Chapter

Cytokine Profile as a Marker of Cell Damage and Immune Dysfunction after Spinal Cord Injury

Georgii Telegin, Aleksandr Chernov, Alexey Belogurov, Irina Balmasova, Nikolai Konovalov and Aleksandr Gabibov

Abstract

The study reviews findings of the recent experiments designed to investigate cytokine profile after a spinal cord injury. The role of key cytokines was assessed in the formation of cellular response to trauma. The specific immunopathogenic interaction of the nervous and immune systems in the immediate and chronic post-traumatic periods is summarized. The practicality of a step-by-step approach to assessing the cytokine profile in spinal cord injury is shown, the need to take into account the combination of pathogenetic and protective components in the implementation regulatory effects of individual cytokines, their integration into regenerative processes in the damaged spinal cord, which allows a rational approach to the organization of the treatment process and the development of new medicines.

Keywords: Spinal cord injury, glial scare, cytokines, cellular response

1. Introduction

Spinal cord injury (SCI) is a significant global public health issue and a common cause of permanent disability in patients [1, 2]. According to the WHO world population estimates, every year up to 500,000 people suffer a spinal cord injury [3], including young adults between the ages of 20 and 35 [4]. The annual incidence rate of traumatic SCI (TSCI) in developed countries is approx. 3 per 100,000 population [5], though these data could be inconsistent with the big picture, since 16%-30% of patients with spinal injuries die before being admitted to the hospital [6, 7]. Thus, functional recovery of the spinal cord with structural damages caused by trauma is recognized as one of the most challenging and socially essential topics of modern regenerative medicine [8].

Mortality from SCI depends mainly on the severity of spinal cord lesion, and at the pre-hospital phase, it reaches 37% [9]. In-hospital mortality rates are affected by the severity of spinal cord damage and the SCI-related early or late complications, as well as the timeliness of specialized health care provision. Mortality rates range between 8 and 58.3% in different medical settings, depending on their capacity [10–12]. High mortality rates (ranging between 16% and 18%) are reported for children. Frequently they are associated with a trauma of the cervical

spine, especially its upper portion [13–16]. The leading causes of death comprise respiratory problems, cardiovascular disorders, thromboembolic events, infectious complications, and suicides [17]. Disability rates after vertebral column and spinal cord injuries vary from 57.5 to 100%, and the data indicate a trend towards an annual increase of people with disabilities after SCI [18].

Prominent underlying SCI causes include road traffic injuries (36–43%), falls from height (24.2–63.2%), shallow water diving (3–32%), sports activities and accidents (22.5%) [19–22], while criminal traumas account for 10-25% of the injuries [23]. The leading causes of injuries vary for different years and across geographic regions [24]. In this context, spinal cord injuries related to ocean waves are commonly reported in the coastal areas, among beachgoers, etc. [25].

Spinal cord injuries resulting from vertebral column trauma are reported for 36–72% of patients [10, 11, 26, 27]. Craniocerebral trauma is more commonly associated with cervical spine fractures (18–72%). Thoracic spine fractures are usually combined with multiple non-vertebral injuries, such as bone fractures (10.3–48%), traumas of the thoracic cavity and its internal organs (as high as 52%), and lumbar spine injuries – with broken limb bones (up to 27%) and pelvic bones (up to 15%), and damage of the abdominal organs (9.8–18.7%) [21, 27–31]. By type, SCIs are divided into open (penetrating) and closed (nonpenetrating) injuries to the spine. In peacetime, closed SCI account for 70.1–88.6% of cases [26, 32].

2. Factors that determine the course of spinal cord injury and its classification

The level and length of SCI, as well as the timeline of the treatment of spinal cord compression, affect the grade and severity of neurological problems and, ultimately, mobility and self-care of patients, as well as their prognosis and recovery, and return to normal life [33]. The cervical spine trauma is associated with spinal cord lesions in 12–70% of injured people and characterized by the predominance of severe damages (contusion, compression, haematomyelia) and high mortality rates (35–70%). Spinal cord lesions occur in 31–75% of thoracic and lumbar spine traumas [21, 26, 27, 29, 34]. In general, injuries of the cervical spine account for 17–61% of cases [30, 34], thoracic – 7.2–40% [26, 29, 34, 35], and lumbar spine – from 8.7 to 57.8% [26, 29, 31, 34].

Types of spinal cord trauma include contusion, concussion, compression, crush, and disruption. The spinal cord's compression is found in 20–26.7% of the injured persons, compression and contusion – in 40–50.5%, compression and crush – in 7–15.7%, and anatomical disruption – in 4.3–7.1% of patients [34]. The grade of the spinal cord injury is one of the principal prognostic factors. The distinction is made between "complete" and "incomplete" SCI, or its morphological disruption (anatomical or axonal). Complete SCI at the cervical level is reported for 33.7–52% of patients, thoracic level – 12.5-54%, and at the lumbar level – 15–21% [33].

In addition to SCI, non-traumatic spinal cord lesions may occur due to epidural abscess and hematoma, intradural tumor or other types of metastatic tumors, and complications after surgical treatment [7, 36]. The treatment of the acute phase in SCI cases takes more time than the treatment of spinal cord lesions of non-traumatic origin. Also, patients with SCI are more likely to have urinary tract infections and other complications [37].

Before early 1990s, a uniform or generally recognized classification system of SCI was not available. Physicians usually distinguished different levels of injury, complete and incomplete SCI.

Then, in 1992 the American Spinal Injury Association (ASIA) developed a classification system for identifying the severity of spinal cord injury based on descriptions of motor and sensory functions [38, 39].

1. A = complete spinal cord injury: no motor or sensory function is preserved in the sacral segments S4-S5;

2. B = incomplete injury: sensory function preserved but not motor function is preserved below the neurological level and includes the sacral segments S4-S5;

3. C = incomplete injury: motor function is preserved below the neurological level, but less than half of key muscles below the neurological level have a muscle grade less than 3 (i.e., they are not strong enough to move against gravity);

4. D = incomplete injury: motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more (i.e., the joints can be moved against gravity);

5. E = normal: motor and sensory functions are normal.

Many researchers indicate that in addition to diagnostic implications the ASIA scale has tremendous prognostic value [38, 40–43]. Later, the AO Subaxial Cervical Spine Injury Classification (SLIC) system was published, which includes morphological information in its scoring that helps determine the extent of the patient's injury [44].

Practicing surgeons and radiologists use classification and scoring systems Subaxial Cervical Injury Classification and Severity (SLICS) and Thoracolumbar Injury Classification and Severity (TLICS), respectively, to evaluate the severity of cervical and thoracolumbar spine injuries [45]. Besides, the Spinal Cord Independence Measure (SCIM) has been developed to assess functional improvements of the spinal cord in the course of treatment and rehabilitation. Also, the SCIM has prognostic value [46].

SCI is classified chronologically into the following four phases:

1. acute phase – less than first 48 hours after the injury; the clinical course comprises of spinal shock and, as a result, the symptoms and signs are similar for various grades of SCI;

2. early (subacute) phase is defined to be 48 h – 14 days after the injury; likewise in the acute phase, clinical observations may include a syndrome of complete block of conduction in the spinal cord due to spinal shock, altered blood and cerebrospinal fluid flow; edema and swelling of the spinal cord;

3. intermediate phase is defined to be 14 days – 3 months; spinal shock symptoms disappear, and the actual severity and range of spinal cord injury is determined;

4. chronic phase – more than 3 months after the injury; the recovery of spinal cord functions occurs depending on the SCI grade; neurological status may deteriorate due to the scarring process, cyst formation, post-traumatic syringomyelia, etc. [23, 47–51].

Spinal cord injury triggers the development of a complex series of pathophysiological reactions, including primary and secondary damage of the nervous tissue [52–54]. The inflammatory response to the primary structural changes in the spinal cord is followed by the release of multiple regulatory peptides, including proinflammatory cytokines [55, 56].

3. A role of the immune system and cytokines in the acute phase of spinal cord injury

3.1 Cells of the nervous system in spinal cord injury as inductors, effectors and targets of inflammatory acute phase reactions

Two different phases are distinguished in the pathogenesis of the acute period of SCI; each of them is associated with a complex series of pathophysiological reactions in response to the nervous tissue damage [57, 58].

The first phase of the injury, which starts on the first day, immediately after mechanical trauma, involves mechanisms of the injury and disorders associated with these mechanisms. Neurons, astrocytes, oligodendrocytes, as well as other components of nerve signal transmission, are physically affected, and these events are accompanied by disorders of vascular components, including the blood–brain barrier (BBB) [56–60], which results in the tissue infiltration by inflammatory cells [61–63].

The inflammatory response to primary structural changes in the SC is associated with the release of multiple regulatory peptides, including proinflammatory ones, and cytokines [64, 65]. Cytokines are synthesized by the activated macro- and microglia, damaged vascular endothelium, as well as the immune system cells mobilized from the circulation system and transported to the site of injury and the adjacent areas due to a change in the BBB permeability [66].

It has been established that several important molecular components of the immune system, including tumor necrosis factor (TNF-α), inducible nitric oxide synthase (iNOS), nuclear factor (NF)-kB, interleukin (IL)-1β, and/or a factor of apoptosis Fas ligand (FasL), are activated as early as within a few minutes after SCI [67–69]. The activation of these molecules further results in inflammation and other kinds of significant neurological disorders [70].

The second phase comprises of endogenously induced degradation of the nervous tissue and associated consequences [70]. Increased glutamate concentration in the damaged spinal cord (SC) tissue induces neuronal excitotoxicity (a pathological process causing the neurotransmitter-mediated damage and death of nerve cells) due to the excess of intracellular Ca^{2+}. This process promotes the accumulation of reactive oxygen species [71–73], which, in turn, affect such cellular components as nucleic acids, proteins, and phospholipids and cause considerable cell losses and subsequent neurological dysfunction [74, 75].

It is important to highlight that the endogenous cells (neurons and glial cells) of human SC (but not the blood leukocytes) contribute to the early production of IL-1β, IL-6, and TNF-α during the post-traumatic inflammatory response [76–78].

Activated astrocytes represent the primary source of all damaging factors: they account for about 30% of the cellular composition; and the overexpression of the microRNA miR-136-5p in these cells during SCI is considered as one of the inducers of proinflammatory factors and chemokines (primarily TNF-α and IL-1β) [79–81]. This process triggers an inflammatory immune response involving type 17 T-helpers [82]. Angiogenesis mediated by microRNA (miR-210) is another SCI-related event [83, 84].

3.2 Distinct role of the innate immune cells and its cytokine release in acute phase reactions to spinal cord injury

However, the role of the immune cells secreting proinflammatory cytokines in SCI should not be underestimated. This process is stimulated by hemorrhages in the SC tissue after its damage [85, 86]. They contribute to the infiltration of affected regions by neutrophils, monocytes/macrophages, and T lymphocytes [87–90], i.e. cells releasing the same factors, i.e. TNF-α, IL-1α, IL-1β, and IL-6 [91, 92].

Typically, these cytokines reach their peak level 6–12 hours after the injury; they also induce an inflammatory response in acute and subacute phases and contribute to the lesion extension in rostral and caudal directions [93–95]. It was shown that activated microglia and macrophages infiltrating the SC are responsible for the subsequent necrosis and apoptosis of neurons, astrocytes, and oligodendrocytes located closely to the site of the lesion [96, 97], thus worsening the neurological outcome [98, 99]. The modulation of proinflammatory and immune effects in the SC tissue during its injury involves interferons through the increase in the number of stimulators of interferon genes (STING) in the tissue [100, 101].

Within the first 24 hours after SCI, an additional immunological effect takes place: the number of natural killer (NK) cells with an activated phenotype increases significantly, which is manifested by the overexpression of CD69, HLA-DR, NKG2D, and NKp30 on their membrane as well as the enhanced cytotoxic activity [102]. Furthermore, an increased level of the brain-derived neurotrophic factor (BDNF) that can be produced by vascular endothelial cells was found in the patients' plasma samples. At this phase of SCI, it strongly correlated with the percentage of NK cells and the expression of CD69 and NKp30 activating molecules on their surface [103].

Early interventions for reducing inflammation and preventing apoptosis have become a common strategy in the targeted medical care provided to SCI patients. However, the latest updates in this field suggest that the inflammatory process has apparent protective aspects that should not be ignored during treatment [104].

As for the cytokine release signals, they can enter the cells through the Toll-like receptors (TLRs) of the SC [105, 106]. TLRs are best known as the structures for pathogen recognition and initiation of the innate immune response [107, 108]. However, they can also detect tissue damage and trigger sterile inflammation by binding to endogenous ligands typical for stressed or damaged cells. In addition to the cells associated with the immune system, TLRs have also been identified in neurons of the central nervous system (CNS) and glial components, including microglia, astrocytes, and oligodendrocytes [109, 110]. To this end, Toll-like receptors may play both direct and indirect roles in SCI [111]. Indirect effects are most likely mediated by microglia or immune system cells penetrating the damaged CNS tissue [112]. It is also established that restorative responses in SCI-related ischemic disorders are taking place with the predominant participation of Toll-like receptor 3 and subsequent regulation by TLR4 [113].

One of the mechanisms of innate immune defense during SCI-related inflammatory response is associated with the unique role of mast cells [114]. Mast cells are abundant in the CNS and play an intricate role in the progression of neuroinflammatory disorders. In particular, it was shown that the experimental mast-cell deficient mice had increased astrogliosis and T-cell infiltration, while their functional recovery after SCI was significantly reduced [115]. Moreover, these mice have significantly increased levels of the cytokines MCP-1, NFα, IL-10, and IL-13 in the SC. The available data demonstrate the relationship between these findings and the fact that, if the same number and functional activity of mast cells are maintained, their chymases cleave MCP-1, IL-6, and IL-13. This suggests

a protective role of the above cellular elements in the development of inflammatory changes in the nervous tissue in SCI cases [116]. It should be noted that, in addition to astrocytes and microglia, IL-10 is also produced by macrophages, B cells, and Th2 cells [117, 118]. Being an immunomodulator, IL-10 stimulates the generation of regulatory T cells while suppressing the activity of Th1 and NK cells [119].

The cytokine and hormone secretion pattern after spinal cord injury largely depends not only on the mechanisms of induction and immune response but also on the level of injury. Thus, the experiments in the rat model clearly demonstrated similar differences in the production of vascular endothelial growth factor (VEGF), leptin, interferon-γ-induced chemokine IP-10, IL-10, IL-18, granulocyte colony-stimulating factor (G-CSF), and chemokine fractalkine in animals' plasma. In contrast to the thoracic spine trauma, injury to the cervical spine is associated with a reduced expression of these mediators. A potential mechanism underlying this finding is sympathetic dysregulation caused by a higher location of the spine injury [120, 121]. Experiments in mice have also demonstrated that cytokines (e.g. interleukins IL-3, IL-6, IL-10, IL-13, and G-CSF) impacted the systemic changes after spinal cord injury in the lower thoracic region (Th910). In parallel, the activation of T lymphocytes and neutrophils was determined during the acute phase of the reported changes [122]. Thus, the immunopathogenic mechanisms primarily linked to innate immune cells and proinflammatory cytokines have a central role in the SCI acute phase.

Damaged neurons and neuroglial cells after spinal cord injury become a source of chemokines (fractalkine, MCP-1, and IP-10) [120, 122] targeting monocytes/macrophages and lymphocytes and promoting their entry into the lesion site. Mast cells represent one of the first cells of the innate immune system that exert their effect in the injury site. As already mentioned, mast cells can regulate chemokine secretion; however, their role is far from being clear. On the one hand, these cells can be a source of cytokines and other mediators promoting inflammation [123]. On the other hand, chymases released from mast cells during their activation and subsequent degranulation can destroy chemokines and proinflammatory cytokines, limiting the intensity of inflammatory response [116].

Most chemokines produced by cells of the injured spinal cord promote the recruitment of monocytes/macrophages [124], which eliminate cell debris, while chemokine IP-10 also recruits NK cells [125]. The involvement of NK cells in the innate immune response is also facilitated by the fact that after SCI the spinal cord cells express injury patterns, particularly stress-induced molecules (MICA, MICB), that are considered as ligands for NKG2D receptors [126]. In turn, their high level of expression by NK cells was demonstrated for spinal cord injury [101]. At first glance, manifestations of NK cells' cytotoxic activity against the nervous tissue in spinal cord injury significantly aggravate the destructive processes during trauma [101]. However, the involvement of NK cells in the elimination of exclusively the cells carrying injury patterns contributes to a more rapid suppression of destructive processes at the site of spinal cord lesion.

The study focused on another crucial player, macrophages, under the conditions of tissue damage has demonstrated that there are two stages of their activation [127]. During the first stage, these cells acquire an inflammatory (M1) phenotype mediated by endogenous molecules released during cellular damage. When reparative processes are triggered in response to damage at later stages, activated macrophages are polarized into the resident (M2) phenotype [127]. Thus, it is suggested that M1 macrophages are predominantly produced during the SCI acute phase. Their induction after SCI is also stimulated by interferons [128] that

accumulate (as mentioned above) in the damaged tissues [100]. The macrophages secrete IL-12, IL-10, IL-1β, IL-6, IL-23, IL-21, TNF-α, and iNOS specific for this phenotype; high levels of these factors have been reported for the described pathological condition [120, 122, 127].

The cytokines have different functions: IL-12 further triggers adaptive cellular responses; IL-10 has an immunosuppressive effect and is involved in the induction of regulatory T cells; IL-1β, IL-6, IL-21, IL-23, and TNF-α exert a proinflammatory effect; TNF-α and iNOS provoke cellular damage reactions [128, 129].

The predominant cytokine profile, as well as the presence of M1 macrophage-producing cells in combination with the effect of autoantigens of the damaged spinal cord, suggests that the population of T lymphocytes involved in the immune response at the initial stage includes Th17 cells whose functional role has already been proven in the SCI acute phase. The functional role of this subpopulation is closely related to achieving the balance T-helper-17/regulatory T-cells (Th17/Treg). Q. Fu et al. [82] described these processes as follows. The Th17/Treg cell balance is regulated by molecules RORγT and FoxP3, while FoxP3 expression can be inhibited by RORγT expression. As mentioned above, SCI is accompanied by the migration of M1 macrophages to the injury site and the release of proinflammatory cytokines, including IL-6 and IL-21. As a result, T-helpers (CD^{4+} T lymphocytes) are able to differentiate into $CD^{4+}IL^{-}17A^{+}$ Th17, which contribute to the inflammatory response by recruiting neutrophilic granulocytes. In combination with proinflammatory cytokines produced at the injury site by macrophages, neurons, and neuroglia cells, the products of Th17 and neutrophils considerably enhance the inflammation process. Researchers consider the latter as a harmful component of the pathogenesis of post-traumatic changes in the spinal cord.

It is worth noting that Th17 induction during the initial phase requires one more cytokine, the transforming growth factor β (TGFβ), which is mainly secreted by Treg cells. The formation of these cells playing an important role in the Th17/Treg balance is mediated primarily by IL-10, which is also secreted by M1 macrophages in relatively small amounts during the initial phase of tissue damage. Like TGFβ, IL-10 has an immunosuppressive effect, limiting an excessive autoimmune inflammatory process after spinal cord injury [127, 130].

Thus, innate immune responses and T cell-mediated responses prevailing during the SCI acute phase could be assessed controversially. On the one hand, they aim to destroy cells in the damaged spinal cord tissue through their apoptosis or cytolysis and to induce inflammatory response enhancing neurological dysfunction. On the other hand, these reactions contribute to the elimination of destroyed cell elements along with their intrinsic autoantigens, injury patterns, and inflammation mediators, and also involve the inflammatory response regulation mechanisms. Based on these conclusions, a simplified approach cannot be used for assessing the role of immune processes in spinal cord injury. These processes are also important for selecting a treatment strategy during the SCI acute phase. It is necessary to evaluate the balance between the immune mechanisms prevailing in each particular case and exhibiting either a protective or pathogenic effect, instead of relying on individual indicators.

Already during the acute phase, spinal cord injury induces a strong inflammatory response [131] and a robust immune response both within and beyond the injury site [132]; these responses do not tend to resolve. In this case, the interaction takes place between the CNS and the immune system (i.e., the two central systems maintaining homeostasis in the entire body). That is why the process is not limited by the immune response in the site of spinal cord injury but also affects the whole immune system [133].

4. Role of the immune system and cytokines in the chronic phase of spinal cord injury

4.1 The importance of immunosuppressive manifestations in the chronic phase of spinal cord injury

The functions of the immune system change dramatically as the SCI acute phase progresses to the chronic stage. The failure or insufficient activity of vegetative innervation in the lymphatic and endocrine tissues disturb immune function for a long time after the initial trauma [134]. The main manifestations of such disorders are immune depression and the autoimmune process [133], although inflammatory reactions also maintain their significant role in pathogenesis.

Systemic changes at the level of cell populations and lymphocyte subpopulations during the SCI chronic phase are mainly related to the T cell-mediated adaptive immunity. Thus, it has been demonstrated that the total count of T cells (CD3+) and T helper cell subpopulation (CD3+ CD4+) in the blood is declining, although the count of activated CD4+ T cells (HLA-DR + CD4+) remains elevated [135]. This situation may occur if the count of T helper cells in the blood decreases due to their migration to the affected organ.

Regulatory T cells (Tregs) exhibiting suppressive properties are of special interest in this scenario. These cells have a CD3 + CD4 + CD25 + CD127lo phenotype with the predominance of activated CCR4 + HLA-Dr + fraction. The level of transforming growth factor β (TGFβ), the major cytokine of these cells, is considerably increased in SCI cases, which largely explains the observed immune dysfunction and its consequences, such as the impaired defense against infections and/or persistent chronic inflammation [88, 135].

The deficiency of T-cell-mediated immunity at the systemic level is also accompanied by a significant decrease in NK cell count during the chronic phase of SCI, which eventually leads to lethal infection [136].

Thus, starting on day 7 after the spinal cord injury, signs of regeneration of the myelin sheath of neurons associated with biochemically detectable activity of oligodendrocytes and production of proinflammatory cytokines TNF-α, IL-1β, and IL-6 were found [137]. Meanwhile, it was noted that a higher level of proinflammatory cytokines during the chronic phase correlated with a faster remission after SCI [51].

In fact, the proinflammatory cytokines trigger activation of astrocytes in the spinal cord glial tissue [138]. Astrocytes undergo proliferation and acquire one of the two phenotypes. Astrocytes having one phenotype actively secrete a glial fibrillary acidic protein (GFAP), which contributes to neuroregeneration. Contrariwise, astrocytes of the other phenotype secrete glutamine synthetase, which participates in glutamate accumulation and slows down neuronal regeneration in the injured spinal cord region. The balance between astrocytes of these two phenotypes determines the efficiency of repair processes in the neuronal tissue [139]. Neurons secrete neuregulin-1 (Nrg-1), which stimulates cell regeneration, contributes to the preservation of the spinal cord white matter, and positively regulates the functions of macrophages, T cells, and B cells. Today, it is even recommended as a medication for patients with spinal cord injury [140]. Although this positive regulation may occur, it is necessary to remember that all the described processes occur in the CNS; therefore, they can have both local and systemic manifestations.

Speaking about one of the key mechanisms of induction of the observed changes, a reference should be made to the data published by C.J. Ferrante and S.J. Leibovich [127]. They reported that after the acute phase of tissue damage, the macrophage phenotype switched abruptly from M1 to M2, which differs much from the

typical M2 cells in terms of cytokine secretion. This variety was called the angiogenic M2d phenotype. The main products of M2d macrophage secretion included vascular endothelial growth factor (VEGF) and IL-10, inducing the formation of regulatory T cells. That is why the angiogenic and immunosuppressive effects are predominant. Similar transformations were also found for macrophage microglial cells [141].

Special focus is placed on the role of tumor necrosis factor α during the SCI chronic phase. During this phase, the level of brain-derived neurotrophic factor (BDNF) is decreasing in the hippocampus, and at the same time, it is rising in the lateral part of the spinal cord. A deletion within the gene encoding TNF-α receptor blocks this effect, but the presence of this cytokine restores the effect. These findings suggest that various structural synaptic changes in the spinal cord and hippocampal neurons are mediated by the overproduction of TNF-α in activated microglial cells, which can be associated with the development of chronic neuropathic pain and memory deficit after spinal cord injury [142]. IL-1β reducing the efficiency of calcium pump function in neurons also contributes to the development of neuropathic pain [143].

4.2 Autoimmune component of the chronic phase in spinal cord injury

Particular attention should be paid to the autoimmune processes associated with spinal cord injury. D.P. Ankeny et al. [144] demonstrated that spinal cord injury and related immunodepression cause profound long-lasting changes in the functions of B cells of the peripheral lymphoid tissue (the bone marrow and spleen) and the injured spinal cord. In particular, after their differentiation, the activated B cells are able to secrete autoantibodies that bind CNS proteins and nuclear antigens, including DNA and RNA. In patients with systemic lupus erythematosus, anti-DNA antibodies cross-reactively interact with glutamate receptors, causing excitotoxicity [145]. The same effect is reported for SCI-related autoantibodies, which exhibit similar neurotoxic properties.

After spinal cord injury, the autoimmunity can also promote CNS regeneration and/or neuroprotection, though a tendency towards neurotoxicity manifestations can still be present. Myelin-reactive T cells exhibit a similar neuroprotective effect in the rat model of SCI [146]. The data on the role played by autoantibodies are inconsistent. After all, the antibodies specific to CNS proteins can promote axonal regeneration and remyelination [147], as well as demyelination, because anti-myelin antibodies can participate in building a "bridge" between myelin of nerve fibers and oligodendrocytes [148]. In any case, despite the ambiguity of the effects and their interpretations, it has been verified that B cells infiltrate the injured spinal cord during the chronic phase [144].

The presented review demonstrates that the interpretation of the results is challenging because it is difficult to distinguish local and systemic effects after spinal cord injury. In this regard, the feasibility of differentiating between the local and systemic manifestations of immune response opens up certain prospects. For example, significant changes in the cytokine profile after SCI, especially during the chronic phase, were found not only in blood. Changes in the cytokine profile in CSF were even more informative. Thus, A.R. Taylor et al. [149] determined the levels of IL-2, IL-6, IL-7, IL-8, IL-10, IL-15, IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ), keratinocyte chemoattractant (KC-like protein), IFNγ-inducible protein 10 (IP-10), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor α (TNF-α) in cerebrospinal fluid as criteria characterizing the intensity of chronic inflammation. The concentrations of most cytokines and chemokines in CSF of animals after SCI correlated with the

injury duration and trauma severity at sampling and the long-term neurological outcome. Thus, after spinal cord injury, the IL-8 level was significantly higher than in the control group of healthy animals but showed a negative correlation with the injury duration. At the same time, the levels of colony-stimulating factors and MCP-1 negatively correlated with the long-term positive outcome.

5. Conclusions

The review of publications focused on the problem of SCI-related immune (including cytokine) processes demonstrates that the available data are inconsistent and difficult to interpret.

Both the nervous and the immune systems have essential regulatory functions in the body and are tightly interrelated, while their interaction mechanisms are very diverse. Both local and systemic effects are associated with the neurological and immune changes occurring after spinal cord injury.

Along with these general aspects, the SCI-related local and systemic changes in the central nervous system and immune processes should be assessed on a stage-by-stage basis [150, 151]. Each phase is characterized by specific prevailing pathogenesis, which is initially linked to the response to injury and targeted at eliminating the damaged cells; then focus moves towards the inflammatory response with the aim of containing the affected area. Finally, a transition from local reactions to systemic processes occurs during later stages; the outcome of the pathological process depends on the efficiency of these phases. Each phase is associated with a specific category of immune response. In this respect, various cell subpopulations characterizing the innate and adaptive immunity or cytokines, the products secreted by these cells, can serve as markers of these immune responses [152, 153].

A specific feature of cytokines as markers of pathological changes after spinal cord injury is that they are secreted not only by immune cells but also by cells of the damaged spinal cord. The interaction between the nervous and immune systems can be characterized using the cytokine profile model. It has both theoretical research implications and diagnostic value and provides an opportunity to highlight the critical therapeutic targets.

Thus, cytokines contribute significantly to the pathogenesis of SCI-related traumatic disease and are responsible for its various manifestations. The cytokines can be secreted by immune cells; however, neurons of the damaged spinal cord are the main source of these biologically active substances. Therefore, the SCI-related cytokine pattern characterizes both the immune and neurological status and has a tremendous diagnostic and prognostic value.

Abbreviations

SC	spinal cord
SCI	spinal cord injury
CNS	central nervous system
BBB	blood–brain barrier

Author details

Georgii Telegin[1*], Aleksandr Chernov[1], Alexey Belogurov[2], Irina Balmasova[3], Nikolai Konovalov[4] and Aleksandr Gabibov[2]

1 Branch of Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Pushchino, Russia

2 Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia

3 Evdokimov Moscow State University of Medicine and Dentistry of Russia's Ministry of Health, Moscow, Russia

4 N.N. Burdenko National Scientific and Practical Center for Neurosurgery, Russian Federation Health Ministry, Moscow, Russia

*Address all correspondence to: telegin@bibch.ru

References

[1] Karsy M., Hawryluk G. Pharmacologic Management of Acute Spinal Cord Injury // Neurosurg Clin N Am. 2017. Vol. 28, № 1. P. 49-62.

[2] La Placa M.C., Simon C.M., Prado G.R., Cullen D.K. CNS injury biomechanics and experimental models // Prog Brain Res. 2007. Vol. 161. P. 13-26.

[3] Information bulleten WHO, № 384, November 2013.

[4] Braken M.B. Steroids for acute spinal cord injury // Cochrane Database Syst Rev. 2012. Vol. 1. CD001046.

[5] Safar P., Bicher N.D. Cardiopulmonary and cerebral resuscitation // M.: Medicine. 1997. 552 p.

[6] Leontiev M.A. Social adaptation of young disabled people with spinal cord injury by means of adaptive physical culture // Abstract of dissertation, Ph.D. Novokuzneck. 2003. 24 p.

[7] Sekhon L.H.S., Fehlings M.G. Epidemiology, demographics, and pathophysiology of acute spinal cord injury // Spine (Phila Pa 1976). 2001. Vol. 26. P. 2-12.

[8] Friedli L., Rosenzweig E.S., Barraud Q. et al. Pronounced species divergence in corticospinal tract reorganization and functional recovery after lateralized spinal cord injury favors primates // Sci Transl Med. 2015.- Vol. 7, №N 302. P. 134.

[9] Chipman J.G., Deuser W.E., Beilman G.J. Early surgery for thoracolumbar spine injuries decreases complications // J Trauma. 2004. Vol. 56, № l. P. 52-57.

[10] Gren' A.A. Surgical treatment of patients with spinal and spinal cord injuries with associated trauma // Abstract of dissertation, Ph.D. Moscow, 2008. 48 p.

[11] Orlov S.V., Shedrenko V.V., Mogychaya O.V. // Abstract science speech conference. Cheboksaru. 2006. P. 130-132.

[12] Bellet F.D., Rashid S.M., Jusabani M.A. et al. Traumatic Spine Injury: Which Discrepancy Between the Research Output and the Actual Burden of the Disease? // Pan Afr Med J. 2019. Vol. 33. P. 82.

[13] Nitecki S., Moir C.R. Predictive factors of the outcome of traumatic cervical spine fracture in children // J Pediatr Surg. 1994. Vol. 29, № 11. P. 1409-1411.

[14] Osenbach R.K., Menezes A.H. Pediatric spinal cord and vertebral column injury // Neurosurgery. 992. Vol. 30, № 3. P. 385-390.

[15] Eubanks J.D., Gilmore A., Bess S., Cooperman D.R. Clearing the pediatric cervical spine following injury // J Am Acad Orthop Surg. 2006. Vol. 14, № 9. p. 552-564.

[16] Poorman G.W., Segreto F.A., Beaubrun B.M. et al. Traumatic Fracture of the Pediatric Cervical Spine: Etiology, Epidemiology, Concurrent Injuries, and an Analysis of Perioperative Outcomes Using the Kids' Inpatient Database // Int J Spine Surg. 2019. Vol. 13, № 1. P. 68-78.

[17] Yeo J.D., Walsh J., Rutkowski S. et al. Mortality following spinal cord injury // Spinal Cord. 1998. Vol. 36. P. 329-336.

[18] Bogdanova L.P. A new complex of restorative treatment of patients with traumatic disease with complicated spine fractures // Abstract science speech conference. VI physiotherapeutic forum. SPb, 2006. P. 188.

[19] Kaikov A.K., Grin' A.A. TORACOSCOPIC SURGERY FOR INJURY OF THE CHEST SPINE // Grin' Tez. report All-Russian. scientific - practical. conf. "Polenov Readings". SPb. 2009. P. 89-90.

[20] Klimov V.S., Kostina E.V., Kireev D.O. Experience in treating patients with spinal cord injury in an emergency hospital // Abstract science speech conference VIII "Polenov Readings". SPb. 2009. P. 93.

[21] Mlavuxh S.G. Surgical tactics for unstable isolated and combined injuries of the thoracic and lumbar spine // Abstract of dissertation, Ph.D. M. 2009. 27 p.

[22] Gomes-Osman J., Cortes M., Guest J., Pascual-Leone A. A Systematic Review of Experimental Strategies Aimed at Improving Motor Function after Acute and Chronic Spinal Cord Injury // J Neurotrauma. 2016. Vol. 33, N 5. P. 425-438.

[23] Канн S.L., Chyrlauev Yu.A. Intensive care for severe spinal cord injury // Politrauma. 2007. № 2. P. 65-75.

[24] H.-L. Li, H.Xu, Y.-L.Li et al. Epidemiology of traumatic spinal cord injury in Tianjin, China: An 18-year retrospective study of 735 cases // J Spinal Cord Med. 2019. Vol. 42, N 6. P. 778-785.

[25] Steinemann S., Galanis D.J., J.Cheng J. et al. Unique Epidemiology of Spinal Cord Injury in Hawai'i: Wave-related Incidents // Hawaii J Health Soc Welf. 2019. Vol. 78, №12. P. 365-370.

[26] Akshulakov S.K., Kerimbaev T.T. Epidemiology of spine and spinal cord injuries // Abstract science of conference neurosurgery Russia. SPb. 2002. P. 182.

[27] Alikov Z.U., Verhovskii A.I. Immediate results of surgical treatment of combined injuries of the thoracic and lumbar spine // Abstract science of conference «Surgery of spinal collum – full spectrum». M. 2007. P. 262-264.

[28] Voronovich I.R., Beleckii A.V., Dylyb O.I. et al. Diagnostics and treatment of traumatic polysegmental lesions of the spinal cord // Abstract science of conference «Surgery of spinal collum – full spectrum». M. 2007. P. 281-283.

[29] Dovlatov B.N., Maksudov B.M. Diagnostic algorithms and treatment tactics for multiple and concomitant spinal injuries // Abstract science of conference «Surgery of spinal collum – full spectrum». M. 2007. P. 288-289.

[30] Samoxvalov I.M., Badalov V.I., Korostulev K.E. et al. Treatment of severe concomitant spinal injuries // Tez. report All-Russian. scientific - practical. conf. "Polenov Readings". SPb. 2009. P. 99-100.

[31] Soloviev V.A., Telejkin V.V., Soloviev I.V. Our experience in the treatment of spinal injuries at the craniovertebral level // Tez. report All-Russian. scientific - practical. conf. Yioshkar-Ola. 2007. P. 83-85.

[32] Ball S.T., Vaccaro A.R., Albert T.J., Cotler J.M. Injuries of the thoracolumbar spine associated with restraint use in head-on motor vehicle accidents // Spinal Disorders. 2000. Vol. 13, N 4. P. 297-304.

[33] Morozov I.N., Mliavux S.G. Epidemiology of spine-spinal injury // Medical almanah (Niznii Novgorod). 2011. № 4 (17). 157-159.

[34] Perlmutter O.A. Compression of the spinal cord and its roots (diagnostics, surgical tactics) // Abstract of dissertation, Ph.D. M. 2000. 46 p.

[35] Dragun V.M. Surgical treatment of traumatic injuries of the middle

and lower cervical vertebrae // Traumatology and Orthopedics of Russia. 2008. № 3. P.82-83.

[36] Fassett D.R., Harrop J.S., Maltenfort M. et al. Mortality rates in geriatric patients with spinal cord injuries // J Neurosurg Spine. 2007. Vol. 7. P. 277-281.

[37] Gedde M.H., Lilleberg H.S., Abmus J. et al. Traumatic vs non-traumatic spinal cord injury: A comparison of primary rehabilitation outcomes and complications during hospitalization // J Spinal Cord Med. 2019. Vol. 42, N 6. P. 695-701.

[38] Vazquez X.M., Rodriguez M.S., Peñaranda J.M. et al. Determining prognosis after spinal cord injury // J Forensic Leg Med. 2008. Vol. 15, N 1. P. 20-23.

[39] Roberts T.T., Leonard G.R., Cepela D.J. Classifications in brief: American spinal injury association (ASIA) impairment scale // Clin Orthop Relat Res. 2017. Vol. 145, N 5. P. 1499-1504.

[40] Van Middendorp J.J., Hosman A.J., Donders A.R. et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study // Lancet. - 2011. - Vol. 377, N 9770. P. 1004-1010.

[41] Van Middendorp J.J., Hosman A.J., Pouw M.H. et al. EM-SCI Study Group. ASIA impairment scale conversion in traumatic SCI: is it related with the ability to walk? A descriptive comparison with functional ambulation outcome measures in 273 patients // Spinal Cord. 2009. Vol. 47, N 7. P. 555-560.

[42] Van Middendorp J.J., Hosman A.J., Pouw M.H. et al. Is determination between complete and incomplete traumatic spinal cord injury clinically relevant? Validation of the ASIA sacral sparing criteria in a prospective cohort of 432 patients // Spinal Cord. 2009. Vol. 47, N 11. P. 809-816.

[43] Yarkony G., Chen D. Rehabilitation of patients with spinal cord injuries // In: R. Braddon (ed). Physical medicine and rehabilitation - W.B. Saunders Company. 1996. P. 1149-1179.

[44] H. Mushlin H., Kole M.J., Chryssikos T. et al. AOSpine Subaxial Cervical Spine Injury Classification System: The Relationship Between Injury Morphology, Admission Injury Severity, and Long-Term Neurologic Outcome // World Neurosurg. 2019. Vol. 130. P. 368-374.

[45] Perlmutter O.A. Spine and spinal cord injury // N. Novgorod. 2000. 144 p.

[46] Franceschini M., Bonavita J., Cecconi L. et al. Traumatic spinal cord injury in Italy 20 years later: current epidemiological trend and early predictors of rehabilitation outcome // Spinal Cord. 2020. 58(7):768-777.

[47] Berne J.D., Velmahos G.C., El-Tawil Q. et al. Value of complete cervical helical computed tomographic scanning in identifying cervical spine injury in the unevaluable blunt trauma patient with multiple injuries: a prospective study // J Trauma. 1999. Vol. 47. P. 896-902.

[48] Aimone J.B., Leasure J.L., Perreau V.M., Thallmair M. Spatial and temporal gene expression profiling of the contused rat spinal cord // Exp Neurol. 2004. Vol. 189, № 2. P. 204-221.

[49] Shechter R., Miller O., Yovel G. et al. Recruitment of Beneficial M2 Macrophages to Injured Spinal Cord Is Orchestrated by Remote Brain Choroid Plexus // Immunity. 2013. Vol. 38, N 3. P. 555-569.

[50] Chamankhah M., Eftekharpour E., Karimi-Abdolrezaee S. et al.

Genome-wide gene expression profiling of stress response in a spinal cord clip compression injury model // BMC Genomics. 2013. Vol. 14. P. 583-607.

[51] Moghaddam A., Child C., Bruckner T. et al. Posttraumatic Inflammation as a Key to Neuro-regeneration after Traumatic Spinal Cord Injury // Int J Mol Sci. 2015. Vol. 16, №4. P. 7900-7916.

[52] Marcol W., Slusarczyk W., Gzik M. et al. Air gun impactor--a novel model of graded white matter spinal cord injury in rodents // J Reconstr Microsurg. 2012. Vol. 28, № 8. P. 561-568.

[53] Oyinbo CA Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade // Acta Neurobiol Exp (Wars). 2011;71(2):281-99.

[54] Ren H., Chen X., Tian M. et al. Regulation of Inflammatory Cytokines for Spinal Cord Injury Repair Through Local Delivery of Therapeutic Agents // Adv. Sci. 2018, 5, 1800529.

[55] Zhang N., Yin Y., Xu S.J. et al. Inflammation and apoptosis in spinal cord injury // Indian J Med Res. 2012, 135 (3); 287-296.

[56] Cruz C. D., Coelho A., Antunes-Lopes T., Cruz F. Biomarkers of spinal cord injury and ensuing bladder dysfunction // Adv. Drug Delivery Rev. 2015, 82-83, 153.

[57] Gruys E, Toussaint MJ, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins // J Zhejiang Univ Sci B. 2005;6(11):1045-1056. doi:10.1631/jzus.2005.B1045.

[58] Zhang N., Yin Y., Xu S.J., Wu Y.P., Chen W.S. Inflammation & apoptosis in spinal cord injury // Indian J. Med. Res. 2012. V. 135. № 3. P. 287-296.

[59] Wilcox J.T., Satkunendrarajah K., Nasirzadeh Y., et. al Generating level-dependent models of cervical and thoracic spinal cord injury: Exploring the interplay of neuroanatomy, physiology, and function.// Neurobiol. Dis. 2017. V. 105. P. 194-212.

[60] Figley S.A., Khosravi R., Legasto J.M., Tseng Y.-F., Fehlings M.G. Characterization of vascular disruption and blood-spinal cord barrier permeability following traumatic spinal cord injury // J. Neurotrauma. 2014. V. 31. № 6. P. 541-552.

[61] Kunis G., Baruch K., Rosenzweig N., Kertser A., Miller O., Berkutzki T., Schwartz M. IFN-γ-dependent activation of the brain's choroid plexus for CNS immune surveillance and repair // Brain. 2013. V. 136. № 11. P. 3427-3440.

[62] Li Y., Lucas-Osma A.M., Black S., Bandet M.V., Stephens M.J., Vavrek R., Sanelli L., Fenrich K.K., Di Narzo A.F., Dracheva S., et al. Pericytes impair capillary blood flow and motor function after chronic spinal cord injury // Nat. Med. 2017. V. 23. № 6. P. 733-741.

[63] Shechter R., Miller O., Yovel O.G., Rosenzweig N., London A., Ruckh J., Kim K.-W., Klein E., Kalchenko V., Bendel P., et al. Recruitment of beneficial M2 macrophages to injured spinal cord is orchestrated by remote brain choroid plexus // Immunity. 2013. V. 38. № 3. P. 555-569.

[64] Goss J.R., Taffe K.M., Kochanek P.M., DeKosky S.T. The antioxidant enzymes glutathione peroxidase and catalase increase following traumatic brain injury in the rat // Exp. Neurol. 1997. V. 146. № 1. P. 291-294.

[65] Ren H., Chen X., Tian M., Zhou J., Ouyang H., Zhang Z. Regulation of Inflammatory Cytokines for Spinal Cord Injury Repair Through Local Delivery of Therapeutic Agents // Adv. Sci. 2018. V. 5. № 11. P. 1800529.

[66] Sutherland TC, Mathews KJ, Mao Y, Nguyen T, Gorrie CA. Differences in the Cellular Response to Acute Spinal Cord Injury between Developing and Mature Rats Highlights the Potential Significance of the Inflammatory Response // Front. Cell Neurosci. 2017. V. 10. P. 310.

[67] Shohami E., Bass R., Wallach D., Yamin A., Gallily R. Inhibition of tumor necrosis factor alpha (TNFalpha) activity in rat brain is associated with cerebroprotection after closed head injury // J. Cereb. Blood Metabol. 1996. V. 16. № 3. P. 378-384.

[68] Yu W.R., Fehlings M.G. Fas/FasL-mediated apoptosis and inflammation are key features of acute human spinal cord injury: implications for translational, clinical application // Acta Neuropathol. 2011. V. 122. № 6. P. 747-761.

[69] Chen S., Ye J., Chen X., Shi J., Wu W., Lin W., Lin W., Li Y., Fu H., Li S. Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-κB pathway dependent of HDAC3 // J. Neuroinflammation. 2018. V. 15. № 1. P. 150-163.

[70] Jorge A., Taylor T., Agarwal N., Hamilton D.K. Current agents and related therapeutic targets for inflammation after acute traumatic spinal cord injury // World Neurosurg. 2019. V. 132. P. 138-147.

[71] Breckwoldt M.O., Pfister F.M., Bradley P.M., Marinković P., Williams P.R., Brill M.S., Plomer B., Schmalz A., St Clair D.K., Naumann R., et al. Multiparametric optical analysis of mitochondrial redox signals during neuronal physiology and pathology in vivo // Nat. Med. 2014. V. 20. № 5. P. 555-560.

[72] Ouardouz M., Coderre E., Basak A., Chen A., Zamponi G.W., Hameed S., Rehak R., Yin X., Trapp B.D., Stys P.K. Glutamate receptors on myelinated spinal cord axons: I. GluR6 kainate receptors // Ann. Neurol. 2009. V. 65. № 2. P. 151-159.

[73] Yin H.Z., Hsu C.I., Yu S., Rao S.D., Sorkin L.S., Weiss J.H. TNF-α triggers rapid membrane insertion of Ca2+ permeable AMPA receptors into adult motor neurons and enhances their susceptibility to slow excitotoxic injury // Exp. Neurol. 2012. V. 238. № 2. P. 93-102.

[74] Khayrullina G., Bermudez S., Byrnes K.R. Inhibition of NOX2 reduces locomotor impairment, inflammation, and oxidative stress after spinal cord injury // J. Neuroinflammation. 2015. V. 12. P. 172-182.

[75] Von Leden R.E., Khayrullina G., Moritz K.E., Byrnes K.R. Age exacerbates microglial activation, oxidative stress, inflammatory and NOX2 gene expression, and delays functional recovery in a middle-aged rodent model of spinal cord injury // J. Neuroinflammation. 2017. V. 14. № 1. P. 161-174.

[76] Pineau I., Lacroix S. Proinflammatory cytokine synthesis in the injured mouse spinal cord: multiphasic expression pattern and identification of the cell types involved // J. Comp. Neurol. 2007. V. 500. № 2. P. 267-285.

[77] Yang L., Blumbergs P.C., Jones N.R., Manavis J., Sarvestani G.T., Ghabriel M.N. Early expression and cellular localization of proinflammatory cytokines interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in human traumatic spinal cord injury // Spine. 2004. V. 29. № 9. P. 966-971.

[78] Yang L., Jones N.R., Blumbergs P.C., van den Heuvel C., Moore E.J., Manavis J., Sarvestani G.T., Ghabriel M.N. Severity-dependent

expression of pro-inflammatory cytokines in traumatic spinal cord injury in the rat // J. Clin. Neurosci. 2005. V. 12. № 3. P. 276-284.

[79] Deng G., Gao Y., Cen Z., He J., Cao B., Zeng G., Zong S. miR-136-5p Regulates the Inflammatory Response by Targeting the IKKβ/NF-κB/A20 Pathway After Spinal Cord Injury // Cell Biochem. 2018. V. 50. № 2. P. 512-524.

[80] He J., Zhao J., Peng X., Shi X., Zong S., Zeng G. Molecular Mechanism of MiR-136-5p Targeting NF-κB/A20 in the IL-17-Mediated Inflammatory Response after Spinal Cord Injury // Cell Physiol. Biochem. 2017. V. 44. № 3. P. 1224-1241.

[81] Beilerli O.A., Azizova Sh.T., Konovalov N.A., Akhmedov A.D., Gareev I.F., Belogurov A.A. Non-coding rna as therapeutic targets for spinal cord injury // Questions of neurosurgery named after N.N. Burdenko . 2020. Vol. 84. № 4. P. 104-110.

[82] Fu Q., Liu Y., Liu X., Zhang Q., Chen L., Peng J., Ao J., Li Y., Wang S., Song G., et al. Engrafted peripheral blood-derived mesenchymal stem cells promote locomotive recovery in adult rats after spinal cord injury // Am. J. Transl. Res. 2017. V. 9. № 9. P. 3950-3966.

[83] Cao Y., Wu T.D., Wu H., Lang Y., Li D.Z., Ni S.F., Lu H.B., Hu J.Z. Synchrotron radiation micro-CT as a novel tool to evaluate the effect of agomir-210 in a rat spinal cord injury model // Brain Res. 2017. V. 1655. P. 55-65.

[84] Ujigo S., Kamei N., Hadoush H., Fujioka Y., Miyaki S., Nakasa T., Tanaka N., Nakanishi K., Eguchi A., Sunagawa T., et al. Administration of microRNA-210 promotes spinal cord regeneration in mice // Spine. 2014. V. 39. № 14. P. 1099-1107.

[85] Saiwai H., Ohkawa Y., Yamada H., Kumamaru H., Harada A., Okano H., Yokomizo T., Iwamoto Y., Okada S. The LTB4-BLT1 axis mediates neutrophil infiltration and secondary injury in experimental spinal cord injury // Am. J. Pathol. 2010. V. 176. № 5. P. 2352-2366.

[86] Yokota K., Saito T., Kobayakawa K., Kubota K., Hara M., Murata M., Ohkawa Y., Iwamoto Y., Okada S. The feasibility of in vivo imaging of infiltrating blood cells for predicting the functional prognosis after spinal cord injury // Sci. Rep. 2016. V. 6. P. 25673-25684.

[87] Ankeny D.P., Guan Z., Popovich P.G. B cells produce pathogenic antibodies and impair recovery after spinal cord injury in mice // J. Clin. Invest. 2009. V. 119. № 10. P. 2990-2999.

[88] Beck K.D., Nguyen H.X., Galvan M.D., Salazar D.L., Woodruff T.M., Anderson A.J. Quantitative analysis of cellular inflammation after traumatic spinal cord injury: evidence for a multiphasic inflammatory response in the acute to chronic environment // Brain. 2010. V. 133. Pt. 2. P. 433-447.

[89] Raposo C., Graubardt N., Cohen M., Eitan C., London A., Berkutzki T., Schwartz M. CNS repair requires both effector and regulatory T cells with distinct temporal and spatial profiles // J. Neurosci. 2014. V. 34. № 31. P. 10141-10155.

[90] Saiwai H., Kumamaru H., Ohkawa Y., Kubota K., Kobayakawa K., Yamada H., Yokomizo T., Iwamoto Y., Okada S. // J. Neurochem. 2013. V. 125. № 1. P. 74-88.

[91] Kumamaru H., Saiwai H., Ohkawa Y., Yamada H., Iwamoto Y., Okada S., Ly6C+ Ly6GMyeloid-derived suppressor cells play a critical role in the resolution of acute inflammation and the subsequent tissue repair process after spinal cord injury // J. Cell Physiol. 2012. V. 227. № 4. P. 1335-1346.

[92] Nguyen D.H., Cho N., Satkunendrarajah K., Austin J.W., Wang J., Fehlings M.G. Immunoglobulin G (IgG) attenuates neuroinflammation and improves neurobehavioral recovery after cervical spinal cord injury // J. Neuroinflammation. 2012. V. 9. P. 224-237.

[93] Min K.J., Jeong H.K., Kim B., Hwang D.H., Shin H.Y., Nguyen A.T., Kim J.H., Jou I., Kim B.G., Joe E.H. Spatial and temporal correlation in progressive degeneration of neurons and astrocytes in contusion-induced spinal cord injury // J. Neuroinflammation. 2012. V. 9. P. 100-112.

[94] Smith P.D., Puskas F., Meng X., Lee J.H., Cleveland J.C. Jr., Weyant M.J., Fullerton D.A., Reece T.B. The evolution of chemokine release supports a bimodal mechanism of spinal cord ischemia and reperfusion injury // Circulation. 2012. V. 126. № 11(1). P. 110-117.

[95] Zhu P., Li J.X., Fujino M., Zhuang J., Li X.K. Development and treatments of inflammatory cells and cytokines in spinal cord ischemia-reperfusion injury // Mediators Inflamm. 2013. V. 2013. P. 701970.

[96] Akhmetzyanova E., Kletenkov K., Mukhamedshina Y., Rizvanov A. Different Approaches to Modulation of Microglia Phenotypes After Spinal Cord Injury // Front. Syst. Neurosci. 2019. V. 13. P. 37-48.

[97] Chu G.K., Yu W., Fehlings M.G. The p75 neurotrophin receptor is essential for neuronal cell survival and improvement of functional recovery after spinal cord injury // Neuroscience. 2007. V. 148. № 3. P. 668-682.

[98] Floriddia E.M., Rathore K.I., Tedeschi A., Quadrato G., Wuttke A., Lueckmann J.M., Kigerl K.A., Popovich P.G., Di Giovanni S. p53 Regulates the neuronal intrinsic and extrinsic responses affecting the recovery of motor function following spinal cord injury // J. Neurosci. 2012. V. 32. № 40. P. 13956-13970.

[99] Horn K.P., Busch S.A., Hawthorne A.L., van Rooijen N., Silver J. Another barrier to regeneration in the CNS: activated macrophages induce extensive retraction of dystrophic axons through direct physical interactions // J. Neurosci. 2008. V. 28. № 38. P. 9330-9341.

[100] Roselli F., Chandrasekar A., Morganti-Kossmann M.C. Interferons in Traumatic Brain and Spinal Cord Injury: Current Evidence for Translational Application // Front. Neurol. 2018. V. 9. P. 458.

[101] Wang Y.Y., Shen D., Zhao L.J., Zeng N., Hu T.H. Sting is a critical regulator of spinal cord injury by regulating microglial inflammation via interacting with TBK1 in mice // Biochem. Biophys. Res. Commun. 2019. V. 517. № 4. P. 741-748.

[102] Laginha I., Kopp M.A., Druschel C., Schaser K.D., Brommer B., Hellmann R.C., Watzlawick R., Ossami-Saidi R.R., Prüss H., Failli V., et al Natural Killer (NK) Cell Functionality after human Spinal Cord Injury (SCI): protocol of a prospective, longitudinal study // BMC Neurol. 2016. V. 16. № 1. P. 170.

[103] Xu L., Zhang Y., Zhang R., Zhang H., Song P., Ma T., Li Y., Wang X., Hou X., Li Q., et al. Elevated plasma BDNF levels are correlated with NK cell activation in patients with traumatic spinal cord injury // Int. Immunopharmacol. 2019. V. 74. P. 105722.

[104] Rust R., Kaiser J. Insights into the Dual Role of Inflammation after Spinal Cord Injury // J. Neurosci. 2017. V. 37. № 18. P. 4658-4660.

[105] Azam S., Jakaria M., Kim I.S., Kim J., Haque M.E., Choi D.K. Regulation of Toll-Like Receptor (TLR) Signaling Pathway by Polyphenols in the Treatment of Age-Linked Neurodegenerative Diseases: Focus on TLR4 Signaling // Front. Immunol. 2019. V. 10. P. 1000.

[106] Kigerl K.A., Popovich P.G. Toll-like receptors in spinal cord injury // Curr. Top Microbiol. Immunol. 2009. V. 336. P. 121-136.

[107] Hug H., Mohajeri M.H., La Fata G. Toll-Like Receptors: Regulators of the Immune Response in the Human Gut // Nutrients. 2018. V. 10. № 2. P. 203.

[108] Kawasaki T., Kawai T. Toll-like receptor signaling pathways // Front. Immunol. 2014. V. 5. P. 461.

[109] Marinelli C., Di Liddo R., Facci L., Bertalot T., Conconi M.T., Zusso M., Skaper S.D., Giusti P. Ligand engagement of Toll-like receptors regulates their expression in cortical microglia and astrocytes / J. Neuroinflammation. 2015. V. 12. P. 244.

[110] Trudler D., Farfara D., Frenkel D. Toll-like receptors expression and signaling in glia cells in neuro-amyloidogenic diseases: towards future therapeutic application / Mediators Inflamm. 2010. V. 2010. P. 497987.

[111] Lacagnina M.J., Watkins L.R., Grace P.M. Toll-like receptors and their role in persistent pain // Pharmacol. Ther. 2018. V. 184. P. 145-158.

[112] Heiman A., Pallottie A., Heary R.F., Elkabes S. Toll-like receptors in central nervous system injury and disease: a focus on the spinal cord // Brain Behav. Immun. 2014. V. 42. P. 232-245.

[113] Lobenwein D., Tepekoylu C., Kozarin R. et al. Shock Wave Treatment Protects From Neuronal Degeneration via a Toll-Like Receptor 3 Dependent Mechanism: Implications of a First-Ever Causal Treatment for Ischemic Spinal Cord Injury // J. Am. Heart. Assoc. 2015. V. 4. № 10. e002440.

[114] Mittal A., Sagi V., Gupta M., Gupta K. Mast Cell Neural Interactions in Health and Disease // Front. Cell Neurosci. 2019. V. 13. P. 110-115.

[115] Vangansewinkel T., Geurts N., Quanten K., Nelissen S., Lemmens S., Geboes L., Dooley D., Vidal P.M., Pejler G., Hendrix S. Mast cells promote scar remodeling and functional recovery after spinal cord injury via mouse mast cell protease 6 // FASEB J. 2016. V. 30. № 5. P. 2040-2057.

[116] Nelissen S., Vangansewinkel T., Geurts N., Geboes L., Lemmens E., Vidal P.M., Lemmens S., Willems L., Boato F., Dooley D., et al. Mast cells protect from post-traumatic spinal cord damage in mice by degrading inflammation-associated cytokines via mouse mast cell protease 4 // Neurobiol. Dis. 2014. V. 62. P. 260-272.

[117] Rutz S., Ouyang W. Regulation of Interleukin-10 Expression // Adv. Exp. Med. Biol. 2016. V. 941. P. 89-116.

[118] Rutz S., Ouyang W. Regulation of interleukin-10 and interleukin-22 expression in T helper cells // Curr. Opin. Immunol. 2011. V. 23. № 5. P. 605-612.

[119] Lobo-Silva D., Carriche G.M., Castro A.G., Roque S., Saraiva M. Balancing the immune response in the brain: IL-10 and its regulation // J. Neuroinflammation. 2016. V. 13. № 1. P. 297.

[120] Hong J., Chang A., Zavvarian M.M., Wang J., Liu Y., Fehlings M.G. Level-Specific Differences in Systemic Expression of Pro- and Anti-Inflammatory Cytokines and Chemokines after Spinal Cord Injury // Int. J. Mol. Sci. 2018. V. 19. № 8. P. 2167-2178.

[121] Hong J., Chang A., Liu Y., Wang J., Fehlings M.G. Incomplete Spinal Cord Injury Reverses the Level-Dependence of Spinal Cord Injury Immune Deficiency Syndrome // Int. J. Mol. Sci. 2019. V. 20. № 15. P. 3762.

[122] Yuan X., Wu Q., Tang Y., Jing Y., Li Z., Xiu R. Systemic microcirculation dysfunction after low thoracic spinal cord injury in mice // Life Sci. 2019. V. 221. P. 47-55.

[123] Tsibulkina V.N., Tsibulkin N.A. Mast cell as a polyfunctional element of the immune system // Allergology and immunology in pediatrics. 2017. Vol. 2. P. 4-11.

[124] Sarbaeva N.N., Ponomareva Yu.V., Milyakova M.N. Macrophages: variety of phenotypes and functions, interaction with foreign materials // Genes and cells. 2016. Vol. XI. № 1. P. 9-17.

[125] Zhang Y., Gao Z., Wang D., Zhang T., Sun B., Mu L., Wang J., Liu Y., Kong Q., Liu X., et al. Accumulation of natural killer cells in ischemic brain tissues and the chemotactic effect of IP-10 // J. Neuroinflammation. 2014. V. 11. P. 79.

[126] Balmasova I.P., Shmeleva E.V., Eremina O.F., Dunda N.I. Characteristics of the regulatory-receptor apparatus of natural killer cells in clinically healthy people q // Allergology and immunology. 2009. Vol. 10. № 2. P. 169.

[127] Ferrante C.J., Leibovich S.J. Regulation of Macrophage Polarization and Wound Healing // Adv. Wound Care (New Rochelle). 2012. V. 1. № 1. P. 10-16.

[128] Balmasova I.P., Nesterova I.V., Malova E.S., Sepiashvili R.I. Structural and functional organization of the immune system. Moscow: Practical Medicine, 2019. 72 p.

[129] Chubenko V.A. Immunotherapy based on cytokines (Il-1. Il-2. Tnf. Ksf. Interferons) // Practical oncology. 2016. T. 17. № 2. C. 99-109.

[130] Fasching P., Stradner M., Graninger W., Dejaco C., Fessler J. Therapeutic Potential of Targeting the Th17/Treg Axis in Autoimmune Disorders // Molecules. 2017. V. 22. № 1. P. 134.

[131] Rice T., Larsen J., Rivest S., Yong V.W. Characterization of the early neuroinflammation after spinal cord injury in mice // J. Neuropathol. Exp. Neurol. 2007. V. 66. № 3. P. 184-195.

[132] Irwin M.R., Cole S.W. Reciprocal regulation of the neural and innate immune systems // Nat. Rev. Immunol. 2011. V. 11. № 9. P. 625-632.

[133] Schwab J.M., Zhang Y., Kopp M.A., Brommer B., Popovich P.G. The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury // Exp. Neurol. 2014. V. 258. P. 121-129.

[134] Zhou Y., Li N., Zhu L., Lin Y., Cheng H. The microglial activation profile and associated factors after experimental spinal cord injury in rats // Neuropsychiatr. Dis Treat. 2018. V. 14. P. 2401-2413.

[135] Monahan R., Stein A., Gibbs K., Bank M., Bloom O. Circulating T cell subsets are altered in individuals with chronic spinal cord injury // Immunol. Res. 2015. V. 63. № 1-3. P. 3-10.

[136] Herman P., Stein A., Gibbs K., Korsunsky I., Gregersen P., Bloom O. Persons with Chronic Spinal Cord Injury Have Decreased Natural Killer Cell and Increased Toll-Like Receptor/ Inflammatory Gene Expression // J. Neurotrauma. 2018. V. 35. № 15. P. 1819-1829.

[137] Zhang Y., Guan Z., Reader B., Shawler T., Mandrekar-Colucci S., Huang K., Weil Z., Bratasz A., Wells J., Powell N.D., et al. Autonomic dysreflexia causes chronic immune suppression after spinal cord injury // J. Neurosci. 2013. V. 33. № 32. P. 12970-12981.

[138] Sanz P., Garcia-Gimeno M.A. Reactive Glia Inflammatory Signaling Pathways and Epilepsy // Int. J. Mol. Sci. 2020. V. 21. № 11. P. 4096-4112.

[139] Pekny M., Pekna M. Astrocyte reactivity and reactive astrogliosis: costs and benefits // Physiol. Rev. 2014. V. 94. № 4. P. 1077-1098.

[140] Alizadeh A., Santhosh K.T., Kataria H., Gounni A.S., Karimi-Abdolrezaee S. Neuregulin-1 elicits a regulatory immune response following traumatic spinal cord injury // J. Neuroinflammation. 2018. V. 15. № 1. P. 53-73.

[141] Gensel J.C., Zhang B. Macrophage activation and its role in repair and pathology after spinal cord injury // Brain Res. 2015. V. 1619. P. 1-11.

[142] Liu Y., Zhou L.J., Wang J., Li D., Ren W.J., Peng J., Wei X., Xu T., Xin W.J., Pang R.P., et al. TNF-α Differentially Regulates Synaptic Plasticity in the Hippocampus and Spinal Cord by Microglia-Dependent Mechanisms after Peripheral Nerve Injury// J. Neurosci. 2017. V. 37. № 4. P. 871-881.

[143] Mirabelli E., Ni L., Li L., Acioglu C., Heary R.F., Elkabes S. Pathological pain processing in mouse models of multiple sclerosis and spinal cord injury: contribution of plasma membrane calcium ATPase 2 (PMCA2) // J. Neuroinflammation. 2019. V. 16. № 1. P. 207.

[144] Ankeny D.P., Lucin K.M., Sanders V.M., McGaughy V.M., Popovich P.G. Spinal cord injury triggers systemic autoimmunity: evidence for chronic B lymphocyte activation and lupus-like autoantibody synthesis // J. Neurochem. 2006. V. 99. P. 1073-1087.

[145] DeGiorgio L.A., Konstantinov K.N., Lee S.C., Hardin J.A., Volpe B.T., Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus // Nat. Med. 2001. V. 7. № 11. P. 1189-1193.

[146] Hauben E., Butovsky O., Nevo U., Yoles E., Moalem G., Agranov E., Mor F., Leibowitz-Amit R., Pevsner E., Akselrod S., et al. Passive or Active Immunization with Myelin Basic Protein Promotes Recovery from Spinal Cord Contusion // J. Neurosci. 2000. V. 20. № 17. P. 6421-6430.

[147] Huang D.W., McKerracher L., Braun P.E., David S. A therapeutic vaccine approach to stimulate axon regeneration in the adult mammalian spinal cord // Neuron. 1999. V. 24. № 3. P. 639-647.

[148] Kotter M.R., Li W.W., Zhao C., Franklin R.J. Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation // J. Neurosci. 2006. V. 26. № 1. P. 328-332.

[149] Taylor A.R., Welsh C.J., Young C., Spoor E., Kerwin S.C., Griffin J.F., Levine G.J., Cohen N.D., Levine J.M. Cerebrospinal fluid inflammatory cytokines and chemokines in naturally occurring canine spinal cord injury // J. Neurotrauma. 2014. V. 31. № 18. P. 1561-1569.

[150] Bradbury E.J., Burnside E.R. Moving beyond the glial scar for spinal cord repair // Nat. Commun. 2019. V. 10. P. 3879.

[151] Telegin G.B., Minakov A.N., Chernov A.S., Manskikh V.N.,

Asyutin D.S., Konovalov N.A., Gabibov A.G. Surgical Simulation of a Posttraumatic Spinal Cord Glial Scar in Rats // Acta Naturae. 2019. V. 11. № 3(42). P. 75-81.

[152] Sergeeva S.P., Erofeeva L.M., Gultyaev M.M., Balmasova I.P. Cytokines and cellular immune status after acute disorders of cerebral circulation // Immunopathology, Allergology, Infectology. 2010. № 3. P. 27-31.

[153] Belogurov A.A., Ivanova O.M., Lomakin Ya.A., Ziganshin R.Kh., Vaskina M.I., Knorre V.D., Klimova E.A., Gabibov A.G., Ivanov V .T., Govorun V.M. Mediators and biomarkers of inflammation in meningitis: cytokine and peptidome profiling of the cerebrospinal fluid // Biochemistry. 2016. Vol. 81. № 11. P. 1540-1552.