinsic or receptor-dependent pathway is mediated by Fas ligand and Fas receptor [29] and/or inducible nitric oxide synthase production by macrophages [30], while intrinsic or receptor-

independent pathway is mediated via direct caspase-3 pro-enzyme activation [31] and/or mitochondrial damage, release of cytochrome c and activation of the inducer caspase-9, pathways of caspase-mediated apoptotic death [32].

Receptor-dependent apoptosis is evoked by extracellular signals, the most significant of which is TNF, so it is termed as "extrinsic" pathway; TNF is known to rapidly accumulate in the injured spinal cord, and activation of the Fas receptor of neurons, microglia, and oligodendrocytes induces a programmed sequence of caspase activation. Moreover, additional control of cell death/survival is provided by the balance between major pro-apoptotic proteins such as Bax, Bad, and Bid and anti-apoptotic proteins such as Bcl-XL and Bcl-2.

Apoptotic cells were reached in the grey matter after injury, starting from 1h with a proliferation during the other 8 h [33]. The number of apoptotic cells is increased at the site of injury and are related with axons degeneration [34].

Apoptotic process that is activated in the secondary injury in SCI has recently come under close study, and the precise contribution and potential therapeutic implications of apoptosis in SCI could be helpful to generate new therapeutic approach to treat the secondary events associated to spinal cord injury.

2. Inflammatory/immunologic response

The inflammatory and immunological response to injury within the CNS is different than that which is occurring in other tissues [35]. The inflammatory and immunologic responses to injury involve activation of innate immune cells that provide immediate defence against inflammatory stimuli and in turn help to recruit cells of the adaptive immune system (i.e., T- and B-lymphocytes). The activation of immune system is driven by interactions involving presentation of antigen and release of various inflammatory mediators [36]. Also, cells present at the injury site may sequester debris and carry CNS antigens to secondary lymphoid organs [37], where trigger lymphocyte activation. Recent studies done on mice showed that the number of activated T and B cells increases in the spleen and bone marrow within 24 hours of trauma [38].

2.1. Lymphocytes infiltration

T-lymphocytes are distributed in the intact spinal cord and gradually grow in number after trauma in parallel with the stimulation of microglia and influx of peripheral macrophages. Lymphocytes infiltrate the spinal cord tissue starting from 24 hours until 7 days after injury and return gradually back to normal levels in 4 to 5 weeks [14].

Under normal conditions, activated T cells can cross the Add Blood–brain barrier (BBB) and enter the CNS parenchyma. In contrast with other inflammatory cells enrolled after a trauma, the number of lymphocytes remains low [39]; however, T-lymphocytes play an important role in the CNS immune system, since on activation, T-lymphocytes may kill target cells and produce cytokines [40].

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Once lymphocytes enter the lesion site, they persist indeterminately [38,41], whereas T and B cells increase at the lesion site at least 9 weeks post-injury [42,43], suggesting that cytokine/chemokine gradients exist chronically and regulate integrin expression on endothelia and cells [44,45]. These chemokine gradients and adhesion molecules represent molecular targets for manipulating the effects of intraspinal lymphocytes after SCI [46–48]; the progressive increase in lymphocyte numbers may also be justified by lymphocyte activation and proliferation within the injured centre of spinal cord.

Moreover, induction of immune response could be generated as impaired nerve transmission; increasing the production of pro-inflammatory cytokines in chronic phase of SCI could worsen the damage increasing the axonal injury and demyelination. Furthermore, there are evidences that autoreactive lymphocytes promote neuronal survival *in vivo* through activation not only of autoreactive T cell but also through activation of other non-CNS reactive T cells or B cells such as resident microglia and infiltrating macrophages.

Thus, because lymphocytes remain for long term at the site of the lesion; new strategy of treatment could orientate on these cells that possess a fundamental role in regulating degenerative and regenerative processes after injury.

3. Pharmacologic interventions for acute spinal cord injury

The temporal profile of the secondary injury cascade provides a window within which it is theoretically possible to reduce the pathophysiological processes; many of the current pharmacological and surgical strategies for the treatment of SCI are based on minimising secondary injury and preserving neurological function following trauma to the brain and spinal cord. Over the past couple of decades, a myriad of agents have been nominated as putative neuroprotective therapies, several of these have been tested in the pre-clinical and clinical studies.

The following section briefly highlights some of the most promising neuroprotective approaches that are being pursued.

3.1. Corticosteroids

In the last decade one of the most used approaches to treat patients with a severe SCI is the use of corticosteroids that possess a well-recognized anti-inflammatory properties reducing spinal cord edema. However, the exact mechanisms by which corticosteroids mediated neuroprotection are not yet completely understood but seems that they induce a reduction of inflammatory cytokines production, modulation of the inflammatory/immune cells, inhibition of lipid peroxidation and reduction of oxidative stress. In this regard, methylprednisolone (MP) appears to be particularly efficacious compared with other glucocorticoids. According to the National Acute Spinal Cord Injury Study 2 (NASCIS 2) protocol, MP is usually administered within 8 h after trauma in a high concentration of 30 mg/kg, followed by an infusion of 5.4 mg/kg/h for 23 hours [49,50]. MP is the only well-known pharmacological treatment of SCI injury patients; however, its administration has been shown to be controversial. Some toxic

effects such as infection rates, pulmonary embolism, severe pneumonia and sepsis and even death secondary to respiratory complications appeared to be higher with steroid use.

The anti-inflammatory properties of MP are mediated by different mechanisms that are known as transrepression, this mechanism involves interference with pro-inflammatory transcription factor signalling (such as NF-κB) which is upstream of several inflammatory mediators including COX2, chemokines and cytokines.

Together with the minor functional improvement in humans and risk of adverse side effects, these studies highlighted the compelling need to develop better neuroprotective agents with more convincing efficacy.

3.2. Estrogen as a neuroprotective agent

At present, several effects have been associated to estrogen that acts with different mechanism of action [51]. Recently, the neuroprotective and anti-inflammatory effect of estrogen are of great interest; leukocyte adhesion and microglia activation are also sensitive to estrogen and show significantly decreased superoxide dismutase production and phagocytic activity when treated with estrogen *in vitro* [52].

Moreover, cell death is associated to decreases blood flow in spinal cord and estrogen are involved in increasing post-traumatic blood flow induced by ischemia [53] and TBI [54]. Thus, estrogen treatment has been related with increased expression of pro-apoptotic Bcl-2 in the spinal cord injured tissue, this anti-apoptotic increase in Bcl-2 may be mediated by Akt activation with downstream phosphorylation of cAMP response element binding protein (CREB) [55].

However, estrogen may also act on Add N-methyl-D-aspartate receptor (NMDA) receptors, indicating a potential to limit secondary cell death due to excitotoxicity [56].

3.3. Nuclear hormone receptors family: PPARs receptor

Other members of the nuclear hormone receptors family (NHRs) are now explored for their anti-inflammatory properties in experimental models, including SCI.

Peroxisome proliferator-activated receptors (PPARs) are part of the nuclear hormone receptor superfamily, upon ligand activation regulate gene expression and have been shown to be anti-inflammatory in different model of inflammatory pathology, including SCI. PPAR exists as three isoforms (α, β/δ and γ) that control many cellular functions including lipid metabolism, glucose absorption, cell growth and differentiation, and inflammation.

One mechanism involves direct interaction of PPAR with pro-inflammatory transcription factors, most importantly NFκB and AP-1, and the subsequent reduction of gene transcription. Pioglitazone and rosiglitazone are PPARγ agonists that are in common clinical use for type II diabetes. Beyond their metabolic effects, interest in PPAR γ ligand has grown due to their anti-inflammatory, neuroprotective, and even anti-neoplastic properties, suggesting its potential use after spinal cord trauma [57]. As such, PPAR agonists have already been clinically tested in other disorders with inflammatory pathology, such as Alzheimer's disease (AD), rheuma-

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toid arthritis (RA), and ischemia reperfusion injury, but not in SCI yet. Moreover, in the last few years a great interest has been focused on other PPAR receptors agonist such as for PPARα and β/δ receptors. One of the first reports indicating that PPARα is involved in attenuating inflammation demonstrated that the eicosanoid LTB4 binds and activates PPARα [58]. Several studies on inflammatory cytokine produced in aged mice demonstrated an active interaction of PPARα with NFκB; in fact the oxidative stress in different tissue leads to active NFκB. Treatment with PPARα agonists were found to restore the alteration of oxidative mediators, to inhibit the activation of NFκB and to remove IL-6 and IL-12 produced [59,60].

These features were accompanied by enhanced functional motor recovery and reduced hyperalgesia.

Since PPAR agonists are currently used in medical treatment of diabetes, clinical studies for stroke and different CNS pathologies are to be expected. The knowledge about anti-inflammatory properties of PPAR ligands obtained from cell cultures and animal model of SCI demonstrate that PPARs signalling may be therapeutic targets after spinal cord injury.

4. Conclusion

Thus, recent researches are moving to develop new pharmacological approaches that may offer an effective neuroprotection after spinal cord injury. After spinal cord injury, inflammatory reactions account for a large proportion of the secondary damage to neurons and oligodendrocytes.

Promising research is being carried out to better understand the aspects of inflammation, lipid peroxidation and apoptotic cell death that may be the target of pharmacologic intervention.

Few agents have been studied demonstrating efficacy in animal models of spinal cord injury and may become appropriate for testing in the human setting in the near future.

Clearly, much effort has to be done to bring experimental strategies to clinical fruition, but they do represent promising potential interventions.

Thus, the current medical and surgical interventions for the acutely cord-injured patient attempt to minimize the inflammatory process that possess a crucial role in generating and maintaining secondary damage associated to injury and defend the neural cells that initially survived the mechanical injury.

Author details

Irene Paterniti, Emanuela Esposito* and Salvatore Cuzzocrea

*Address all correspondence to: eesposito@unime.it

Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy

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