



Review

## Mesenchymal stem cells in regenerative rehabilitation

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**Abstract.** [Purpose] Regenerative medicine and rehabilitation contribute in many ways to a specific plan of care based on a patient's medical status. The intrinsic self-renewing, multipotent, regenerative, and immunosuppressive properties of mesenchymal stem cells offer great promise in the treatment of numerous autoimmune, degenerative, and graft-versus-host diseases, as well as tissue injuries. As such, mesenchymal stem cells represent a therapeutic fortune in regenerative medicine. The aim of this review is to discuss possibilities, limitations, and future clinical applications of mesenchymal stem cells. [Subjects and Methods] The authors have identified and discussed clinically and scientifically relevant articles from PubMed that have met the inclusion criteria. [Results] Direct treatment of muscle injuries, stroke, damaged peripheral nerves, and cartilage with mesenchymal stem cells has been demonstrated to be effective, with synergies seen between cellular and physical therapies. Over the past few years, several researchers, including us, have shown that there are certain limitations in the use of mesenchymal stem cells. Aging and spontaneous malignant transformation of mesenchymal stem cells significantly affect the functionality of these cells. [Conclusion] Definitive conclusions cannot be made by these studies because limited numbers of patients were included. Studies clarifying these results are expected in the near future.

**Key words:** Mesenchymal stem cells, Regenerative rehabilitation

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### INTRODUCTION

Regenerative medicine is a new field of medicine that combines information from several medical areas with the aim to recover the organ function lost due to congenital defects, damage, disease, or age<sup>1-8)</sup>. The four main approaches of regenerative medicine include cell therapy, gene therapy, transplantation, and tissue engineering<sup>6, 9-11)</sup>. Previous results from experimental and clinical studies have confirmed the efficacy and safety of these procedures<sup>6, 7, 9, 11-13)</sup>. At the same time, they can contribute to the maintenance of homeostasis, with stem cells sustaining long-term tissue regeneration when a biological system has depleted its own self-repair mechanisms and reserves<sup>14, 15)</sup>. The liver and skeletal muscles have shown good regenerative potential. In addition, recent research suggests that self-repair mechanisms exist in all tissues of the body<sup>14, 16)</sup>.

Mesenchymal stem cells (MSCs) are progenitor cells that have self-renewal and multi-lineage differentiation capabilities

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along with immunomodulatory activities<sup>17</sup>), regenerating all of the cell types in the tissue where they are located<sup>18</sup>). MSCs reside in a specialized physical location known as a niche, which constitutes a three-dimensional microenvironment containing, in addition to the MSCs, neighboring differentiated cell types and the extracellular matrix<sup>19</sup>). MSCs may express greater plasticity than traditionally attributed, since they can cross lineage barriers and be reprogrammed, adopting the functional phenotypes and expression profiles of cells from other tissues. Consequently, these cells may be useful in regenerative medicine and tissue engineering<sup>20–22</sup>).

Previously it was thought that MSCs are not limited in their application, and that they represent a therapeutic fortune. However, several researchers, including us, have recently demonstrated that this notion is incorrect and that there are certain limitations in the use of MSCs<sup>23–25</sup>). The aim of this review is to discuss the possibilities, limitations, and future clinical applications of MSCs (Table 1).

## REGENERATIVE REHABILITATION—A NEW FIELD OF MEDICINE

The definition of regenerative rehabilitation can be found on the American Physical Therapy Association website: “Regenerative Rehabilitation is the integration of principles and approaches from rehabilitation and regenerative medicine with the ultimate goal of developing innovative and effective methods that promote the restoration of function through tissue regeneration and repair.”<sup>26</sup>)

In order to become a functionally vital organ, a regenerated organ must adapt to the existing homeostasis of the entire body. Transplanted organs undergo a number of adaptive processes to resume their potential<sup>27, 28</sup>). Rehabilitation is crucial to the success of regenerative medicine, and regenerative medicine and rehabilitation can contribute in many ways in patient treatment and care plans. The integration of rehabilitation into regenerative medicine is necessary to achieve an optimal end point.

## POSSIBILITIES IN THE APPLICATION OF MSCS TO REGENERATIVE REHABILITATION

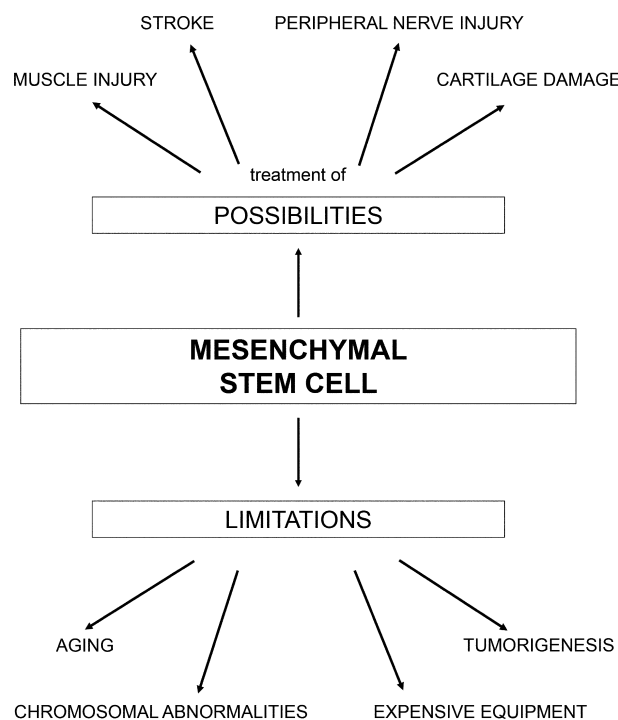
Skeletal muscle treatments have integrated regenerative medicine and rehabilitation. Regardless of the cause of injury, muscle injury recovery consists of degeneration, inflammation, regeneration, and fibrosis<sup>29, 30</sup>). Chronic and severe muscle damage usually only partially heals and scar tissue forms or fibrosis results, while acute and minor injuries heal well in most cases. If a scar lingers, total regeneration of the muscle is impossible. An alternative approach has been introduced by

**Table 1.** Characteristics of the articles included in this review

MSCs in regenerative rehabilitation	Main results	First author, journal, and year of publication (chronology)	Ref.
MSCs in the rehabilitation of damaged muscles	Rejuvenation of the aged skeletal muscle, increased muscle healing after severe injury, slowed muscle tissue degeneration, without significant complications.	McBride TA et al. <i>Mech Ageing Dev</i> , 1995.	43)
		Jubrias SA et al. <i>J Appl Physiol</i> , 2001.	44)
		Dreyer HC et al. <i>Muscle Nerve</i> , 2006.	42)
		Tanaka S et al. <i>J Phys Ther Sci</i> , 2009.	45)
		Ambrosio F et al. <i>Tissue Eng Part A</i> , 2010.	41)
		Tanaka S et al. <i>J Phys Ther Sci</i> , 2015.	46)
MSCs in stroke rehabilitation	Formation of synapses and axons and improvement in electrophysiological parameters, clinical improvement on determined by the Stroke Impact Scale and Action Research Arm Test, without significant complications.	Kondziolka D et al. <i>Neurology</i> , 2000.	47)
		Nelson PT et al. <i>Am J Pathol</i> , 2002.	49)
		Kondziolka D et al. <i>J Neurosurg</i> , 2005.	48)
		Lee JS et al. <i>Stem Cells</i> , 2010.	50)
		Bhasin A et al. <i>Cerebrovasc Dis Extra</i> , 2011.	51)
		Honmou O et al. <i>Brain</i> , 2011.	52)
MSCs in the rehabilitation of damaged peripheral nerves	Improved axonal organization and increased myelin thickness, better functional recovery and improvement in nerve regeneration, without significant complications.	Park K et al. <i>J Phys Ther Sci</i> , 2015.	53)
		Salomone R, et al. <i>Muscle Nerve</i> , 2013.	57)
		Guo ZY et al. <i>Neural Regen Res</i> , 2015.	54)
		Wang P et al. <i>Neurosci Lett</i> , 2015.	55)
		Seyed Foroutan K et al. <i>Trauma Mon</i> , 2015.	56)
MSCs in the rehabilitation of damaged cartilage	Repair of damaged cartilage, cartilage healing, efficient recovery of function, without significant complications.	Lasso JM, et al. <i>J Plast Reconstr Aesthet Surg</i> , 2015.	58)
		Cao L, et al. <i>Biomaterials</i> , 2011.	61)
		Johnson K, et al. <i>Science</i> , 2012.	60)
		Wei X, et al. <i>Acta Pharmacol Sin</i> , 2013.	59)

regenerative medicine, which includes the treatment of skeletal muscle injuries by promoting myofiber regeneration and inhibiting the formation of scar tissue. A factor contributing to the formation of scar tissue is transforming growth factor beta 1, TGF- $\beta$ 1<sup>31, 32</sup>; hence, administration of TGF- $\beta$ 1-specific inhibitors has been suggested as an anti-fibrogenic approach<sup>33–35</sup>. In animal models, TGF- $\beta$ 1 antagonists have decreased fibrosis remarkably, while concomitantly improving myofiber regeneration<sup>33, 34</sup>. The regeneration of myofibers is mostly accomplished by muscle MSCs, or satellite cells (Fig. 1). These cells are concentrated in the myofiber periphery and are activated in response to muscle injury<sup>36–38</sup>. The age-related dysfunction of these muscle stem cells in the elderly leads to an impaired healing response following skeletal muscle injury. Factors circulating in the aged microenvironment force the differentiation of muscle stem cells from a myogenic to a fibrogenic lineage<sup>39</sup>, resulting in enhanced scar tissue formation. Further compromising regeneration, the profibrogenic switch is accompanied by decreased proliferative capacity of aged muscle stem cells. Therefore, it is logical to propose transplanting young muscle stem cells in order to enhance the regenerative potential of aged skeletal muscles. However, this is not advisable. The transplantation of even embryonic stem cells into an aged environment results in a rapid decline in their regenerative potential<sup>40</sup>. Rejuvenation of aged skeletal muscles would help transplanted stem cells in the treatment of skeletal muscle injuries. According to a rodent study, running on a treadmill after stem cell transplantation into severely contused muscle increases the myogenic contribution of the donor cells<sup>41</sup>. Therefore, a synergy between physical and cellular therapies may exist. Thus, muscles capable of producing a contraction may serve as a powerful tool in rejuvenating the regenerative potential of aged muscle. There is plenty of evidence showing that even exercise programs initiated late in life may enhance the ability of muscle healing after severe injury, while concomitantly slowing down tissue degeneration<sup>42–46</sup>.

In addition to application to the recovery of injured muscles, MSCs can be applied in rehabilitation after cerebrovascular insult (Fig. 1). Sixteen years ago Kondziolka et al. published results of the first clinical study of cell therapy for stroke<sup>47</sup>. Twelve patients, 6 months to 6 years after cerebral infarction onset, were treated by transplantation of immortalized NT2N cells into the subcortical grey matter. These cells were treated with retinoic acid, which led to differentiation into functional neurons. Of note, after transplantation in animal models of stroke, the NT2N cells formed synapses and axons and led to improvements in electrophysiological parameters. However, three patients died before the end of the study. The reasons for death were recurrent stroke, myocardial infarct (MI), and pneumonia. In contrast, no complications<sup>48</sup> were observed in the following study that included 14 patients. In these patients, clinical improvement was determined by the Stroke Impact Scale and Action Research Arm Test. However, the drawback of this study was the small number of patients. In addition, one of the treated patients died 27 months after cell transplantation from MI. The autopsy showed that the injected cells survived for at least 2 years after therapy<sup>49</sup>. In the past few years, several clinical studies of cellular therapy<sup>50–53</sup> have resulted in many publications on the topic. In these and similar studies, MSCs were usually applied intravenously from 5–9 days to 3–12 months after stroke. The transplantations were conducted safely, without significant complications. In spite of this, definitive conclusions from these studies cannot be made since the studies included small numbers of patients.



**Fig. 1.** Mesenchymal stem cells: possibilities and limitations in their application

Direct treatment of damaged peripheral nerves with MSCs has also been demonstrated to be effective. Numerous encouraging animal studies have shown that stem or progenitor cell treatments can rescue some degree of neurological function after injury<sup>54-56</sup> (Fig. 1). In a rat model of facial nerve injury, MSCs were applied to a transected facial nerve after anastomosis. The results showed that the MSC-treated nerve showed improvements in terms of axonal organization and myelin thickness when compared to nerves that had only been sutured<sup>57</sup>. In another study, MSCs were injected subepineurally one week after sciatic nerve injury in rabbits. Nerves that were grafted with MSCs showed better functional recovery and improved nerve regeneration<sup>58</sup>.

Although the exact mechanism by which MSCs repair damaged cartilage is still not known, the ability of these cells to induce proliferation and differentiation of resident progenitor cells or their innate ability to differentiate into chondrocytes may contribute to the repair of damaged cartilage (Fig. 1)<sup>59</sup>. Transduced MSCs expressing IL-1Ra or antagonists of TNF may both enhance the reparative process through their inherent chondrogenic potential and retard the degradative process in cartilage lesions<sup>60</sup>. Advances in the fabrication of biodegradable scaffolds that serve as beds for MSC implantation will hopefully lead to better biocompatibility and host tissue integration. In addition, minimal toxicity has been observed in studies using animal models and genetically manipulated stem cells transduced with retroviral and adenoviral vectors<sup>61</sup>. Thus, future strategies may incorporate the use of MSCs as delivery vehicles for chondrogenic and angiogenic growth factors.

Traditional rehabilitation training programs focus on the whole body and physiological responses to mechanical loading and/or modalities. In contrast, regenerative medicine pays more attention to molecular, cellular, and histological aspects of tissue regeneration. The integration of the two approaches is a great challenge, but would likely have a synergetic impact on tissue regeneration.

## LIMITATIONS IN THE APPLICATION OF MSCS TO REGENERATIVE REHABILITATION

The aging process has been shown to alter the immune system, as well as the functionality of stem cells<sup>25</sup>. The proliferative activity of MSCs significantly decreases during the aging process, which limits their potential for differentiation<sup>62</sup>. New results have indicated that age-related changes in MSCs should be taken into account whenever these cells are considered for therapy (Fig. 1). Although MSCs from older volunteers had the ability to form colonies, MSCs obtained from young donors formed a larger number of colonies with more cells<sup>63</sup>. These studies confirmed previous findings in the literature on the impact of aging on the differentiation and therapeutic potential of MSCs.

Tumorigenesis is one of the big obstacles in MSC therapy (Fig. 1). The effect of MSC therapy on the growth or metastasis of existing tumors has not yet been clarified. It is possible that a small number of stem cells may escape and expand in the graft site and form a tumor<sup>64</sup>. As discussed by Reya et al.<sup>65</sup>, there is a relationship between stem cells and tumor cells, and normal stem cells could be the targets of transforming mutations. These results were confirmed by Miura et al.<sup>66</sup>. Their research was focused on investigating murine bone marrow-derived MSCs and their ability to become spontaneously transformed with accumulated chromosomal abnormalities (Fig. 1), i.e., structural and numerical aberrations during passage, to form fibrosarcoma *in vivo*. The process of transformation was clearly documented, leading to the first report on tumorigenesis of murine bone marrow-derived MSCs. Although the authors did not observe spontaneous immortalization during studies on the same type of stem cells derived from humans, this can be explained by the far more complicated mechanisms that keep human cells more stable.

In another study, Rosland et al.<sup>67</sup> demonstrated spontaneous malignant transformation of human MSCs. The procedure for expanding cell lines was carried out independently in two laboratories, showing rates of transformation of 40% and 50%. After malignant transformation, the level of telomerase significantly increased, which is common for human MSCs<sup>68-70</sup>. In summary, the induction of cancer by transplantation and mutational transformation of MSCs cannot yet be excluded<sup>71</sup>.

Additional aspects related to the practicality of MSC application are their handling and commercialization, which makes it difficult to industrialize these processes. It is very important to ensure pure cell lines, not cross-contaminated ones, before MSC therapies can be commercialized. Torsvik et al.<sup>72</sup> clearly showed, after facing many problems they did not expect, such as cross-contamination, that all cell lines should be verified by DNA fingerprinting and the use of electronic databases of authenticated DNA profiles. Furthermore, scientific journals, as well as funders of grant proposals, should require such verification of cell lines used in experiments.

In conclusion, to fully and reliably investigate the therapeutic potential of MSCs, it is crucial to use proper equipment and establish efficient and reproducible processes of isolation, cultivation, and differentiation, so as to obtain a homogenous MSC population for use in clinical applications (Fig. 1). This is one of the biggest challenges for achieving greater successes in this field<sup>73</sup>.

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