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Review

The role of mesenchymal stromal cells in spinal cord injury, regenerative medicine and possible clinical applications

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ABSTRACT

Diseases of the central nervous system still remain among the most challenging pathologies known to mankind, having no or limited therapeutic possibilities and a very pessimistic prognosis. Advances in stem cell biology in the last decade have shown that stem cells might provide an inexhaustible source of neurons and glia as well as exerting a neuroprotective effect on the host tissue, thus opening new horizons for tissue engineering and regenerative medicine. Here, we discuss the progress made in the cell-based therapy of spinal cord injury. An emphasis has been placed on the application of adult mesenchymal stromal cells (MSCs). We then review the latest and most significant results from *in vitro* and *in vivo* research focusing on the regenerative/neuroprotective properties of MSCs. We also attempt to correlate the effect of MSCs with the pathological events that are taking place in the nervous tissue after SCI. Finally, we discuss the results from preclinical and clinical trials involving different routes of MSC application into patients with neurological disorders of the spinal cord.

1. Introduction

An increasing number of people are affected by neurological diseases such as traumatic spinal cord (SCI) and brain injury, neurodegenerative diseases, stroke and central nervous system (CNS) tumors. In this list, spinal cord injuries are among the most devastating disorders, since the affected patients and their families are often deprived of qualities that change their lives forever [1]. According to the National Spinal Cord Injury Statistical Center (NSCISC), it is estimated that new spinal cord injury cases occur worldwide with almost the same frequency, around 40 cases per million of population, excluding those who died at the scene of an accident [2]. Of those, most SCI cases are caused by traffic accidents, followed by violent assaults, falls, sport and industrial traumas.

Generally, human SCIs are very heterogenous, and the therapeutic approach differs depending on the location, extent, stage and time after the SCI. Traumatic SCI can be divided into three phases: acute, subacute and chronic. The acute phase starts after the injury of the spinal cord (SC), when mechanical deformation of the SC and shear forces lead to the rupture of neuronal cell membranes with the subsequent release of their intracellular contents and glutamate from intracellular stores, leading to excitotoxicity, vasospasm, localized edema, the breakdown of the blood–brain barrier, a cascade of biochemical and cellular processes resulting in massive necrotic cell death and a shift of metabolism toward anaerobic glycolysis [3,4]. The acute phase persists for hours up to days and resolves into the subacute phase.

The subacute phase is characterized by processes that lead to secondary damage of the nervous tissue after the initial traumatic shock. These processes trigger a chain of events that are accompanied by an inflammatory reaction, the activation of macroglial and oligodendroglial cells, ongoing demyelination, vascular defects with related hypoxia, a depletion of ATP regeneration, the production of free radicals with subsequent lipid peroxidation [5],

Abbreviations: AMSCs, adipose-derived MSCs; ALS, amyotrophic lateral sclerosis; BDNF, brain-derived neurotrophic factor; BMSC, bone marrow MSC; CNS, central nervous system; CST, corticospinal tracts; ESCs, embryonic stem cells; GRP, glial restricted precursors; GDNF, glia derived neurotrophic factor; GVHD, graft-versus-host disease; hNSC, human neural stem/progenitor cells; hUCB, human umbilical cord blood; iPSCs, induced pluripotent cells; IGF-1, insulin growth factor-1; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cells; MN, motoneurones; MV, microvesicles; NGF, neural growth factor; NF, neurofilament; NMJ, neuromuscular junction; NPCs, neural progenitor cells; SC, spinal cord; SCI, spinal cord injury; NTF, neurotrophic factors; OMgp, oligodendrocytemyelin glycoprotein; PNN, perineuronal nets; SOD1, superoxide dismutase 1 gene; VEGF, vascular endothelial growth factor.

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local inflammation [6], secondary necrotic cell death at the core of the injury site and apoptotic cell death in the surrounding areas, reaching its highest levels at about 1 week after injury [7–12]. The ongoing demyelination [13,14] and degeneration of the fiber tracts leads to neuronal death not only in the immediate proximity of the primary lesion site, but also in more remote locations, such as the motor cortex in the brain [15,16]. At this stage a number of oligodendrocytes and astrocytes die in the core of the injury [10]; meanwhile, there is an activation of astrocytes at the edge of the primary injury site. These astrocytes display an increased metabolism and start to form long neurites, aiming to prevent the spread of an aggressive environment further in both directions [17,18]. This infiltration subsequently acts to block regeneration after SCI due to the formation of a barrier to axonal sprouting across the lesion [19]. The activation of oligodendrocytes is another important mechanism leading to the synthesis of oligodendrocyte-myelin glycoprotein (OMG) and myelin-associated glycoprotein (MAG), both of which have neurite growth inhibitory activity [20–22].

The chronic phase of SCI can last for years and is characterized by ongoing demyelination [14,23,24], local inflammation and apoptosis [25], a decrease in the number of activated macrophages, and the formation of a glial scar and pseudocysts (also called syringomyelia) [26–29]. This phase of SCI presents a major challenge to doctors and scientists and attracts the greatest research interest, as most SCI patients remain in this phase, to a greater or lesser extent, for the rest of their lives.

Regeneration of the adult CNS is limited due to weak neuronal plasticity, an umbrella term referring to a variety of compensatory processes (spontaneous regeneration of affected axons, dendritic remodeling, changes in neuronal and synaptic strength) that are taking place inside the spinal cord after the trauma in order to overcome a number of neurites growth-inhibitory molecules and to restore lost structures and functions [30,31]. On one hand, these powerful intrinsic inhibitory substances and processes that prevent axonal growth are vital for the normal functioning of the adult mammalian spinal cord (SC). On the other hand, these same factors create a major obstacle for functional recovery after SCI, as well as limit the therapeutic effects of drugs that are currently used in the treatment of patients after SCI. Therefore, novel therapeutic strategies, by confronting the above obstacles, including the glial scar components, providing neuroprotective support for the remaining host cells and/or acting as an anti-inflammatory treatment, should stimulate the regeneration of the adult CNS and improve neurological functions, thus providing an effective therapy and improving the quality of the patient's life.

2. Current treatment of spinal cord injury

Therapeutic approaches toward patients with SCI fall into three separate time frames, which target the featured molecular events at the particular injury phase. The first could be described as management of vital functions, immobilization, and transportation to the emergency unit. It is directed at stabilizing vital functions and interrupting the cascade of reactions leading to secondary injury. The aim of the second phase is neuroprotection immediately after the injury. This is the most critical period after the injury, therefore most phase I–III human clinical trials have been organized during this period. The following groups of drugs have been tested: steroids (methylprednisolone, Tirilazard) [32], opiate receptor antagonists (naloxone) [33], gangliosides (GM-1, Sygen®) [34], the potassium channel blocker 4-aminopyridine (fampridine, Acorda Therapeutics) [35], autologous cellular therapy (stimulated homologous macrophages, Proneuron) etc. [36,37]. Of these, methylprednisolone (MP) has been the only drug that has resulted in the significant improvement of motor and sensory functions not just in animal studies, but also in patients after SCI in the NASCIS-3 human trial [32,33,38]. However, an ongoing debate is in progress regarding the mechanism, efficacy and clinical impact of MP's action [39]. Nevertheless, at the present time, the only standard method to treat patients with SCI is surgical intervention, high doses of MP and symptomatic therapy (control or management of urinary and cutaneous infections, pain, spasticity, bladder and bowel management, sexual and reproductive function) followed by rehabilitation. The third therapeutic phase deals with the consequences of SCI. Rehabilitative efforts aim to stabilize the current status and to train the reflexes and residual circuits to achieve optimal living conditions for the patient who has a given deficit.

New neuroregenerative strategies are focused on the neuroprotection or even the replacement of the injured neurons and glial cells by the application of various types of stem cells or their progenitors [40]; however, without a permissive environment only little progress in regeneration can be achieved. In the future, treatment of SCI will be directed toward the enhancement of axonal regeneration (also called rewiring) by inhibiting astroglial scar formation and the synthesis of inhibitory proteoglycans, netrins, semaphorines and ephrines [41–44]; modulation of inflammatory and immune responses [45]; stimulating endogenous stem cells [46,47]; filling the post-injury cavity by biomaterials [48,49]; or blocking myelin-associated glycoproteins and anti-Nogo-A therapy [50].

3. Stem cell therapy in the treatment of SCI

Stem cells are pluripotent or multipotent cells with unlimited self-renewal capacities. In addition, they are able to differentiate into diverse specialized cell types, including neuronal and glial cell lineages [51,52]. It is expected that after their application into the pathological environment within the subacute phase after SCI, the grafted stem cells will be able to stimulate regeneration by: i) the release of neurotrophic factors, modification of extracellular matrix and even downregulation of some inhibitory molecules that will promote and facilitate axonal sprouting [53]; ii) the regeneration of damaged nervous tissue through differentiation or transdifferentiation into mature neural cells (neurons or oligodendrocytes), thus promoting the remyelination of the surviving axons and the restoration of specific connections [51,52,54–56]; iii) the filling of small cavities, thus acting as a scaffold that will support axonal outgrowth between the rostral and caudal stumps and stimulating the revascularization of the damaged nervous tissue etc. [57,58]; iv) the stimulation of endogenous neurogenesis and angiogenesis, the secretion of exosomes, and the activation of endogenous stem cell proliferation, migration and differentiation toward neural cells in certain parts of the adult CNS such as the subventricular zone (SVZ) [59,60]. Interestingly, only the subacute transplantation of stem/precursor cells enhances the recovery of locomotor functions, whereas during the chronic phase of SCI monotherapy with stem cells is not enough [61]. A solution to the above concern might be provided by the implantation of stem cells in combination with biomaterials. Biomaterials have become increasingly important in the development of drug delivery systems and tissue engineering approaches, and can play key roles in overcoming the inherently insufficient protection, repair and regeneration of the nervous tissue [62]. The creation of a mechanical scaffold from natural or artificially synthesized materials and its transplantation into the transected SC or during the chronic phase of SCI could provide a platform for the growth of host cells and guide axons through the glial scar and post-traumatic cysts to form new connections [63]. The implantation of a hydrogel seeded with MSCs into a chronic lesion of the SC stimulates the regeneration of lost sensorimotor functions, promotes axonal and vessel