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Review

More Attention on Segments Remote from the Primary Spinal Cord Lesion Site

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Abstract

Recent findings from multimodal imaging studies point to macrostructural pathological changes in areas significantly distant from the epicenter of spinal cord injury, both in the spinal cord and in the brain. Studies are being performed to determine cellular and molecular mechanisms of these shifts, which are currently poorly understood. Research has demonstrated that the pathological process in the remote area is multifaceted. This process involves astrocytes and microglia, which contribute to the degeneration of nerve fibers passing from and through the immediate impact area, as well as participate in reciprocal activation. As a result, there is accompanying synaptic loss in areas remote to the spinal cord injury location. Reactive astrocytes produce chondroitin sulfate proteoglycans that inhibit axon growth and damage cells. However, neuronal death in the remote area remains controversial. The area of primary injury is the source of numerous neurotoxic molecules that release into the cerebrospinal fluid. It is assumed that these molecules, primarily matrix metalloproteinases, disrupt the blood-spinal cord barrier, which leads to tissue infiltration by macrophage precursors in the remote area. Activated macrophages secrete pro-inflammatory cytokines and matrix metalloproteinases, which, in turn, induce astrocytes and microglia towards a pro-inflammatory phenotype. In addition, reactive microglia, together with astrocytes, secrete numerous pro-inflammatory and neurotoxic molecules that activate inflammatory signaling pathways, consequently exacerbating synaptic depletion and neurological deterioration. It appears likely that the interplay between chronic inflammation and neurodegeneration is a pivotal characteristic of the pathological process in the spinal cord areas distant from the epicenter of the lesion. Pathological changes in the distant areas should be the object of research as potential therapeutic targets.

Keywords: spinal cord injury; distant changes; synaptic loss; myeloid infiltration; microglia; astrocytes; locomotor circuit reorganization

1. Introduction

Remote injury or the lesion-remote effect is a secondary phenomenon that usually occurs after primary central nervous system (CNS) injury in areas that are distant from the primary site of damage, but still functionally related [1]. This phenomenon has been traced both in the brain following spinal cord injury (SCI) [2,3] and, conversely, in the spinal cord following brain injury [4]. Most studies of pathological changes in SCI are directed primarily at the analysis of the lesion epicenter. Evidence is accumulating that pathological changes in chronic SCI affect areas far removed from the epicenter of injury [1,5,6]. Pathological changes in these areas could be an important therapeutic target for restoring neural circuitry and functional recovery after SCI. It is becoming increasingly clear that SCI causes neuroinflammation-associated damage along the entire organ, which consequently reduces plasticity and function recovery. The inflammatory response at the injury site has been characterized in detail, however, it is not well understood in areas remote from the injury epicenter. Studied have demonstrated that pathological changes are present even at a considerable distance from the primary SCI. For example, remote atrophy of brain gray matter, especially in the salient network [7], as well as cortical reorganization [8] has been discovered.

SCI manifestation spreads from the epicenter of injury in the rostral and caudal directions with different dynamics [9]. Today, it seems clear that pathological changes in remote areas primarily depend on the disruption of impulse conduction in axons that project to the remote spinal segments. This observation, first made by von Monakow (1914) and designated by the term diaschisis, not only explained the cause of pathological changes in remote areas of the CNS, but also formed the basis of subsequent fruitful studies of neuronavigation systems and tractography. However, as it turned out later, post-traumatic disruption of patterns of functional connections or their complete blocking is not the only cause of pathological changes in remote areas of the CNS. As an example, a model of thoracic SCI was studied, and numerous changes were found in the lumbar region. Among these were changes in the number of neurons [10–12] and synapses [12,13], microglial response [5,14–16], appearance and effects of myeloid cells [17,18], participation of progenitors [19], extracellular matrix molecules involved in axon growth inhibition [20], some well-known bioactive compounds [5,21,22], etc. In this review, recent evidence has been summarized for lesion-remote effects within spinal cord after SCI, thus emphasizing the need for

better understanding of the various pathogenic mechanisms involved in SCI.

2. Neuronal Loss

The death of neurons at the site of the primary lesion is one of the main factors of neurological deficit following SCI. However, there are only few studies on neuronal death in the remote areas of SCI, and their results are contradictory. However, there is relatively little but convincing data indicating that neuronal death occurs not only in the focus of SCI, but also in remote areas, although the available data are somewhat contradictory. In one study, a dorsal hemisection at the cervical level showed the autophagic death of axotomized rubrospinal neurons during primary and secondary damage, which was accompanied by a functional deficit [23]. In other studies, after complete thoracic spinal cord transection, the number of motoneurons (MNs) in the lumbar region was unchanged [11,12]. Similar results were obtained for MNs of specific groups, for example, m. tibialis anterior MNs after a moderate contusion on T8 [24]. However, the death of MNs in the lumbar region and a decrease in their number of up to 25% was recorded after complete transection at T8-T9 [10]. It can be expected that at a closer distance from the epicenter, the death of neurons will be more pronounced. Still, the observed discrepancies in neuronal survival across various studies may be related to the use of different SCI models and damage severity.

Regarding the synapses, evidence indicates that even after incomplete thoracic SCI, the synaptic connections of the lumbar MNs are affected [13]. Transection in the thoracic region reduced the number of presynaptic boutons in the lumbar MNs [12]. The expression of neuronal activity markers c-fos and calcium/calmodulin dependent protein kinase II alpha (CaMK2a) decreased in these MNs. Nevertheless, the synaptogenic potential of postsynaptic molecules in MNs was preserved, and the expression of acetylcholine-associated molecules was upregulated, which may be due to restored neural activity via raising the synaptic input to distant caudal part from the lesion site [12]. Therefore, encouraging evidence has been obtained that the synaptogenic potential of MNs located caudal to the injury site is maintained even under reduced presynaptic input.

There is now significant evidence that degeneration of presynaptic terminals precedes neuronal death in chronic neurodegenerative diseases of the CNS [25,26]. However, the contribution of axotomy to the neuronal loss in SCI remains controversial. It has been suggested that very distant axotomy is unlikely to result in neuronal death [27]. Especially for chronic SCI, the issue of how long neurons can survive under conditions of deprivation or a decrease in synaptic inputs remains extremely relevant.

It can also be assumed that SCI-related inhibition of activity or degeneration of inhibitory interneurons may be the cause of the death of connected neurons. This cause-and-effect pattern has been postulated for V1 interneurons in amyotrophic lateral sclerosis [28]. It is known that MNs innervating fast-twitch muscle fibers are predominantly degenerated in amyotrophic lateral sclerosis. Studies revealed that fast MNs receive stronger inhibitory synaptic inputs than slow MNs. The death of MNs is preceded by degeneration of V1 interneurons, that is accompanied by the development of a specific locomotor deficit [28].

Another potential cause of neuronal death in the remote area could be SCI-related central neuropathic pain. Remote neuronal loss has been confirmed in the CNS in spinal nerve ligation model of neuropathic pain [29]. However, in the peripheral nerve chronic constriction injury model, it has been established that peripheral neuropathic pain is not accompanied by the death of spinal neurons [30]. Hence, it remains unclear whether peripheral neuropathic pain is an additional factor that enhances the death of spinal neurons, and even more so in relation to central neuropathic pain.

3. Neuro-Gliogenesis

Some areas of the CNS such as the dentate gyrus and subventricular zone retain the ability to generate new neurons and glia from the endogenous progenitor cell pool and compensate for the loss of cells after injury. In the intact or injured adult spinal cord, cell replacement has only been described for glial cells, whereas neurogenesis seems unlikely [31]. Endogenous neural stem cells (NSCs) in the central canal have lost the ability to self-renew. Only a few of these cells respond to injury, proliferate, and migrate towards the lesion site; most of them differentiate into glial scar astrocytes as well as myelinating oligodendrocytes [31–34].

One study demonstrated that, after a severe mid-thoracic contusion-type SCI in a rat model, there was no increase in neurogenesis in non-neurogenic areas such as the motor cortex, corpus callosum and cervical spinal cord, nor in the above-mentioned neurogenic areas. At the same time, an increase in gliogenesis was found in the cervical spinal cord [31]. In another study, a cervical contusion-type SCI was found not to alter NSCs' differentiation profile into doublecortin-positive neuroblasts, glial fibrillary acidic protein (GFAP)-expressing astrocytes, or Olig2-labeled cells of the oligodendrocyte lineage [35].

Thoracic transection-type SCI activates NSCs in the hippocampus [36], leading to a transient increase in neurogenesis and improvement in working memory. The activation of these remote precursors in the hippocampus is controlled by interferon (IFN)-CD95 signaling. Interferon is not expressed by stem cells and niche cells, but is expressed and produced by microglia [36]. The regulation of ependymal cell proliferation and functional recovery after SCI also involves an inflammatory cytokine interleukin (IL)-17, which negatively regulates the secretion of ciliary neurotrophic factor (CNTF), glial cell-derived neurotrophic factor (GDNF), platelet-derived growth factor A (PDGF-A), transforming growth factor beta1 (TGFβ1),

nerve growth factor (NGF) and leukemia inhibitory factor (LIF) by ependymal cells [37]. In the injured spinal cord, these molecules, as neurotrophic and growth factors, maintain neural cell populations, stimulate axonal growth and reorganization, and thus contribute to the regenerative process [37]. These results point to ependymal cells in the spinal cord not only as a potential source for gliogenesis, but also as producers of molecular factors promoting functional recovery following SCI. In SCI, these cells in the region located remotely from the primary injury, should primarily respond to neurotoxic molecules appearing in CSF. In addition, in SCI immune cells migrate to the same remote area, which are the source of neurotoxic molecules, such as the aforementioned IL-17, which also disrupts the function of ependymal cells. The significance of each of these components influencing the behavior of ependymal cells remote from the area of primary SCI remains to be established.

4. Myeloid Cells

Bone marrow-derived myeloid cells migrate in the area of CNS damage, where they differentiate into $CD11b^{+}/CD45.1^{+}$ macrophages. Classically activated (M1) and alternatively activated (M2) macrophages are present at the injury site simultaneously. Lymphocyte antigen 6 complex locus C $(Ly6C)^{hi}$ monocytes, which express chemokine (C-X3-C motif) receptor 1 $(CX3CR1)^{lo}$ and C-C chemokine receptor type 2 $(CCR2)^{hi}$, are considered to be phagocytic and pro-inflammatory [38]. CCR2 downregulation attenuates SCI by suppressing inflammatory monocytes [39].

Myeloid cells in the injured area communicate with activated resident microglia $(CD11b^{+}/CD45.1^{-})$ [40] and maintain the neurotoxic M1 microglial phenotype. Macrophages infiltrating the spinal cord parenchyma actively produce pro-inflammatory cytokines such as TNFα and IL-1β, as well as matrix metalloproteinases (MMPs) (Fig. 1), which subsequently stimulate microglia and astrocytes to produce numerous pro-inflammatory and neurotoxic molecules [41–43].

Crosstalk between monocytes/macrophages and microglia at the site of injury, the timing of activation of both cell types, and the production of chemoattractants and other signaling molecules appear to be especially important for understanding of the mechanisms of traumatic SCI at distant locations. In thoracic SCI, there is evidence for myeloid cell recruitment in the lumbar, but not in the cervical region [17]. Myeloid infiltration was accompanied by a simultaneous increase in the chemoattractant chemokine C-C motif ligand 2 (CCL2) and the cell adhesion molecule ICAM-1 in the lumbar vasculature. In the lumbar region with a preserved blood spinal cord barrier (BSCB), pronounced gray matter infiltration by myeloid cells was detected as early as 24 hours after SCI. This cellular infiltration is indicative of active recruitment of cells throughout the endothelium.

In the lumbar region after thoracic SCI an increase in the expression of MMP-9, inflammatory cytokines IL-1β, interferon (IFN)γ, chemokine CCL2, chemokine (C-X-C motif) ligand 2 (CXCL2), cyclooxygenase 1 (COX-1), receptors chemokine (C-C motif) receptor 2 (CCR2) and Ly6C has been identified [18].

A more pronounced infiltration of myeloid cells in the lumbar region compared to the cervical region observed in this experimental model may be associated with differences in the microvasculature in these regions. Thus, in mice, despite the fact that the density of pericytes in the capillaries of the cervical and thoracic spinal cord does not differ, the pericyte coverage indicator in the cervical region is higher than in the lumbar region [44]. Reduced pericyte coverage is correlated with increased myeloid cells permeability. It is highly likely that the structural differences in microvessels may be one of the reasons for more pronounced myeloid infiltration in the lumbar region after trauma in the thoracic region.

In SCI, MMPs also play an active role in contributing to pathological changes. Of all the MMPs, the most studied is MMP-9, which is present in the intact brain in the meninges and neurons. In addition, MMP-9 is detected in blood vessels, neutrophils, and macrophages [45]. Expression of MMPs increases rapidly during the first week after injury and is found in glia, macrophages, neutrophils, and vascular elements in the injured spinal cord [46,47]. MMPs increase the permeability of the BSCB and are involved in destructive inflammatory events and phagocytosis [47].

MMPs cleave the main components of extracellular matrix that control the growth of axons by releasing damage-associated molecular patterns (DAMPs), such as chondroitin sulfate proteoglycans (CSPGs) and tenascin fragments, which increase inflammation and neurotoxicity [48]. MMP inhibitors, such as the anti-inflammatory drug minocycline, which has been extensively studied in SCI, have a neuroprotective effect [49]. Through the modulation of early vascular shifts and BSCB status, MMPs indirectly limit the recovery of function [46,50].

Myeloid infiltration is believed to be a consequence of an increase in MMP-9 at the primary lesion and in regions distant from the injury epicenter. As an example, after thoracic SCI, an increase in MMP-9 was also shown to be associated with inhibition of motor function in the lumbar region [22]. Therefore, it can reasonably be assumed that an increase in the presence of MMPs is the one of the main causes of post-traumatic myeloid infiltration and concomitant inflammatory toxicity in the spinal cord.

It has been suggested that an increase in MMPs in the primary lesion site results in the appearance of MMPs and possibly other cell injury molecules such as DAMPs in the cerebrospinal fluid (CSF). This, in turn, leads to a change in vascular permeability for myeloid cells in the remote area, which can cause an additional increase in MMPs in this area and, regardless of MMP presence, have a deteriorating ef-

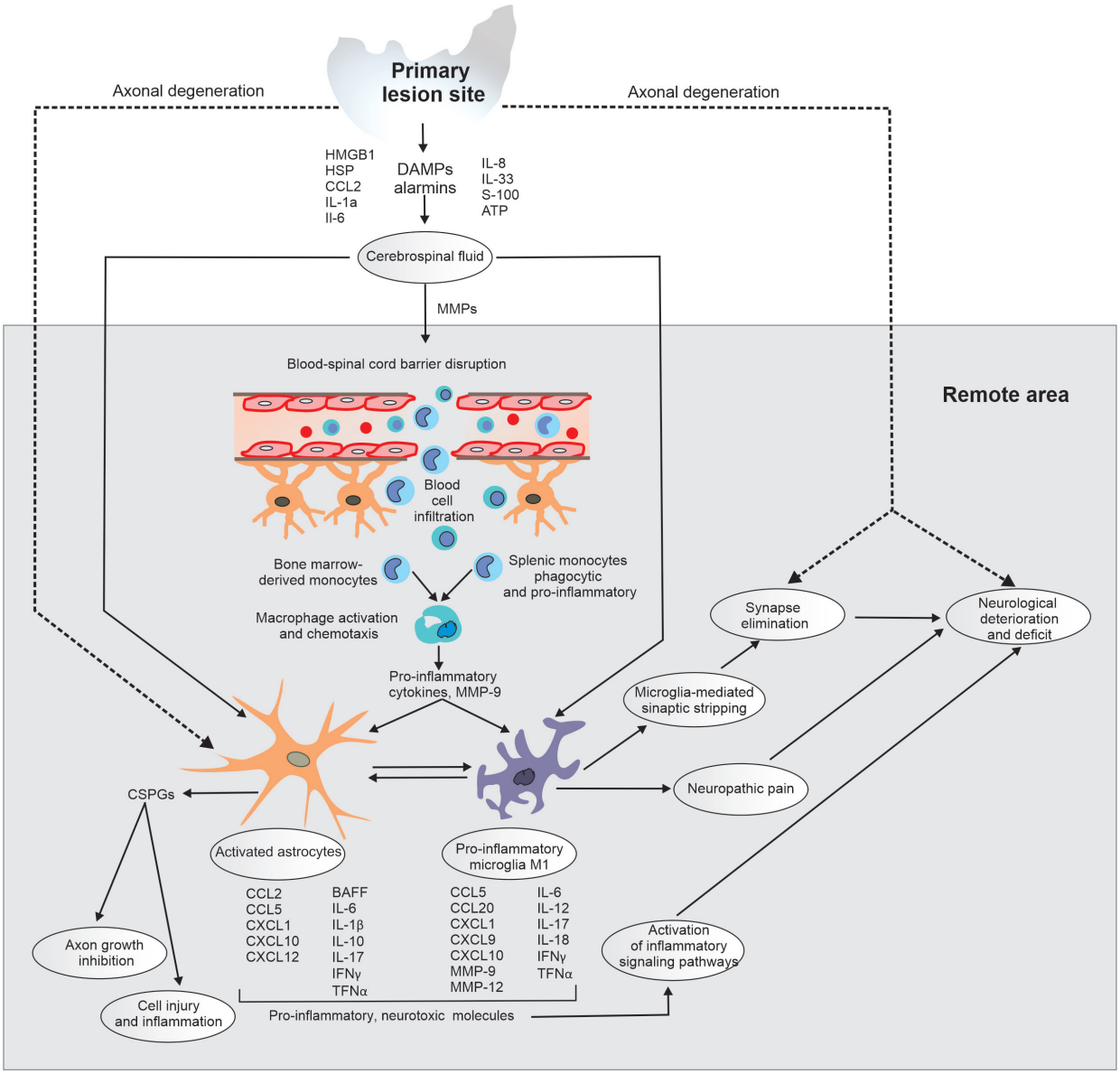

Fig. 1. Hypothesized mechanism of lesion-remote reactions in spinal cord injury. The area of primary injury is the source of numerous neurotoxic molecules that enter the cerebrospinal fluid. These molecules, primarily MMPs, disrupt the blood-spinal cord barrier in distant area, leading to tissue infiltration with pro-inflammatory bone marrow and splenic macrophage progenitors. Activated macrophages release pro-inflammatory cytokines and MMP-9, which in turn induce astrocytes and microglia toward the pro-inflammatory phenotype. Degeneration of the axons that projected to the remote area leads to the elimination of synapses and neurological deficit. Astrocytes react to axon degeneration and elimination of synapses, passing into a reactive state. Reactive astrocytes produce CSPGs that inhibit axon growth and damage cells. In addition, reactive astrocytes, together with microglia, produce and secrete numerous pro-inflammatory and neurotoxic molecules that activate inflammatory signaling pathways, leading to synaptic depletion and neurological deterioration. BAFF, B-cell activating factor; CCL, chemokine (C-C motif) ligand; CSPGs, chondroitin sulfate proteoglycans; CXCL, chemokine (C-X-C motif) ligand; DAMP, damage-associated molecular pattern; IFN, interferon; HMGB1, high-mobility group protein box-1; HSP, heat shock protein; IL, interleukin; MMP, matrix metalloproteinase; S-100 protein; TNF, tumor necrosis factor.

fect on spinal structures (Fig. 1). The possibility of an increase in MMP-9 in a remote area due to the migration or activation of myeloid CD11b^{+}/CD45^{high} cells and/or resident microglia (CD11b^{+}/CD45.1^{-}) in this area needs to be confirmed. Be that as it may, is it clear that MMPs are active players in the pathobiology of SCI, although their exact role requires further examination.

Future studies are needed to follow up on the fundamental aspects of transmigration, activation and behavior of myeloid cells in regions remote from the primary injury site. For the remote area, the ability for microglia to recruit myeloid cells should be established, for example, by

the production and secretion of the monocyte chemoattractant CCL2, which occurs at the epicenter of traumatic injury. It is also necessary to show that myeloid cells in the remote site, as well as in the epicenter of the injury, maintain the cytotoxic microglia phenotype. The bone marrow-derived cell phenotype in the remote area also requires clarification, as this characterization has only been performed for myeloid cells in the epicenter of damage and the area directly adjacent to it [38,51].

To summarize the role of myeloid cells infiltration in the remote area, it can be concluded that their presence here may impair functional recovery. This is especially important in relation to the lumbar region, where central pattern generators (CPGs) are located playing an important role in comprehensive locomotor outcomes. The same area includes a network of motor synergy encoding (MSE) interneurons, that is extremely important in coordinating the neural input and complex movements [52]. Therefore, therapies or drugs targeting at preventing BSCB disruption may be a proposing prospect for the treatment of SCI.

5. Microglia

SCI causes a multiphasic immune response, the key component of which is microglia activation [53]. When bone marrow-derived myeloid cells populate the epicenter of damage, resident microglia are predominantly present in the perilesional area [54]. In response to SCI, multiple signaling cascades mediate the upregulation of pro-inflammatory cytokines in rapidly activated microglia. After secondary SCI, advanced oxidation protein products induce microglia-mediated neuroinflammation via the mitogen-activated protein kinase (MAPK)-nuclear factor kappa B (NFκB) signaling pathway and pyroptosis [55].

Pro-inflammatory M1-polarized microglia demonstrate the ability to induce neuronal loss after SCI [54]. The mechanism of neuronal death involving microglia has been characterized in sufficient detail in various pathologies. Microglia is a proven killer of neurons in neurotrauma [54], neurodegenerative diseases [56,57], ischemic stroke [58], etc. Studies show that the neurons themselves are the source of signals for the activation of microglia, which, in turn, kills the neurons. An example of such signals is the cysteine–cysteine chemokine ligand 21 (CCL21), which is released from glutamate-treated neurons and acts on microglia through chemokine (C-X-C motif) receptor 3 (CXCR3) [59,60].

Microglial cells are now recognized as key players in CNS synaptic changes [61] as they are shown to interact with synapses in both healthy and disease conditions [62]. For example, microglia are known to play a key role in synapse elimination, which is regulated by complement components C1q and C3b [63]. Microglia recognize these components deposited onto synaptic membrane and engulf synapses via a mechanism that is not entirely understood. Loss of synapses, along with ischemia and inflammation, causes neuronal stress. Consequently, stressed neurons expose phosphatidylserine, which binds to complement component C1q, and then binds to microglial low-density lipoprotein receptor-related protein [57,58]. The role of C1q in the elimination of synapses has been shown in SCI, which seems to be mediated by the mechanism described above. Moreover, findings suggest that complement-mediated synapse elimination is the primary mechanism underlying the neurodegeneration in SCI [64]. Deficiency in the complement C1q improves functional locomotor outcome after SCI [65]. The precise role of C1q and C1q-associated molecular and cellular mechanisms in synaptic emission in a remote area of SCI remains to be established.

Upon damage to the CNS, activated microglia appear not only in the primary lesion site, but also in distant areas [59,60,66]. For example, after a mid-thoracic moderate contusion injury, microglial activation was shown in the lumbar spinal cord. This activation was accompanied by an increase in TNFα and IL-1β in the L5 dorsal horns by 7 day post injury (dpi) and returned to the initial level by 35 dpi [5]. In this model, an increase in the levels of pro-inflammatory cytokines and an onset of allodynia was observed even in the thalamus. Inhibition of these molecules in the acute period can restrain microglial activation and reduce neurological deterioration and deficit not only in the area of damage, but also in the remote area, where microglial cells are also activated.

In intact tissue, neuronal regulatory molecules influence microglia, thus inhibiting its activation. When damaged, this control is disrupted, leading to the activation of microglia [67,68]. One of the consequences of remote activation of microglia is neuropathic pain [5,60,69,70].

Furthermore, molecules that appear in the CSF after SCI, known as protein biomarkers of SCI, can be considered as signals in the mechanism of remote microglia activation (Fig. 1). Pro-inflammatory cytokines, chemokines, MMPs, and DAMPs are the most likely candidates contributing to the activation process [5,71,72]. These damage markers can activate microglia throughout the spinal cord and have a negative impact on neuronal survival along the entire rostro-caudal axis of the spinal cord. It can be expected that the most vulnerable area of the spinal cord will be the enlargements, where the neurons are concentrated in large numbers.

Another aspect of the negative influence of microglia in the area of damage concerns the possible triggering effect of activated microglia in the formation of the pro-inflammatory neurotoxic phenotype of astrocytes [73], however, this concept remains largely unexplored.

6. Astrocytes

After mild-contusion thoracic SCI, an increase in a specific marker of astrocyte reactivity, GFAP, was found only in the epicenter of the injury, but not in the remote

sites of the spinal cord [19]. This astrocyte reactivity did not coincide with the reaction of microglia, which was significantly activated in the area of damage, with the activated microglia also spreading to the lumbar enlargement. In a rat model of thoracic displacement injury, Detloff *et al*. [5] also noted that they did not find any evidence of astrocyte hypertrophy or increased GFAP in L5 dorsal horns. However, later, another group showed an increase in GFAP immunoreactivity in the rat lumbar dorsal horn 30 days after T10 moderate SCI [74]. In the lumbar dorsal horn, an increase in GFAP was documented on day 8, followed by decrease by day 28, as well as a decrease in glial glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1) levels after T8 contusion injury [75]. Restoration of GLAST and GLT-1 was not accompanied by any global effect on the activation of astrocytes and microglia, nor by changes in the expression of cytokines and growth factors [75]. In the lumbar spinal cord, gamma-aminobutyric acid (GABA)Aγ2 receptor subunit was elevated in astrocytes surrounding MNs approximately 3 months after a complete mid-thoracic spinal cord transection in postnatal rats [76].

Astrocytes and microglia release and respond to cytokines and play a significant role in the immune response in the CNS. The remote downregulation in GLAST and GLT-1 expression in the lumbar dorsal horn appears to be related to the influence of the pro-inflammatory cytokines TNFα [77–80], IL-6 [81], and IL-1β [82].

After a contusion to the thoracic spinal cord, an increased level of the astrocyte marker aquaporin 4 (AQP4) was observed to spread away from the injury epicenter to cervical and lumbar segments, but only in chronically injured spinal cords [83]. Of interest, hypertrophied astrocytes were also revealed in the most rostral but not caudal segments of the lumbar enlargement [24].

Among the cellular and molecular changes in the remote area associated with astrocytes, particular attention should be paid to extracellular components that are inhibitory to neural regeneration and plasticity. Data on this subject are sparse and relate predominantly to CSPGs known as markers of the reactive astrocytes. CSPGs inhibit axonal growth, neuronal survival, and, acting as DAMPs, support inflammatory and neurotoxic responses in CNS injury [48] (Fig. 1). After a severe contusion in the thoracic region, neurocan, a member of lectican proteoglycan family, significantly increased in the cervical and lumbar regions, as was seen in the epicenter of the lesion [20]. An elevation in neurocan in the distal spinal cord correlated with an increase in reactive astrogliosis. On the contrary, the levels of the aggrecan and brevican, which are of the same lectican family, decreased sharply at the site of injury and remained unchanged in the distal segments. In the CSPGs family, the transmembrane polyfunctional molecule NG2 (CSPG4) has attracted special attention in relation to the CNS regeneration. The extracellular domain of this proteoglycan has been shown to modulate neuronal electrogenesis, affect axon growth, and stimulate synaptogenesis [84–86]. Moreover, the expression of NG2 proteoglycan (CSPG4) increased in the lumbar region, but not in the cervical region. Long-term maintenance of elevated neurocan expression in the gray matter of the distal segments may contribute to the limitation of plasticity in the chronic phase [20]. Thus, astroglia can react away from the injury site and produce molecules that inhibit neural regeneration. If the role of reactive astroglia in the epicenter is recognized as positive in the context of limiting the lesion spreading, then, with the absence of clear signs of structural deterioration at a distance from the epicenter of damage, it can be postulated that remote activation of astrocytes, conversely, plays a negative role. In this regard, the possibility of transformation of neurotoxic A1 to neuroprotective A2 reactive astrocytes at a remote site should be evaluated, along with its related temporal parameters.

One of the reasons for changes in the behavior of astrocytes in the remote area may be associated with the anterograde axonal degeneration of the descending tracts and the remodeling of connections, reactions to the appearance of myeloid cells, and the influence of activated microglia [55,87]. Another cause for the activation of astrocytes in the remote area may be related to the previously-mentioned reaction of the spinal cord parenchyma to myeloid infiltration (Fig. 1). For macrophages there are two major polarization states, namely the classically activated pro-inflammatory type 1 (M1) and the alternatively activated protective type 2 (M2). In the acute phase of contusion SCI, a mixed reaction of M1/M2 macrophages is observed in the lesion site. M1 macrophages indirectly induce a reactive astrocyte gene expression pattern through the secretion of soluble factors [88]. M2-polarized macrophages, on the contrary, inhibit reactive astrogliosis [88]. M2-stimulated astrocytes, in turn, are able to reduce the proliferation of M1 and M2 macrophages and reduce TNFα production in M1 macrophages [88,89]. Whether such a situation also occurs in remote areas remains unclear.

In remote areas, the reaction of astrocytes may be due to the influence of previously-activated microglia in this area. Microglia are more sensitive to the action of damage-associated molecules and pathogens than astrocytes. These molecules activate M1 microglia through TLR4. Thus, DNA-binding high-mobility group protein box-1 (HMGB1), which appears during SCI in CSF [90,91], can trigger microglial activation via TLR4 and increase TNFα production, which, in turn, stimulates microglia to release a large amount of HMGB1 for greater microglia activity. Microglia are activated early in the pathological process and exhibit the M1 phenotype, producing inflammatory signals, such as IL-1, TNFα, and complement component C1a, that activate astroglia to form A1-polarized cells. As the pathology progresses, M1-like microglia switch to the M2 phenotype, which communicates with A2 astrocytes [55]. Thus, considering the high activity of microglia in the

tissue of the remote site, the distinct influence of reactive microglia on astrocytes in this site seems quite probable.

7. Locomotor Circuit Reorganization

The lumbar enlargement is of particular interest for elucidating the mechanisms of the lesion-remote effects. Neural circuits in the lumbar region are essential for maintaining motor function. Despite the traditional focus on the primary lesion, the area of lumbar enlargement is becoming an increasingly relevant therapeutic target for restoring motor function in chronic SCI. Locomotor function, mediated by lumbar neural circuitry, is modulated by descending spinal pathways including the corticospinal, rubrospinal, serotonergic, and dopaminergic pathways and, to no lesser extent, descending propriospinal pathways [92]. The plasticity of intact chains serves as the basis for improved functional recovery after SCI. Spontaneous functional recovery is hypothesized to result from reorganization of the descending motor pathways unaffected by injury [93]. Moreover, disturbance of descending supraspinal commands disrupts the functioning of the central pattern generator (CPG) that is primarily located in the lumbar spinal cord [94].

SCI interrupts descending projections and denervates lumbar MNs. In lumbar MNs, thoracic contusion injury causes dendritic arbor reorganization and dendritic atrophy [95,96]. Synaptic connections of identified MNs innervating specific muscles (e.g., gastrocnemius and tibialis anterior) were studied using a model of complete transection of the rat spinal cord in the thoracic region [97]. This model showed a decrease to one third of the number of interneurons that form connections with MNs. MNs of different motor units differ in their vulnerability to axotomy-induced damage. Slight changes were found in the density and size of inhibitory and excitatory inputs on the perikarya of some identified MNs. Although, the number of connections with interneurons decreased on the perikarya of MNs for other motor units.

After thoracic SCI, an increase in the expression of glutamate decarboxylase 67 (GAD67), along with myeloid infiltration, was found in the lumbar region [17]. The significance of GAD67 dynamics for repair functions of neural networks in the lumbar enlargement is not entirely understood. However, it has been shown that restoration of its inhibition in an injured spinal cord leads to functional recovery [98]. However, the increase in GAD67 and early release of GABA may be associated with the initiation of spinal shock. On the other hand, a relative deficit of GABAergic mechanisms may contribute to spasticity [99]. In the lumbar spinal cord, upregulation of the ionotropic anion permeable channel GABAAγ2 receptor subunit in muscle-specific MNs was shown approximately 3 months after a complete mid-thoracic spinal cord transection in 5 day-old rat pups. At the same time, expression of the GABAAγ2 receptor subunit was differentially modulated on the soma of MNs for different muscles and astrocytes [76].

Activation type A γ-aminobutyric acid receptors depends on the gradient of chloride (Cl^-) across the plasma membrane. This gradient is mainly established by the K^+-Cl^- co-transporter 2 (KCC2) that extrudes chloride out of the neuron. Recently, this molecule has been actively studied within the framework of regeneration problems in the CNS. In SCI, a decrease in KCC2 expression is associated with the development of spasticity, and maintenance of KCC2 inhibits this effect. KCC2 expression is suppressed in MNs caudal to SCI site [100]. Complete transection of the rat spinal cord in the thoracic region showed a decrease in KCC2 in the lumbar MNs' membranes, which led to depolarization of the Cl^- equilibrium potential and a decrease in the strength of postsynaptic inhibition [97]. In a model of bilateral thoracic hemisection, in which the lumbar spinal cord is deprived of all direct brain innervation, but inactive relay circuits are preserved, KCC2 expression in lumbar inhibitory neurons leads to the restoration of inhibition and functional recovery [98]. KCC2 is one of the most studied molecules that controls electrogenesis and the critical process of inhibition in neurons remote from the area of incomplete SCI.

Injury activates plastic potential in the spinal cord by downregulating KCC2, which reduces GABAergic inhibition. This promotes learning within the context of neurorehabilitation, but also fuels over-excitation and nociceptive sensitization [101].

After a complete thoracic transection, despite the depression of the presynaptic input, cholinergic activity and synaptogenic potential in the MNs of the lumbar region were maintained, as evidenced by the absence of shifts in the expression of genes of choline-related molecules choline acetyltransferase (ChAT) and vesicular acetylcholine transporter (VAChT) [12]. Parallel molecular genetic analysis revealed a significant decrease in markers of neuronal activity c-fos, CaMK2a, and the glutamate receptor AMPAR3. Preservation of the synaptogenic potential and activity of MNs after injury in the distant part of the spinal cord can be considered as a positive feature, potentially contributing to the restoration of neural connections and functional recovery. Under these conditions, in the lumbar region, the expression of growth factor receptors GDNF (c-Ret, GFRa1) and neurotrophin receptor p75 significantly increased, while the expression of the tropomyosin receptor kinase (Trk) family of neurotrophin receptors TrkA, TrkB, and TrkC did not change [12]. As for the activation of some neurotrophic factors in the area of impaired innervation, it seems to have positive effects for the survival of denervated neurons, the possibility of axonal regeneration, and restoration of function. At the same time, it remains unclear why the expression is increased for some neurotrophic factors and not changed for others.

In conclusion, we note once again that among the factors that affect the remote lumbar region after trauma in the proximal region, it is necessary to point out the blockage of

descending projections to the lumbar spinal cord and deneravation of this distant area. It has become increasingly clear that neural networks in the remote area may be affected by other previously-mentioned factors, such as endogenous DAMPs and alarmins (a subset of endogenous DAMPs) that appear in the CSF after trauma, as well as disruption of the BSCB followed by subsequent monocyte infiltration. The separate evaluation of the effect of each of these factors in the pathological response in the lumbar spine is critical information that can be leveraged in the development of new therapeutic approaches in order to more effectively restore motor function.

8. Bioactive Molecules and Biomarkers in CSF

As a result of primary and secondary damage to the spinal cord, some molecules appear in CSF, which is considered as a cardinal sign of disintegration of cells and extracellular matrix in the immediate impact area. CSF biomarkers are used as tools in assessing severity, prognosis, and treatment and rehabilitation regimes of patients with SCI [102,103]. Damage biomarkers reflect the degree of involvement in the pathological process of the entire organ along the rostro-caudal axis. Hence, it is important to evaluate the potential role of these bioactive molecules in the lesion-remote effects.

In SCI, markers of neuronal disintegration appear in CSF, such as neuronal cell body injury marker ubiquitin C-terminal hydrolase-L1 (UCH-L1), axonal injury marker phosphorylated neurofilament-H (pNF-H), and tau protein [104–108], are hypothesized to potentially affect not only neurons, but also glia in the remote area. For example, it has been shown that CSF level of GFAP is elevated in patients with chronic spinal cord injury and neurological deterioration [108]. Astrogliosis/astroglial injury markers GFAP and GFAP breakdown products GBDPs (GBDP44, GBDP38) [105–109] may also affect neural cells and circuits in the remote area.

After neurotrauma increased concentration of extracellular matrix components brevican, tenascin-C and tenascin-R were found in the CSF [110,111]. Moreover, CSPGs act on neurons through the receptor-type tyrosine-protein phosphatase sigma (PTPsigma), Nogo receptor 1 (NgR1), and leukocyte common antigen related phosphatase (LAR) receptor complexes, which activates the RhoA/ROCK signaling pathway, followed by growth cone collapse, neurite retraction, and neuronal apoptosis [112]. After SCI, small GTPase RhoA participates in neuronal apoptosis in a way that demonstrates an effect of axotomy or other pathological mechanisms [113]. RhoA is considered as a point of convergence for the inhibition of both axonal regeneration and neuronal survival after SCI [114].

It seems quite likely that CSF neuroinflammation cytokines such as IL-1β, IL-6, IL-8, IFNγ, chemokines CCL2, CCR2, CXCL2, MMP-9, and other molecules act as DAMPs [105,106,109] and in a remote area can either directly affect resident target cells or modulate microglia and migrating monocyte/macrophage-mediated effects, as previously described. On the other hand, examples of endogenous protein DAMPs and alarmins are IL-1α, IL-33, HMGB1, and the S100 class of proteins, all of which bind specific receptors and promote initiation of inflammation after injury [90,115,116]. Of note, ubiquitously-expressed DNA-binding protein HMGB1 is a potent systemic inflammatory cytokine. Increased CSF levels of HMGB1 have been shown after SCI [91]. HMGB1 acts through the HMGB1/TLR4/NFκB signaling pathway. Inhibiting the HMGB1-RAGE axis prevents pro-inflammatory polarization of macrophages/microglia through the RAGE-NFκB pathway and leads to significantly decreased neuronal loss and demyelination after SCI [117].

Another nuclear alarmin, IL-33, which is expressed in gray matter oligodendrocytes and astrocytes, is released from injured tissue, appears in CSF, and drives chemokine production critical for monocyte recruitment after SCI [118]. DAMPs and alarmins promote apoptosis and necrosis, and activate phagocytosis and an immune response through the stimulation of pattern recognition receptors (PRRs) [119].

Thus, a change in the chemical composition of the CSF may be a decisive factor in identifying pathological changes in areas of the spinal cord remote from the epicenter of injury. As has already been demonstrated, biomarkers in the CSF already allow for the severity of injury to be determined and, importantly, for the potential for functional recovery to be predicted [105,109].

9. Perilesional Zone — Adjacent Segments

In the previous sections of the review, we have considered reactions in areas far away from the injury site. In this section, we will touch on the consideration of the cellular and molecular reactions in 1–2 spinal segments adjacent to the area of damage. The area of interest does not include lesion penumbra, moving gradually away from it. Gray matter in these segments includes multicellular components such as reactive glia, astrocytes, microglia, oligodendrocytes, and NG2 cells. These cells are preserved and are generally identified as cells with an unchanged or slightly changed structure. Here, and especially in the immediate vicinity of the astroglial scar layer, intact tissue areas are interspersed with areas displaying architectural disruption. In the perilesional zone, areas of significant gray and white matter tissue degeneration and inflammation alternate with areas of intact neurons and axons [120]. There are also differences in the distribution of myeloid cells that are found at a distance from the lesion site; the infiltrating cells at the margins of the lesion site are Ly6C$^+$, whereas the distal ones are Ly6C$^-$ [40]. Within two spinal segments, rostral and caudal to the injury site, the acute tissue swelling was revealed prior to chronic atrophy along with rostro-caudal

asymmetries in white and gray matter volume loss [121].

The perilesion perimeter in the ventral horns (VH) was characterized by shifts in the expression of molecules that control neuroplasticity and axonal growth [122]. After severe thoracic SCI in a rat model, in the VH of 1–2 adjacent caudal segments a significant decrease was shown in the number of descending serotonergic axons that control basic locomotion [123].

Astrocytes near the injury site are actively involved in the remodeling of the extracellular matrix and synthesis of CSPGs that specifically inhibit axonal growth. Analysis of the astrocyte marker GFAP showed increased expression in adjacent segments, spreading more distally from the injury site [122,123]. These data indicate that the inhibitory effect of these molecules on axon growth manifests not only in the well-known immediate vicinity of the injury epicenter, but also at a distance from it.

In the VH of 1–2 segments adjacent to the primary lesion, an increase in CSPGs is shown in both the acute and chronic phases. In this area, lecticans exhibited different temporal expression patterns after SCI. Neurocan peaked at 7 dpi, while brevican and versican were maximally expressed at 14 dpi. Proteoglycan levels exhibited different changes after SCI in areas near neuronal soma and in areas distant from them [122]. Thus, an increase in CSPGs not only within the astroglial scar, but also in adjacent segments would be expected to inhibit axon growth, induce caspase-3 dependent apoptosis in neural progenitor cells, oligodendrocyte progenitor cells and oligodendrocytes that is mediated by both receptor tyrosine phosphatase sigma (RPTPσ) and LAR. In the same area, an increase in CSPGs will likely, as elsewhere, limit the repair process by maintaining a pro-inflammatory immune response and inhibit the switch of the microglia/macrophages phenotype to the pro-regenerative M2 phenotype [124,125]. In segments adjacent to the epicenter of severe contusion injury, these shifts in the expression of CSPGs coincided with the appearance of reactive astrocytes and a reduction in astrocytic glutamate transporter 1 (GLT-1). Significant downregulation in GLT-1 expression was revealed in the astrocyte processes both directly in contact with the neuronal perikarya and located at a distance from them [122]. Paradoxically, astrocyte perisynaptic processes marker GLT-1 was only increased in expression in 2–3 segments adjacent to the epicenter, which was measured both at 7 and 30 dpi. At 30 dpi, the square occupied by synaptophysin spots on the MNs perikarya and dendritic spines decreased [123]. These data indicate that, at least in the caudal direction, the synaptic loss is observed both near and at the already mentioned above greater distance from the area of damage. These changes in the glutamate transporter, pre- and postsynapse molecules suggest a dysfunction of synapses in the perilesional zone and indicate a high probability of disturbances in the same area of intercellular interactions in neuron-astrocytic and inter-astrocytic networks, which are implicated in the propagation of Ca^{2+} waves [126,127].

Of note, there is a gradient of NG2/CSPG4 expression, with the highest level focused close to the injury site. A decrease in NG2/CSPG4 correlates with a decrease in the number of NG2 cells more distally [123]. After SCI, in segments 1–2 adjacent to the epicenter, the GFAP-positive processes expression of NG2/CSPG4 depends on the distance of these processes from the perikaryon of neurons. For example, increased proximity to the perikaryon results in increased expression of NG2/CSPG4 [122]. These data indicate the involvement of neurons in the local regulation of NG2/CSPG4 expression on the surface of adjacent astrocytes and, possibly, the cleavage of a functionally significant extracellular domain of this molecule, which can be included in the perisynaptic matrix to regulate the synaptic activity [84].

The Rho/ROCK/PTEN signaling pathway is actively involved in pathological reactions in SCI. In adjacent segments following severe thoracic contusion injury, the expression of RhoA and phosphatase as well as tensin homolog deleted on chromosome 10 (PTEN) increased and the expression of the postsynaptic density protein 95 (PSD95) reduced [128]. Under the same experimental conditions, an upregulation was shown for other small GTPase cdc42, which coincided with increased expression of CSPGs and reduced GLT-1 expression in astrocytic processes [122]. As a result, it can be assumed that Rho/ROCK/PTEN activation in the astrocytic processes may be important for their remodeling during the posttraumatic synapse repair in adjacent segments.

Thus, in segments adjacent to the area of primary damage, the restructure of the neural network is apparent. Astrocytes are actively involved in this process. In conclusion, it can be stated that the astroglial scar, despite its positive role in preventing the spread of destruction to intact tissue, is limited in its ability to contain detrimental reactions in neighboring tissue.

10. Conclusions

In SCI, pathological changes have been revealed in areas of CNS remote from the zone of primary injury. These reactions are most commonly observed in the lumbar region with an injury in the thoracic region. These reactions were most often observed in the lumbar region with trauma to the thoracic region. These reactions after the trauma to the thoracic region were usually observed in the lumbar region. There are few studies performed in other parts of the spinal cord and they evaluate only few parameters and therefore are less informative. The apparent cause of these reactions in the remote area is posttraumatic degeneration of axons that pass through the area of primary injury and project into the remote area. Axonal degeneration causes elimination of synapses and disruption of neural circuits in a remote area, where the possibility of retrograde and anterograde degeneration of neurons is not excluded. In general, these

changes in the remote area exacerbate the detrimental effect of primary damage as the main cause of the functional deficit. Recently, other mechanisms of remote injury that are not directly related to the aforementioned axonal degeneration have received increasing attention. Such mechanisms include neurotoxic molecules entering the CSF from the area of the primary focus and negatively affecting the entire CNS. Also, MMPs from CSF cause BSCB disruption and immune cell infiltration into the spinal cords and remote areas. Until now, the tissue response to axonal degeneration has not been separated from the detrimental influence of CSF neurotoxic molecules and the effect of blood cell infiltration in the remote area. Data are accumulating on spatiotemporal dynamics of neurodegeneration in the remote rostral and caudal areas to the injury site. Spatiotemporal analysis of the gray and white matter of the spinal cord at a distance from the epicenter of injury shows the differential pattern and severity of pathological reactions, gene expression, and molecular regulation in the rostral and caudal regions. However, little is known about the reasons for these differences. When studying the pathophysiology of SCI, one should also consider reactions in segments adjacent to the primary lesion, i.e., in the tissue located outside of the astroglial scar. It is becoming increasingly clear that the assessment of cellular and molecular changes in this area is important for evaluating the potential for long-distance axonal growth. In conclusion, posttraumatic reactions in distant regions have demonstrated distinct impacts on the pathology of SCI, and must be taken into account when researching prospects for functional outcomes. Thus, remote area is a promising target for the development of therapeutic interventions in the treatment of SCI.

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