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Chapter

Mesenchymal Stem Cell Therapies for Paraplegia: Preclinical and Clinical Studies

Fereshteh Azedi, Kazem Mousavizadeh and Mohammad Taghi Joghataei

Abstract

Paraplegia is the damage or loss of function in motor and/or sensory abilities. This insult can be observed in the thoracic, lumbar, or sacral parts of spinal column. Besides, paraplegia may be occurring because of any injuries or diseases of the lower segments or peripheral nerves or by cerebral palsy (CP). This damage can be seen as a result of a tumor or blood clot on the spinal cord. By now, there is not any curative treatment for paraplegia. Using mesenchymal stem cells (MSCs) in the treatment of spinal cord injury is a promising tested strategy because of their simplicity of isolation/preservation and their properties. Several preclinical studies in this field can be found; however, MSCs showed weak and conflicting outcomes in trials. In this chapter book, we will discuss about the therapeutic role of these cells in the treatment of paraplegia, with emphasis on their characterization, relevance, boundaries, and prospect views.

Keywords: paraplegia, stem cell therapy, mesenchymal stem cell, preclinical study, clinical study

1. Introduction

Paralysis of the lower parts of the body (paraplegia) can be caused by any damage to the spinal cord [1, 2]. Traumatic and nontraumatic injuries are classifications of this disease [3]. Paraplegia causes severe and in most cases lasting changes in the patient's lifetime and lifestyle [4, 5].

Attempts to find a complete cure for paraplegia and several discoveries show that in adult mammalian, by the preparation of appropriate microenvironment, regeneration of spinal cord axons can be obtained [6]. But then, why can we see the huge delay in the processing of bench to bedside in spite of these findings? Unfortunately, spinal cord scientists find a new barrier in the regeneration field. In fact, axons do regenerate up and down through a graft or transplant placed at the damage site; however, when they reach healthy cord tissue beyond the injury zone, they fail to regenerate more at once [7]. The most important cause for this provision is that the axons of neural networks need to cross through during sufficient stabilized conditions which are unreceptive and intractable to new restoration. Successful elongated distance regeneration is probable only within destabilized neural tissues [8].

Recently, rapid progresses in multipotent stem cell (routinely called mesenchymal stromal/stem cells) investigations increase the interest of scientists to study about the cell therapy and regenerative medicine [9–11].

Mesenchymal stem cell transplantation in patients suffering paraplegia is considered as a strategy for increasing neuroregeneration [12–14]. Notably, because of the disproportion in the technique and method of MSC preparation for paraplegia treatment like how they administrate and which criteria are chosen for selecting patients, MSC transplantation is in the initial stages, and there is confusion about the consequences at present [15].

MSCs have various sources in the body including the bone marrow [16, 17], adipose [18], muscle [19], peripheral blood [20], umbilical cord [21–23], placenta [24], endometrial [25, 26] and menstrual blood [27–29], fetal tissue [30], and amniotic fluid [31]. Previous finding indicated that these clonal cells can adhere to plastic; express cluster of differentiation (CD) markers like CD73, CD90, and CD105 markers [32]; and can differentiate into adipogenic [33], chondrogenic [34], osteogenic [35, 36], and neurogenic [37–39] lineages in the experimental condition (in vitro). However, it can be observed many different reports in their strength and self-renewal potential [40]. Accordingly, when we compare previous surveys, variable or even conflicting results can be seen. The lack of uniform methods in MSC characterization, both in preclinical and clinical studies, contributes to this confusion. It is interesting that even the name "MSCs" has still been gradually questioned. Actually, an urgent demand is required to understand the novel sources and potencies of MSCs especially for applying in SCI treatment.

Previous findings showed that the optimistic effect of MSC in treatment of spinal cord and peripheral nerve injury ascribed to their differentiation ability. They can differentiate into various cell lineages and modulate the inflammation process and immunomodulatory responses. [41] MSCs can diminish cell apoptosis and secrete various neurotrophic factors [42, 43].

According to previous studies, transplanting enough cells is important to obtain the best outcome after MSC transplantation and also applying especial techniques for achieving the highest possible survival of MSCs. Likewise, it seems that repeated doses of MSC therapy might be helpful [44].

Findings obtained about clinical trials for SCI treatment demonstrated that the efficacy of MSCs in human studies is not beneficial like in preclinical studies [45]. For these reasons protocol standardization of basic and preclinical studies using MSCs should emphasize to translate to the clinical setting. This chapter book is based on preclinical studies and clinical trials dealing with MSC therapy for paraplegia with emphasis on the challenges in this field.

2. Paraplegia: mechanisms of degeneration

SCI is included in two mechanisms: primary and secondary damage. When the direct physical injury to the spinal cord happened like any contusion, compression, contraction, and laceration, it can be called primary injury [46]. In this condition, axons separate from each other, mechanical injury to cells occurs directly, and blood vessels rupture. The progress of the injury site can occur in secondary phase, and it can be led to the restorative process [47]. This phase is including alterations in concentration of local ionic, blood pressure dysregulation (local and systemic), decrease of blood flow in the spine, disruption in the blood-brain barrier (BBB), diffusion of proteins from serum into the spinal cord, alterations in inflammatory chemokines and cytokines, cell apoptosis, excitotoxicity, activation of calpain proteases, accumulation of neurotransmitter, production of free radicals, lipid

peroxidation, and activation of matrix metalloproteinases (MMPs). All of these changes can lead to demyelination of axons and also ischemia, necrosis, and apoptosis of spinal cord tissue [48]. As a result of these alterations, the inhibitory prospect overcomes, and axonal regrowth constrains. By this reason, injured axons cannot regenerate for a second time [49].

3. Mesenchymal stem cells: a historical outline

The pathologist Cohnheim in 1867 could show the first evidence of nonhematopoietic stem cells in the bone marrow (BM) and their potency to be the source of fibroblasts involved in wound healing [50]. However, only a century later (50 years ago), the isolation and culture of these cells in an experimental condition successfully could be done. Friedenstein and his colleagues found that, when isolated cells from the rat bone marrow are cultured, a population of fibroblastic-shape nonhematopoietic cells that adhered to the plastic of the cell culture dish could be seen. Then these cells were called as a colony-forming unit fibroblast (CFU-F). These cells were capable of self-maintenance and multi-lineage differentiation like adipocytes, chondrocytes, and osteocytes in vitro and also could support hematopoietic stroma when a single cell was transplanted into animal models [51]. In 1988, Owen showed that a stromal system existed, with a stromal stem cell (CFU-F) at the base of the hierarchy, popularizing the stromal cell terminology [52]. Altogether, this information was generated from in vivo studies.

Only in 1992, Haynesworth and his colleagues enriched and expanded cells in culture with the osteochondrogenic potential of the human bone marrow [53]. In the early 1990s, the proliferation and differentiation potency of these cells in an experimental condition and also multipotency and self-renewal properties after transplantation lead to characteristics of the "stemness" [54]. Thus, the term mesenchymal stem cell (MSC) was proposed by Caplan for progenitor cells, which were isolated from the human adult bone marrow (BM) instead of the term "stromal" or "osteogenic" stem cell and acquired a broad recognition [55]. **Figure 1** shows the representation of the most imperative results related to MSC discovery, characterization, and clinical relevance.

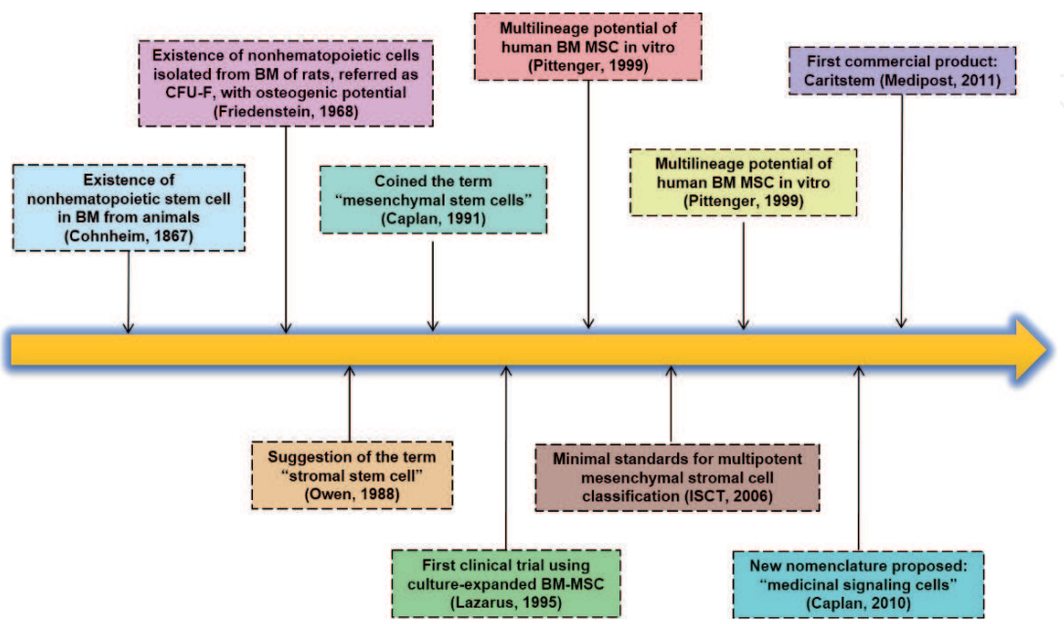

Figure 1.
Representation of the most significant findings associated with MSC discovery, description, and clinical purpose.

4. Preclinical researches using mesenchymal stem cells for paraplegia treatment

Transplantation of MSCs has been well established by several researchers. MSCs have significant effects on the several cellular and molecular cascades. Therefore,

Animal	Type of lesion	Cell source	Route of administration	Effects on neural regeneration	Ref.
Rat	Contusion	Human mesenchymal precursor cells	Lesion site	Functional recovery enhancement and tissue sparing and cyst volume decrease	[69]
Rat	Contusion	Human bone marrow MSCs	Lesion site, intracisternal, intravenous	Improvement in functional recovery	[70]
Rat	Hemisection	Bone marrow MSCs induced in Schwann cells	Lesion site	Progress in locomotor and sensory scores, axonal regeneration and remyelination	[71]
Rat	Contusion	Bone marrow MSCs	Lesion site, intravenous	Enhancement in locomotor scores and nerve growth factor (NGF) expression	[72]
Rat	Transection to the dorsal columns and tracts	Bone marrow MSCs, adipose derived-MSCs	Lesion site	Progress in locomotor scores, increased angiogenesis, preserved axons, reduced numbers of ED1-positive	[73]
Rat	Hemisection	Human umbilical cord-derived MSCs	Lesion site	Suppression of mechanical allodynia modulation of microglia in the spinal cord	[74]
Rat	Hemisection	Human bone marrow MSCs	Lesion site	Improvement of locomotor aspect, shorter latency of somatosensory-evoked potentials and different cell types	[75]
Rat	Hemisection	Bone marrow-MSCs	Lesion site	Enhancement in locomotor aspect and reduction of lesion cavity formation	[76]

Animal	Type of lesion	Cell source	Route of administration	Effects on neural regeneration	Ref.
Rat	Contusion	Human bone marrow MSCs	Lesion site	Improvement in functional recovery, tissue sparing and decrease in the volume of lesion cavity and in the white matter loss	[77]
Mouse	Compression	Bone marrow MSCs	Lesion site	Improvement in locomotor and sensory scores and reduced lesion volume	[78]
Mouse	Transection	Bone marrow MSCs	Lesion site	Improvement in functional recovery and neuronal survival, reduction of cavity volume and decrease of inflammation, progress in angiogenesis, and reduction of cavity formation	[79]
Dog	Compression	Bone marrow, adipose, Wharton's jelly, umbilical cord derived MSCs	Lesion site	Improvement in functional recovery scores, elevated numbers of surviving neurons, lesser lesion sizes and fewer microglia, and reactive astrocytes in the epicenter of the lesion	[80]
Dog	Compression	Neural-induced adipose derived-MSCs	Lesion site	Improvement in functional recovery and neuronal regeneration and decline of fibrosis	[81]
Dog	Compression	Umbilical cord MSCs	Lesion site	Improvement in functional recovery, promotion of neuronal regeneration, and diminishing of fibrosis	[82]
Dog	Compression	Human umbilical cord MSCs	Lesion site	Amelioration in functional recovery and remyelination	[83]

Animal	Type of lesion	Cell source	Route of administration	Effects on neural regeneration	Ref.
Dog	Chronic paraplegia (≥6 months)	Adipose tissue derived MSCs	Lesion site, intraparenchymal	Improved locomotion, no adverse effects or complexity, no changes in deep pain perception	[84]
Monkey	Dorsal SCI	Differentiated BM-MSCs into neural lineage cells	Lesion site	Motor-evoked potential (MEP), somatosensory-evoked potential in cortex (CSEP), and functional recovery and de novo neurogenesis	[85]

Table 1.
Summary of preclinical surveys using MSCs for treatment of paraplegia.

they can be regarded as a possible candidate for treating of CNS diseases [56]. MSCs have anti-inflammatory representation [57], immunomodulatory regulation [58, 59], and neuroprotective [60] effects. Moreover, previous findings showed that these cells could secrete trophic factors; thus they could motivate axon regeneration finally leading to functional recovery improvement [61, 62].

Regarding to the paracrine effect, MSCs can produce trophic and neurotropic factors such as insulin-like growth factor (IGF), brain-derived neurotrophic factor (BDNF) [63], vascular endothelial growth factor (VEGF) [64], granulocyte-macrophage colony-stimulating factor (GMCSF), fibroblast growth factor-2 (FGF2) [65], and transforming growth factor beta (TGF-β) [66]. In addition, gene therapy is another field that MSC therapy can be combined with, for example, introducing special genes into MSCs to generate molecules that have great curative ability and can increase neural survival and regeneration [67, 68]. **Table 1** presents a summary of preclinical studies by applying MSCs for paraplegia.

5. Clinical trials using mesenchymal stem cell for paraplegia

The clinical trials conducted for the treatment of paraplegia include three different phases. Phase 1 trials begin with the cell transplantation to a human participant, and the aim of these trials is to study any events such as adverse or toxic effects and also the safety of this intervention. During these trials, subjects may be exposed to some risks and obtain low benefits at the end. In phase 2, the goal of the trial is to determine the potential and variety of an intervention compared to a control group. Typically, the participants are recruited and arbitrarily assigned to the groups as experimental or control, and both participants and investigators are in blind condition, which means they do not have any insight about which of them have been assigned [86]. In phase 3, the conclusive clinical trial and the objective normally affirm the preliminary results obtained at the phase 2, with a significant clinical profit of the therapeutic intervention which has been proved by statistic methods. The number of participants is also larger, and manifold centers are elaborated in the trial [87]. By now, the majority of the studies using MSCs for paraplegia treatment are in phase 1 or 2 (**Table 2**).

Title	Lesion type	Cell source	Phase of the study	Effects on neural regeneration	ClinicalTrials.gov identifier
Safety study of local administration of autologous bone marrow stromal cells in chronic paraplegia (CME-LEM1)	Chronic paraplegia	Autologous bone marrow stromal cells	Phase I, completed	Motor enhancement, alteration in the chronic pain, improvement of neurophysiological parameters, and morphology changes in the spinal cord on neuroimaging follow-up	NCT01909154
Autologous mesenchymal stem cells transplantation in thoracolumbar chronic and complete spinal cord injury spinal cord injury	Thoracolumbar chronic and complete SCI	Autologous bone marrow mesenchymal stem cells	Phase II, not yet recruiting	Not informed	NCT02574585
Autologous mesenchymal stem cells transplantation for spinal cord injury—a phase I clinical study	Traumatic spinal cord injury at the thoracic level	Autologous BM MSCs	Completed	Intrathecal administration of BMMSCs is safe with no adverse events	NCT02482194
The effect of intrathecal transplantation of autologous adipose tissue derived MSCs in the patients with SCI, phase I clinical study	Clinical diagnosis of SCI	Autologous adipose-derived MSCs	Phase I, completed	Mild improvements in neurological function, free of serious adverse events	NCT01624779
Phase I, single center, trial to assess safety and tolerability of the intrathecal infusion of ex-vivo expanded bone-marrow derived MSCs for the treatment of SCI	SCI clinical diagnosis (ASIA A)	Autologous bone marrow MSCs	Active, not recruiting	Not informed	NCT01162915
Study the safety and efficacy of bone marrow derived autologous cells for the treatment of SCI	SCI clinical diagnosis	Autologous bone marrow MSCs	Recruiting	Not informed	NCT01730183
Phase I study of autologous bone marrow stem cell transplantation in patients with spinal cord injury	Traumatic thoracic or lumbar SCI	Autologous bone marrow MSCs	Phase I	Transplantation of autologous BMSCs is a feasible and safe technique	NCT01325103
Surgical transplantation of autologous bone marrow stem cells with glial scar resection for patients of chronic SCI and intra-thecal injection for acute and subacute injury—a preliminary study	Complete transection of spinal cord	Autologous bone marrow MSCs	Completed	Not informed	NCT01186679

Title	Lesion type	Cell source	Phase of the study	Effects on neural regeneration	ClinicalTrials.gov identifier
Autologous adipose derived MSCs transplantation in patient with spinal cord injury	Clinical diagnosis of spinal cord injury	Autologous AD MSCs	Phase I, completed	Intravenous administration of AD-MSCs is safe with no adverse events	NCT01274975
Difference between rehabilitation therapy and stem cells transplantation in patients with spinal cord injury in China	Traumatic injury, spinal cord injury	U-MSCs	Phase II, completed	Patients receiving U-MSCs demonstrate improved urinary control, muscle tension, motion, and self-care ability	NCT01393977

Table 2.
Summary of trials using mesenchymal stem cell for treatment of paraplegia.

Currently, clinical trials with applying mesenchymal stem cells for treatment of paraplegia are growing, suggesting that despite the existence of numerous questions at primary and preclinical levels, the MSC is considered supposedly valuable for translational researches [46].

6. Why mesenchymal stem cell functions do not soundly shift these cells toward clinic yet?

It is well established that, despite promising preclinical findings about mesenchymal stem cells, clinical trials failed to be impressive in SCI treatment and are still away from obtaining behavioral and functional improvement and repairing neural circuits totally [88].

Regarding the previous researches, studies using animal models are usually performed by applying standardized protocols of lesions, treatments, and specific timings of transplantation in each group of investigation [89]. However, these conditions are often incomparable with human subjects because timing and therapies are dependent on emergency setting and many variables such as lesion site damage at the cord [90]. Most of animal studies are necessarily done with rodents such as mice and rat, and, despite many anatomical or behavioral similarities, clinical trials with human participants should be the main goal of stem cell research. Therefore, making a strong bridge between preclinical and clinical studies is mandatory for finding the best trail in cell therapy [91].

As well, it is necessary to run more rigorous clinical trials such as RCTs and also animal researches in providing MSC therapy as a safe, effective, and beneficial approach for various diseases. Already, completed human trials displayed only limited outcome. However, applying MSCs in SCIs seems to cause no harm. Different trials [92, 93] indicated the safety of MSC therapy showing no side effects [94]. Regardless of these findings about safety of stem cell therapy, clinical outcomes showed poor results compared to expectations. Among the others, it seems that not many studies particularly encourage cell therapy [95].

Consequently, ongoing trials will almost certainly help and develop comprehension about the outcomes of stem cell therapy [96]. Unfortunately, translation of encouraging data from preclinical studies into clinical administration seems intricate. This probably reflects the multivariable and sophisticated paraplegia physiopathology, requiring a multi-aspect curative approach. To tell the truth, many points require further illuminating and depicting, such as:

1. The best therapeutic protocols with respect to the preparation method, type, and amount of stem cells transplanted.

2. The paracrine effects and their impact on behavioral and functional improvement.

3. The rout of stem cell delivery and timing of transplantation.

4. The substance of cellular matrix and microenvironment.

5. The ability of neuroplasticity and production of new connections from injured neuronal cells.

6. The ethical aspects and financial challenges associated with stem cell research [97].

As a result, prospect preclinical and clinical studies based on MSCs should put emphasis on multivariable factors [98]. For instance, considering donor-related properties like sex, age, and comorbidities that may have an effect on the capacity and excellence of cells is important. Moreover, a better appreciation of the accurate and beneficial methods of action calling for ad hoc investigations will also able to scrutinize MSC complexity, for instance, stem versus stromal. MSC interactions with host tissues have to be considered too. The development of precious in vitro and in vivo models is to be applied in a number of medical conditions; and choosing reagents and techniques that may be administrated from experimental studies to clinical developments for preserving cell consistency and eventually reducing manufacturing expenses is imperative markedly [99].

7. Conclusion

Nowadays, the advancements in cell marketing with the progress in cell isolation, description, and quality control will positively encourage scientists to apply MSCs for treating several diseases and disorders, even with all remaining challenges.

Preclinical studies revealed the importance of MSC therapy in the SCI and paraplegia field. Unluckily, the effect of MSC therapy is not typically seen in the human studies, and the results need a long time from being similar to preclinical studies. Consequently, among other concerns, the protocol standardization in source of cells, culture conditions, time of cell delivery after paraplegia, number and administration rout of cells, plasticity, and potential of MSCs after isolation and expansion in vitro is of urgency. Confidently, preliminary studies with emphasis on these key points will be helpful in terms of their winning implementation of human studies.

Conflict of interest

The authors declare no conflict of interest.

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