REVIEW

Mesenchymal stem cells and the neuronal microenvironment in the area of spinal cord injury

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Abstract

Cell-based technologies are used as a therapeutic strategy in spinal cord injury (SCI). Mesenchymal stem cells (MSCs), which secrete various neurotrophic factors and cytokines, have immunomodulatory, anti-apoptotic and anti-inflammatory effects, modulate reactivity/phenotype of astrocytes and the microglia, thereby promoting neuroregeneration seem to be the most promising. The therapeutic effect of MSCs is due to a paracrine mechanism of their action, therefore the survival of MSCs and their secretory phenotype is of particular importance. Nevertheless, these data are not always reported in efficacy studies of MSC therapy in SCI. Here, we provide a review with summaries of preclinical trials data evaluating the efficacy of MSCs in animal models of SCI. Based on the data collected, we have tried (1) to establish the behavior of MSCs after transplantation in SCI with an evaluation of cell survival, migration potential, distribution in the area of injured and intact tissue and possible differentiation; (2) to determine the effects MSCs on neuronal microenvironment and correlate them with the efficacy of functional recovery in SCI; (3) to ascertain the conditions under which MSCs demonstrate their best survival and greatest efficacy.

Key Words: *spinal cord injury; mesenchymal stem cells; survival; migration; Rho/ROCK/PTEN; astrocytes; microglia; myelin-forming cells; axon growth; tissue integrity*

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Introduction

Spinal cord injury (SCI) leads to activation/inhibition of numerous cascades of intracellular and intercellular communication, and a change of transcription and translation levels of different genes involved in post-traumatic response (Mortazavi et al., 2015; Witiw and Fehlings, 2015; Quadri et al., 2018). Despite advances in understanding of the pathogenesis of a traumatic injury of the nervous system, current treatments for SCI are insufficient. There is a compelling need for novel treatment approaches based on the understanding of molecular and cellular mechanisms of SCI. Cell-based therapy is one of the approaches to prevent consequences of traumatic injury and to maintain the regeneration of nerve fibers. The use of stem and progenitor cells is aimed at restoring a tissue matrix with pathways to guide axonal growth, maintenance and re-myelination of axons, a trophic supply of injured and viable neurons, and the proliferation of the spinal cord's own stem cells (Sabapathy et al., 2015; Assinck et al., 2017; Galieva et al., 2017).

At present mesenchymal stem cells (MSCs) are considered a promising material to stimulate neuroregeneration, related to their high biosafety and immunomodulatory properties; their ability to synthesize neurotrophic and proangiogenic factors by promoting the survival and regeneration of neurons and the growth of axons and angiogenesis (Laroni et al., 2015; Qu and Zhang, 2017; Khan et al., 2018). Various methods of MSC transplantation, even under conditions of multiple administrations, cause neither toxicity, nor induce tumor formation in animals and humans (Ra et al., 2011; Barkholt et al., 2013; Rengasamy et al., 2016). Preclinical studies demonstrate positive and promising results of MSC-based therapy in SCI. Attempts are being made to discover cellular and molecular mechanisms of MSC-mediated effects on reactivity/phenotype of astrocytes and microglia, the maintenance of a pool of myelin-forming cells and neurons, axonal growth and tissue integrity in general. Methods and sources for obtaining MSCs, as well as conditions of their culture might have a significant impact on the metabolic and secretory profile and the membrane expression profile of a resulting cell-based product. As the paracrine mechanism of MSCs action determines their therapeutic effect, special attention is paid to important aspects such as the preservation of MSCs viability and the optimal delivery of secreted therapeutic factors by them into the area of SCI. However, there is still a necessity to understand the cellular and molecular mechanisms by which MSCs ameliorate a SCI outcome (Park, 2018).

This review includes summaries of preclinical trials data evaluating the efficacy of MSCs in animal models of SCI. Based on the data collected we have tried (1) to establish the behavior of MSCs after transplantation in SCI with an evaluation of cell survival, migration potential, distribution in the area of injured and intact tissue and possible differentiation; (2) to determine effects MSCs on neuronal microenvironment and correlate them with the efficacy of functional

recovery in SCI; (3) to ascertain the conditions under which MSCs demonstrate their best survival and greatest efficacy.

An electronic search of the Medline datebase for articles describing animal model of SCI from 1992 to 2018 was performed using the folowing conditions: SCI model (animal: rats, mice, pigs, dogs, non-human primates), MSC transplantation, animal behavior/physiology. The results were further screened by title/abstract and non-SCI experiments and review articles were excluded.

Behavior of MSCs in the Area of SCI

Essential cytogenetic processes such as the viability of MSCs, their migration potential, proliferative activity, self-maintenance and differentiation are controlled by numerous molecular signals from their microenvironment. These signals converge *via* specific receptor inputs on intracellular signaling pathways whose number is quite limited. Despite a large number of studies where MSC viability in the area of SCI was evaluated, to date there are still contradictory data. **Additional Table 1** contains the published data available on the duration of MSC survival in the area of SCI, their migration potential and possible differentiation.

The behavior of MSCs in the area of SCI depends on the route (intraspinal, intrathecal, intravenous and others) and type of cell transplantation, (xenogenic, allogenic), methods of cell labeling (green fluorescent protein-transgenic mice/rats, antibodies, green fluorescent protein-expressing viral vectors, fluorescent nanoparticles and other tracers of cells) and imaging techniques (confocal microscopy, *in vivo* imaging instruments (IVIS) system *etc.*). The SCI model (contusion, compression, ischemia, hemisection or transection) can also play a great role in homing and survival of MSCs. The latter is due to the different nature of nervous tissue alterations leading to disimilar pathophysiological mechanisms. Among SCI models, the most suitable for clinical use is the model of a dosed contused injury of spinal cord (Gruner, 1992). As a result of this contusion, the destruction of the nervous tissue occurs is similar to the damage observed in humans, including gliosis, demyelination and cyst formation.

MSCs demonstrate good survival (for at least 4–8 weeks) after an intraspinal injection of allogenic cells in the area of SCI (Ryu et al., 2012; Takahashi et al., 2018a). The results obtained are associated with an increased expression by implanted MSCs of the prosurvival signaling factors such as Akt and extracellular regulated protein kinase 1/2. However, intraspinal injections of MSCs were shown preferential distribution in the spinal cord lesion site (Ryu et al., 2012; Ribeiro et al., 2015; Takahashi et al., 2018a) and less often rostrally and caudally from the epicenter (Nakajima et al., 2012). Neirinckx et al. (Neirinckx et al., 2015) detected no Cell Tracker Green labeled MSCs in the area of SCI at 4 weeks after an intraspinal injection that might be due to low signal retention of fluorescent dye data. For example, it has been previously shown that Cell Tracker Green CMFDA cannot be reliably used to evaluate the migration of bone-marrow derived angiogenic cells (Beem and Segal, 2013).

Intravenously implanted MSCs are capable of targeted migration towards the SCI epicenter (Kim et al., 2015; Ramalho et al., 2018). At the same time, they demonstrated a better survival rostrally from the injury epicenter with distribution both in the grey and white matter of the spinal cord and around the cavitation area (Yang et al., 2018). The data obtained by Matsushita et al. (2015) stand out from the studies available, who found no migration of intravenously implanted MSCs into either contused or intact spinal cords. The authors based the evidence on stabilization of the blood-spinal cord barrier and improved locomotor functions and related this with indirect effects (by means of secreted factors) of MSCs implanted in the spinal cord vasculature.

Intrathecal (an intraventricular injection is its special case) and intra-arterial injections of MSCs in SCI are less often used in preclinical trials of their transplantation. The latter is more often associated with technical difficulties of reproducing these manipulations. With the intrathecal injection there is a low MSC migration into the lesion site (Urdzíková et al., 2014; Krupa et al., 2018). This might have caused the lack of available data on long-term survival of MSCs in the area of SCI after such administration.

The application of MSCs combined with scaffolds on top of the injury has become increasingly popular due to the possibilities of clinical use of this cell-based therapy in SCI. This type of transplantation demonstrates good MSC survival (for at least ten weeks) in the area of SCI (Mukhamedshina et al., 2017a; Sabino et al., 2018), that might be due to the possibility of maintaining matrix-enclosed cells which create a specific microenvironment similar to the natural one. It should be noted that the available data on MSCs survival in their xenotransplantation in SCI are not significantly different when compared to similar options of allogenic cells transplantation (**Additional Table 1**). A comparative analysis of survival of MSCs derived from different sources (adipose tissue, bone marrow, umbilical cord blood and Wharton's jelly) in the area of SCI showed a shorter survival of bone marrow derived-MSCs (Ryu et al., 2012; Takahashi et al., 2018a). This might be due to a low expression level of chemokine (C-X-C motif) ligand (CXCL)12 in bone marrow derived-MSCs which can improve MSC survival and proliferation *in vitro* (Liu et al., 2011; Takahashi et al., 2018a).

The possibilities of unorthodox MSC plasticity/transdifferentiation were shown in induction medium culture *in vitro* (Reyes and Verfaillie, 1999; Hermann et al., 2004) and in experimental models of various pathologies when these cells were administered *in vivo*, including in SCI (Ryu et al., 2012; Sabino et al., 2018). Previously investigators have most actively described the possibilities of MSC transdifferentiation into the neural lineage, using the capabilities of these cells to acquire specific morphology and the expression of neuron and glial cell markers. However, video time-lapse microscopy of the MSCs culture showed that specific morphological alterations (MSC's assumption of a neural and glial cell shape) were not genuine transdifferentiation but resulted from degenerative changes when exposed to

the cell culture medium used to induce the neural lineage (Bertani et al., 2005). The expression of neural markers detected with immunocytochemistry takes place very rapidly as a rule for genuine transformation to occur. For example, Sabino et al. (2018) showed that on day 7 after application of MSCs combined with a fibrin matrix in the site of transection the transplanted cells had already started expressing Nestin, NG2, β-III tubulin, Vimentin, neurofilament (NF) and neuron specific enolase. In another study the MSCs injected into the area of SCI began to express NF160, NeuN and glial fibrillary acidic protein (GFAP) at eight weeks after transplantation (Ryu et al., 2012). However, the specificity of neural markers such as βIII-tubuline and NeuN raises doubts and their production might result from the increased expression of MSC-specific genes (Pontius et al., 2003). Immunophenotyping which analyzes few markers in the cells taken out of their physiological "context" is not considered to be sufficient evidence to identify a particular cell type (Vladimirskaya, 2007; Vellosillo et al., 2017).

Gene expression profiling which makes it possible to analyze the transcriptome of hundreds and thousands of genes can be the most convincing evidence of MSC transdifferentiation into non-mesenchymal cell types. However, in this respect MSCs are also considered to be a complex object owing to the very high gene expression by these cells. For example, the number and diversity of MSC expressed genes are significantly higher than those of hematopoietic stem cells (Silva et al., 2003). Expression profiling of more than 21,000 genes performed with chemical induction of MSC neural differentiation *in vitro* demonstrated the lack of transcription of nervous tissue-specific genes and activation of the same genes as in MSC transformation into other cell types (Bertani et al., 2005). Thus, it was concluded that there is no absolutely reliable evidence of MSC transdifferentiation *in vitro* into non-mesenchymal cell types.

Rho/ROCK/PTEN Signaling Pathway in Mesenchymal Stem Cells

Rho/ROCK/PTEN (small Rho GTPases, Rho-associated kinase, phosphatase and the tensin homolog that is deleted on chromosome 10) is one of the key intracellular signaling pathways where numerous molecular signals from the microenvironment converge *via* special receptor inputs. Despite the significant interest of MSC researchers, the evidence disclosing the role the intracellular Rho/ROCK/PTEN signaling pathway plays in phenotype control, survival, proliferation and migration potential of MSCs is still lacking. ROCK inhibitors were shown to improve the physiological function of cryopreserved MSCs significantly within a cytoskeleton (Bit et al., 2017).

The effect of inhibiting the intracellular Rho/ROCK/PTEN signaling pathway on the phenotype and behavior of cells when transplanted *in vivo* in order to prevent neurodegeneration has not been studied. In this respect two approaches can be considered related. The first involves the management of neurodegeneration and stimulation of neuroregeneration using inhibitors of RhoA (Lord-Fontaine et al., 2008; McKerracher and Anderson, 2013; Drummond et al., 2014; Wu and Xu, 2016), ROCK (Furuya et al., 2009; Chiba et al., 2010; Yu et al., 2016; Li et al., 2017) and PTEN (Chen et al., 2015; Knafo et al., 2016) in different experimental models. The second targets the silencing of genes encoding for key molecules of the Rho/ROCK/PTEN signaling pathway through genetic constructions such as anti-sense oligonucleotides (Huang et al., 2015), microRNA (Lu et al., 2015), small interfering RNA (Wen et al., 2014; Ding et al., 2015; Gwak et al., 2017), and RNA spikes (Zukor et al., 2013; Haws et al., 2014; Lewandowski and Steward, 2014), inserted with viral vectors directly into spinal cord structures as well as using the Cre-Lox recombination technology (Willenberg et al., 2016).

There are data on a combined use of selective inhibitors of small GTPase, ROCK and PTEN with stem cell transplantation in order to prevent consequences of neurodegeneration. For example, the administration of fasudil, a ROCK selective inhibitor, for two weeks combined with transplantation of bone marrow-derived stromal cells significantly increased the number of regenerating axons in the corticospinal tract ingrowing through the area of SCI in rats but did not enhance the locomotor recovery (Chiba et al., 2010). However, another group of researchers managed to demonstrate improved locomotor rather than sense function, increased numbers of regenerating axons and serotonergic fibers in an area rostral to the injury epicenter as well as significantly reduced abnormal cavities with co-administration of fasudil intrathecally for 4 weeks and a single injection of bone marrow-derived stromal cells into the lesion site (Furuya et al., 2009). A positive synergistic effect of fasudil and transplantation of bone marrow-derived MSCs was demonstrated in experimental autoimmune encephalomyelitis in mice (Yu et al., 2016). In this case fasudil inhibited the effect of proinflammatory molecules such as TLR-4/MyD88, interferon (IFN)-γ, interleukin (IL)-1β and tumor necrosis factor-α (TNF-α), and activated the production of a glial-cell derived neurotrophic factor and a brain-derived neurotrophic factor (BDNF). It should be noted however that whether the ROCK inhibitor affects survival, phenotype characteristics and synthetic activity of the cells transplanted, MSCs in particular, remains unclear in all experiments of fasudil co-administration with cell-based therapy.

Cdc42 is a significant factor in extension of axonal growth cones and regulation of cell proliferation, and is involved in lipotoxic effects of palmitate in culturing Wharton's jelly-derived MSCs. The delivery of constitutively active Cdc42 into the area of SCI reduces the number of reactive astrocytes and chondroitin sulfate proteoglycan deposition (Jain et al., 2011). At the same time, the use of shRNA against Cdc42 attenuated palmitate-induced synthesis of proinflammatory cytokines and cell death (Lu et al., 2017). These results indicate a mechanistic role of Cdc42 in Wharton's jelly-derived MSCs proliferation and determine that the Cdc42 activity is a promising pharmacological target to reduce lipotoxic cell dysfunction and death.

Molecular and Cellular Mechanisms Mediating Impact of Mesenchymal Stem Cells on Neuronal Microenvironment in the Area of Spinal Cord Injury

Astrocytes

Traditionally, studies aimed to assess the efficacy of MSCs use for the purpose of neuroregeneration in SCI are focused on the state of reactive astrocytes and extracellular matrix in the glial scar. For this purpose, usually the expression level of GFAP and less often that of proteoglycans are determined in the area of SCI (**Additional Table 2**). When the expression of these markers is decreased, it is often concluded that the glial barrier is reduced and axonal growth results (Liu et al., 2018; Yang et al., 2018). Such a judgement is not entirely objective, since the glial barrier is a complex and multicomponent structure. The glial barrier is composed not only of reactive astrocytes, but also macroglia precursors and reactive microglia/macrophages actively penetrating into a scar; there are also fibroblasts and perivascular cells present (Chelyshev et al., 2013; Yuan and He, 2013). Different post-traumatic periods are evaluated for changes in the glial scar and astrocyte activation in MSC transplantation. In this context the role of the glial barrier and reactive astrocytes is most often considered a negative one despite a known positive role in maintaining the spinal cord tissue structural integrity and the process of neuroregeneration during an early post-traumatic period (Adams and Gallo, 2018). Kim et al. (2015) demonstrated that an early intravenous administration of allogenic MSCs to dogs increased the expression of GFAP by 7 days after SCI. They consider the results obtained as positive taking into account the formation of a neuroprotective microenvironment by GFAP-expressing astrocytes for neurogenesis with transplanted MSCs.

However, most studies with MSC transplantation in SCI give evidence to reduced astrocyte responsiveness both in acute (Liu et al., 2018), subacute (Ruppert et al., 2018), and chronic periods after injury (Ryu et al., 2012; Krupa et al., 2018; Mukhamedshina et al., 2018; Yang et al., 2018). The possibilities of preventing astrocytosis are attributed to the ability of MSCs to decrease cyclooxygenase-2 (COX-2) and IL-6 cytokine levels (Nakajima et al., 2012; Ryu et al., 2012; Liu et al., 2018; Sun et al., 2018) (**Figure 1**). It has previously been shown that reactive and hypertrophic astrocytes start expressing COX-2 within the area of ischemia in response to proinflammatory stimuli or an injection of neurotoxins (Hirst et al., 1999; Maślińska et al., 1999; Font-Nieves et al., 2012). Thus there are approaches involving the use of COX-2 inhibitors after SCI, that reduce oxidative stress and promote neuroprotection (Hakan et al., 2011; Hou et al., 2015; Yuksel et al., 2018). A decreased COX-2 level in MSC transplantation in SCI can be considered positive and results from reduced levels of prostaglandins which regulate MSC differentiation into osteoblastic cells (Zhang et al., 2002; Banovac et al., 2004). Heterotypic ossification is thereby prevented which is the most common orthopedic complication after SCI (Banovac et al., 2004).

IL-6 can play a double role, being involved in either a classic signaling pathway and thereby promoting a reduction of inflammation and enhanced regeneration, or a trans-signaling pathway important for cellular communication (Campbell et al., 2014; Scheller et al., 2014; Schaper and Rose-John, 2015). IL-6 is synthesized mainly by activated astrocytes in the central nervous system (Guptarak et al., 2013; Choi et al., 2014; Gruol, 2016). Decreased IL-6 levels are mediated by MSC secretion of TNF-stimulated gene-6 (TSG-6), released within exosomes (Wang et al., 2012; Qi et al., 2014; Song et al., 2017; Chaubey et al., 2018). Later TSG-6 reduces NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling, thereby modulating a diminishing cascade of proinflammatory cytokines (TNF, IL-1β, IL-6, IL-1α, *etc.*).

It should be noted that astrocytes exist in at least two distinct reactive states such as A1 neuroinflammatory reactive astrocytes and ischemia-induced A2 neuroprotective reactive astrocytes (Liddelow and Barres, 2017). A1 reactive astrocytes induced by microglia activation quite rapidly respond to neurotrauma and lead to death of axotomized neurons (Liddelow and Barres, 2017). It was not until recently that it became possible to distinguish between different activation states of reactive astrocytes by means of complement component C3 which is specifically upregulated only in A1 neuroinflammatory reactive astrocytes (Liddelow and Barres, 2017). This resulted in the advent of publications evaluating a phenotype of reactive astrocytes in the area of SCI following MSC-based therapy. For example, Liu et al. (2018) were the first to demonstrate that an intravenous injection of MSCs-derived exosomes after SCI resulted in a decreased number of $C3^+$/$GFAP^+$-astrocytes in the lesion area as early as in 24 hours. The results obtained may be attributed to the secretion of TSG-6 by MSCs and consequently decreased NF-κB signaling, which induces A1 neuroinflammatory reactive astrocytes (Lian et al., 2015; Liddelow et al., 2017).

Despite the great progress in studying astrocytes in general and the MSC impact on them in particular, there is a need for communications between these cells in the setting of the pathological conditions in SCI to be more completely elucidated. Eventually this would provide a more complete understanding of the contribution of astrocytes during various post-traumatic periods and how we can modulate their inflammatory or neuroprotective potential with the use of MSCs.

Microglia and inflammation

The activation of microglia which are the first to respond to nervous tissue damage is one of the essential events of post-traumatic reactions. The phase of primary microglia activation peaks at post-traumatic day 7, its reactivation occurring in 2 weeks and lasting for up to 180 days (Kigerl et al., 2006; Beck et al., 2010). Activated microglia can synthesize not only trophic biomolecules such as neurotrophins, glutamate transporters and antioxidants, but also effectors that can be potentially neurotoxic, such as nitric oxide and pro-inflammatory cytokines (Persson et al., 2005; Lai and

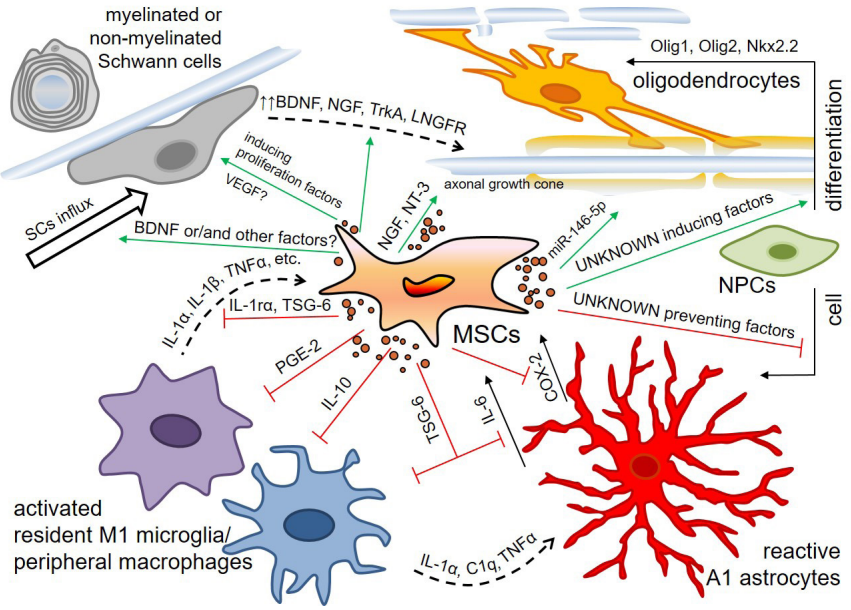

Figure 1 Schematic diagram for some effects of mesenchymal stem cells (MSCs) on the neuronal microenvironment in the area of spinal cord injury (SCI).
Activated resident microglia and peripheral macrophages attracted in the area of SCI produce proinflammatory cytokines such as interleukin (IL)-1α, IL-1β, tumor necrosis factor (TNF)-α, C1q and so on and activate A1 astrocytes and MSCs. In response to these stimuli and probably other signals the MSCs start to secret anti-inflammatory factors such as IL-1ra, TNF-stimulated gene-6 (TSG-6), prostaglandin E2 (PGE2), and IL-10 and modulate a phenotype of microglia/macrophages toward the anti-inflammatory M2 one and reduce the reactivity of astrocytes. The MSCs induce neural progenitor cells differentiation into oligodendrocytes and prevent differentiation into astrocytes. They facilitate myelination and axon growth by producing miR-146-5p and neurotrophic factors, lead not only to influx of Schwann cells in the area of SCI, but promote an increased expression of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and its high- and low-affinity receptors (TrkA and LNGFR) in these cells. COX-2: Cyclooxygenase-2; NT-3: neurotrophin-3.

Todd, 2006; Hellwig et al., 2013). Owing to this dual nature the role that microglia play in regulating neuroregeneration at different port-traumatic time points is still controversial.

To date several states of microglia polarization are distinguished - they are classic activation (M1), alternative activation (M2a), alternative type II activation (M2b) and acquired deactivation (M2c). A number of investigators question whether the microglia can acquire a M3 phenotype (Walker and Lue, 2015). A number of proliferation studies showed which markers were specific for the microglia activated by a classic or alternative pathway (Martinez et al., 2006, 2013). Classically activated (M1) cells can produce reactive oxygen intermediates as well as proinflammatory cytokines such as TNF-α, IL-1β and IL-6, concurrently mediating inflammatory tissue damage. M2 microglia/macrophages are a phenotype of cells responding to IL-4 and IL-13, at present known as M2a. The phenotype M2a microglia is considered to have increased phagocytic activity and to produce growth factors such as an insulin-like growth factor-1 and proinflammatory cytokines such as IL-10 (Martinez and Gordon, 2014). The microglia of this type can dispose of cellular debris and stimulate tissue regeneration. An alternative activation was subdivided into two subcategories such as M2b and M2c. M2b is induced by ligation of immunoglobulin Fc-gamma-receptors that results in the IL-12 expression, increased IL-10 secretion and HLA-DR expression. This phenotype is also characterized by an increased expression of CD32 and CD64, which were found to be expressed by the cerebral microglia in Alzheimer's disease (Peress et al., 1993) and to be related to increased phagocytosis activity. M2c (acquired deactivation) can be caused by the anti-inflammatory cytokine IL-10 or glucocorticoids, an increased expression of the transforming growth factor), sphingosine kinase (SPHK1) and CD163, a membrane-bound receptor for haptoglobin/hemoglobin complexes (Wilcock, 2014).

Some evidence indicates that MSCs can modulate a phenotype of microglia/macrophages toward the anti-inflammatory M2 phenotype in SCI (without detection of alternative activation) (**Additional Table 2**). Previous studies *in vitro* may have attracted separate attention to the polarization of microglia/macrophages in MSC transplantation after SCI. MSCs co-cultured with macrophages showed a high expression level of soluble (IL-10) and surface (CD206) markers for M2 macrophages and increased phagocytic activity (Kim and Hematti, 2009). Subsequently it was shown in models of sepsis and peritonitis that mechanisms of MSC-mediated regulation on macrophages might depend upon PGE2 and TSG-6 secretion (Németh et al., 2009; Choi et al., 2011) (**Figure 1**). In SCI models transplantation of both MSCs and MSC-derived microvesicles increased the number of M2 microglia/macrophages on post-injury day 7–9, promoting a proregenerative environment (Nakajima et al., 2012; Caron et al., 2016; Sun et al., 2018). This effect of MSCs might be attributed to MSC-mediated increased level of IL-4, IL-13 and IL-10, which promote modulation of microglia/macrophages toward M2a and M2c neuroprotective phenotypes, respectively, as well as decreased levels of TNF-α and IFN-γ which promote polarization into the M1 phenotype. This assumption was confirmed by studies *in vitro* (Zhang et al., 2010; Pietilä et al., 2012; Shin et al., 2016) and *in vivo* (Nakajima et al., 2012; Sun et al., 2018).

In addition to polarization into the M2 phenotype MSC transplantation in SCI results in a decreased total number of microglia/macrophages in the area of injury. Pan markers such as Iba1 and CD68 are often used for this evaluation. There was a decreased total microglia/macrophages number in the area of SCI after MSC injection in acute (Liu et al., 2018), subacute (Zeng et al., 2011; Ruppert et al., 2018) and chronic periods of SCI (Neirinckx et al., 2015; Liu et al., 2018; Mukhamedshina et al., 2018; Yang et al., 2018). Only

a few publications provide evidence for the lack of changes in total number of microglia/macrophages at a lesion site following transplantation of MSCs or their microvesicles (Neirinckx et al., 2015; Sun et al., 2018).

There is a direct relationship between the M2 microglia activation and anti-inflammatory effects in MSC transplantation in SCI. IL-1α and other molecules released within a focus of tissue destruction activate the resident microglia and migrating macrophages in the area of injury. The latter in turn activate MSCs by producing proinflammatory cytokines such as IL-1α, IL-1β or TNF-α. In response the MSCs start secreting anti-inflammatory factors such as TSG-6, PGE2 and IL-1ra, which both modulate the activation of M2 microglia/macrophages and reduce the effects of proinflammatory cytokines (Prockop and Oh, 2012). A subsequent decrease in IL-1β and TNF-α, which was observed in MSC transplantation in SCI and correlates with a functional outcome (Zeng et al., 2011, 2016; Urdzíková et al., 2014; Liu et al., 2018), is related to MSC-mediated suppression of NLRP3 inflammasome including by means of PGE2 action (Oh et al., 2014; Shin et al., 2016).

In conclusion, MSCs can act as cellular modulators of microglia/macrophages polarization by regulating the production of different cytokines and a proinflammatory response as a whole that results in attractive therapeutic outcomes for such type of stem cells.

Oligodendrocytes and Schwann cells

Demyelination is part of a general process of secondary degeneration in SCI. The number of demyelinated axons was shown in a rat model of SCI to peak 24 hours after injury, to decline over the next 1–2 weeks and to increase progressively by 450 days post injury (Totoiu and Keirstead, 2005). There were demyelinated axons at all experimental time points, indicating that post-traumatic processes were still ongoing. At the same time, not only oligodendrocytes but also Schwann cells were involved in the process of remyelination by the end of week 2. The latter were shown to migrate from peripheral nervous structures resulting from a disruption of the barrier integrity, to participate not only in remyelination of central axons in the area of injury, but also in the restoration of conduction (Franklin and Hinks, 1999; Jasmin et al., 2000; Shaymardanova et al., 2013; Mukhamedshina et al., 2017b; Galieva et al., 2018).

MSC-derived soluble factors have been previously shown to induce oligodendrogenesis by reducing the anti-oligodendrogenic determinant Id2 and increasing the pro-oligodendrogenic factor Olig2 expression in neural progenitor cells (Li et al., 2009; Steffenhagen et al., 2012). It was shown *in vitro* that MSCs could not only direct proliferating NPCs toward an oligodendrocyte fate but also induce oligodendrocyte differentiation (Rivera et al., 2006). The MSCs facilitate myelination by producing miR-146-5p and delivering them *via* exosomes (Lindsay et al., 2016). In co-culture the MSCs lead not only to improved survival and proliferation of Schwann cells, but promote an increased expression of BDNF, nerve growth factor (NGF) and its high- and low-affinity receptors (TrkA and LNGFR) in these cells (Wang et al., 2009) (**Figure 1**).

Not more than 1/3 of publications devoted to the evaluation of MSCs efficacy in SCI *in vivo*, carry out an analysis of post-traumatic changes in the population of myelin-producing cells and myelination as a whole (**Additional Table 2**). Various MSC transplantations demonstrate an increase of myelin retention and the number of myelinated axons in the lesion site during a chronic post-injury period (Papa et al., 2018; Ramalho et al., 2018). Using electron microscopy Nakano et al. (2013) found in the same period that the number of Schwann cells associated with axons in the astrocyte-devoid lesion site increased following an intraventricular injection of MSCs. It was shown that MSCs could elicit the influx of Schwann cells into the site of injury and improve their survival (Ding et al., 2014). The influx and proliferation of Schwann cells can also be attributed to MSC secretion of BDNF, vascular endothelial growth factor (VEGF) and other unknown inducing factors. BDNF was shown to promote a significant expansion in the number of Schwann cells at three weeks after SCI, with VEGF stimulating their proliferation (Sondell et al., 2000; Blesch and Tuszynski, 2007). An intravenous injection of MSCs in the early post-injury period increased the expression of GalC, a marker of mature oligodendrocytes (Kim et al., 2015). However, the expression of an oligodendrocyte transcription factor (*Olig2*), which regulates oligodendrocyte differentiation does not seem to change, since the mRNA analysis of the *Olig2* gene shows no significant differences with control groups (Urdzíková et al., 2014; Mukhamedshina et al., 2018).

Thus an increased number of functioning oligodendrocytes and Schwann cells in the area of demyelination in SCI is important for assessing the effectiveness of its regeneration following cell-based therapy that must maintain the survival and differentiation of not only the spinal cord cells but also endogenous migrants. The further elucidation of molecular mechanisms of MSC-derived activity in relation to myelin-producing cells will be essential for the treatment of not only neurotrauma, but also demyelinating diseases.

Axonal outgrowth

The issue of axon regeneration, which is normally low due to the small intrinsic capacity of central nervous system axons for regeneration as well as the synthesis of growth inhibitor molecules upon injury is pressing in SCI (Sakamoto and Kadomatsu, 2017). The MSC capacity to stimulate axonal outgrowth has been identified (Lin et al., 2018). However, molecular and cellular mechanisms of stimulating axonal growth and sprouting by MSCs are not completely clarified. In order to evaluate possible effects of transplanted MSCs on axon regeneration usually the expression level of neurofilaments (NF200) and less often that of GAP-43 (axon growth associated protein) are determined in the area of SCI (**Additional Table 2**). However, it must be remembered that the increased expression of these proteins cannot yet indicate successful axon regeneration. The process of axonal regeneration involves 5 stages and has to end in synapse formation

and the restoration of conduction along the axons as a result (Sakamoto and Kadomatsu, 2017). Therefore, axonal regeneration following MSC therapy must be confirmed with electrophysiological studies.

Axon growth following MSC transplantation is most often associated with their ability to form bridges *via* a spinal cord cavity and reduce a glial scar (Zurita and Vaquero, 2006; Wright et al., 2007; Lin et al., 2018). *In vitro* studies demonstrate that MSCs can act as "cellular bridges" and stimulate neurite outgrowth by reducing inhibitory substrates (Wright et al., 2007). Krupa et al. (2018) found the expression of GAP-43 increased and that of GFAP decreased in a dose-dependent manner – the higher the number of cells transplanted, the more intense axonal sprouting was at 9 weeks post injury after an intrathecal injection of MSCs. It has previously been demonstrated *in vitro* that MSCs cultured with brain slices start secreting trophic factors such as NGF and NT-3 (Pisati et al., 2007). These results were translated *in vivo*, therefore some researchers attribute a positive effect of MSCs on axon growth to the increased expression of NGF and NT-3, which play an important role in this process (Li et al., 2016; Ramalho et al., 2018).

The search for a most effective promoter for axonal regeneration in SCI is still ongoing. MSC-based therapy can mediate axonal outgrowth that has been shown in some animal experiments. However, studies which evaluate post-traumatic changes in axonal regeneration following MSC transplantation in SCI have to be more detailed, and to reveal not only the potential for axonal growth and sprouting but also the functional competence of the changes observed, that is, the possibilities for the restoration of long-term conduction along these axons.

Neuroprotection

The anti-apoptotic effect of MSCs which is associated with the synthesis of bioactive molecules capable of inhibiting apoptosis is of a great importance in their gross neuroprotective effects. It was shown in experiments *in vivo* in a model of SCI that MSCs can affect a decrease in the expression of pro-apoptotic molecules and an increase of that of anti-apoptotic ones (Mukhamedshina et al., 2017a; Liu et al., 2018). However, when assessing the efficacy of MSCs in SCI most often terminal dexynucleotidyl transferase-mediated dUTP nick end labeling $(TUNEL)^+$-cells are generally assessed, where their decrease following therapy has been reported (Xiong et al., 2017; Liu et al., 2018; Takahashi et al., 2018b; Yang et al., 2018). Still, the molecular mechanisms of MSC-mediated anti-apoptotic effects have not yet been completely discovered.

The maintenance of adequate blood perfusion in the site of injury, in rostral and caudal regions of the spinal cord is essential for neuroprotection. Therefore the angiogenic activity of MSCs is significant for neuroregeneration. When detecting the MSCs in the walls of blood vessels an assumption was made that these cells might be involved in regulation of their growth and maintenance of a stable vessel. Subsequently the ability of MSCs to stimulate the growth of blood vessels including those regenerating after various injuries was established. The main mechanisms of angiogenic activity of MSCs are due to their ability to secrete pro-angiogenic factors and cytokines (VEGF, fibroblast growth factor-2, transforming growth factor-β, hepatocyte growth factor, *etc.*), as well as to express the adhesion receptor integrin α6β1, promote vessel sprouting, MSC proliferation and pericyte differentiation (Carrion et al., 2013). The transplantation of MSCs was shown to promote angiogenesis and reconstruction of the microvasculature network that enhances a functional recovery after SCI (Zeng et al., 2011; Zhou et al., 2016; Huang et al., 2017). This effect is most often interpreted when increased $CD31^+$- and rat endothelial cell antigen-1^+-cell levels and enhanced VEGF expression are detected. An increased VEGF expression by MSCs is in turn related to the action of IL-8 (Hou et al., 2014). The MSCs transplanted closely associate with endothelial cells after SCI, that is due to performing a pericyte function and the possibility of contact stabilization of growing and formed blood vessels in later stages of angiogenesis (Zeng et al., 2011).

In general the neuroprotective effect of MSCs is due to their secretion of neurotrophic factors and cytokines. The latter have the above effects which MSCs exert through various signaling pathways, activated *via* specific receptors on target cells. Therefore the quality of MSCs derived from various sources is now top priority, being ahead of issues of delivery, dosage, *etc.*

Tissue integrity

The primary injury of the spinal cord associated with progressive tissue necrosis results in post-traumatic cavitation and triggers processes of a secondary injury which cause death of neurons and glial cells away from the injury epicenter (Priestley et al., 2012; Ward et al., 2014). The regulation of a cell response in an acute period is critical to inhibit rapid progression of a secondary injury after SCI. Therefore, MSC transplantation during the acute period of SCI may be targeted not only to replace the cells lost, but also to modulate a cell response, to enhance anti-oxidant and pro-inflammatory mechanisms preventing further injury.

The reduction of both a total area of abnormal cavities and lesion/cavity volumes were reported in numerous publications on MSC transplantation in SCI (Nakajima et al., 2012; Nakano et al., 2013; Neirinckx et al., 2015; Liu et al., 2018; Mukhamedshina et al., 2018; Sun et al., 2018). In this case tissue integrity also increases; however, there are controversial data on the integrity of the white and grey matter (Urdzíková et al., 2014; Krupa et al., 2018; Mukhamedshina et al., 2018). MSC-mediated anatomical improvement is due to their complex action by which the MSC graft induces tissue protection/repair in a manner unlike that in acute and chronic periods of SCI. For example, MSC transplantation in an acute period may have beneficial effects through their anti-inflammatory activity and microglia polarization, whereas in the subacute/chronic phase after SCI, the MSCs may be used for neurostimulatory, glial scar reducing and cell bridging effects (Wright et al., 2011; Nakajima et al., 2012).

Not all studies confirm the MSC ability to improve the retention of spinal cord injured tissue (Kim et al., 2015; Takahashi et al., 2018b). The contradictory results might be attributed to different approaches to MSC transplantation and a too early evaluation of their efficacy under these criteria (in post-injury week 1). The timing of cell transplantation and the cell number, routes of administration (intraspinal, intrathecal, intravenous, application to the area of injury as part of a matrix), immunosuppression, as well as the quality of MSCs generated in culture are certain to be relevant. In general, all these issues have a direct impact on the efficacy of MSC-mediated regulation of the neuronal microenvironment discussed above.

Conclusion

The use of MSCs is presently associated with possible advances of regenerative medicine. The number of advocates and opponents of this trend is more and more rising both in science and in society. The increased number of skeptics is largely due to the lack of a complete disclosure of mechanisms underlying the therapeutic effect of MSCs and data on long-term results of their use. Existing preclinical studies give evidence to the ability of MSCs to stimulate neuroregeneration, in SCI in particular. Nevertheless, it seems difficult to interpret the results obtained and draw a parallel between observed posttraumatic reactions, which often lack a complete and objective evaluation, and the resulting functional outcome. Sometimes observed controversial data on the efficacy evaluation of MSC-based therapy in SCI are primarily due to a different secretory profile of the cells obtained, and only then by differences in protocol details.

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Additional files:
Additional Table 1: *Behavior of MSCs in the area of SCI based on preclinical trials data.*
Additional Table 2: *Preclinical in vivo trials using MSCs transplantation after SCI and obtained results in the interpretation of the authors.*
Additional file 1: *Open peer review reports 1 and 2.*

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