



MINI-REVIEW

Mesenchymal Stem Cells; Defining the Future of Regenerative Medicine

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ABSTRACT

Cell therapy has been considered as the third pillar of medicine. There are several kinds of cells attracted researchers attention whereas the growing interest in mesenchymal stem cells (MSCs) for regenerative purposes has enabled them to explore the versatile characteristics for regenerative purposes. So far, near about 5000 clinical trials using MSCs, authenticating the clinical applicability of these cells. Their multipotent differentiation and unique immunosuppressive properties have made them ideal candidate in cell therapeutic approaches. Recent advances have been observed in the homing of these cells to enhance their transplantation efficacy. These cells have been proposed as the ideal candidates for cancer therapy and have been engineered for targeted cancer therapy. Their successful applications and responses have termed them the ideal cells for the future of regenerative medicine.

Keywords: Mesenchymal stem cells, regenerative medicine, cell therapy, clinical practice, stromal cells

Mesenchymal stem cells also known as multipotent stem cells (MSCs) which have been identified by Friedenstein in 1976, are the main cells of connective tissue which are present in almost all kind of tissues and represent the origin of stromal cells [3]. They can differentiate into different cell types such as adipocytes, osteocytes, chondrocytes, and muscle cells. [1, 2]. These cells have been characterized as positive for CD105 (SH2), CD73 (SH3), CD44 and CD90

cell surface markers and negative for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules. Furthermore, plastic-adherence characteristics and their differentiation to different lineages confirm their multipotency [4]. MSCs isolated from different tissues is different ranging their numbers from 0.001 to 0.01% in a tissue [5]. It has been proven that from 1g of adipose tissue 5×10^3 MSCs can be isolated, which is 500 times more cells than 1g bone marrow [6, 7] representing

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adipose tissue as a good source of MSCs for clinical purposes [8]. MSCs have been isolated from almost all types of tissues, some of them are given in table 1. As these are termed as multipotent stem cells, they have potential to differentiate themselves towards almost all kinds of cells as shown in table 2.

Table 1: Source of MSCs and their isolation year

Sr No.	Source of MSCs	Year of Isolation	References
1	Bone marrow	1998	[9, 10]
2	Trabecular bone	2003	[11]
3	Periosteum	2004	[12]
4	Articular cartilage	2004	[13]
5	Synovium	2001	[14]
6	Synovial fluid	2004	[15]
7	Muscles	2001	[16]
8	Adipose tissue	2003	[17]
9	Tendons	2003	[18]
10	Blood	2001	[19]
11	Blood vessels	2004	[20, 21]
12	Umbilical cord vasculature	2003	[22]
13	Fetal tissues	2002-3	[23, 24]
14	Skin	2001	[16]
15	Spleen and Thymus	2004	[20]

Table 2: In vitro differentiation potential of MSCs showing their source of isolation and differentiated lineage.

Sr No.	Isolated Cells	Differentiated Lineage	References
1	BM-MPCs	Osteoblasts	[10]
2	BM-MPCs	Chondrocytes	[10, 25]
3	BM-MPCs	Adipocytes	[10]
4	BMCs	Cardiac myocytes	[26]
5	Ad-MSCs	Fibroblasts	[8]
6	Ad-MSCs	Myofibroblasts	[8, 27]
7	BM-MFbs	pericytes	[28]
8	SM-MSCs	Skeletal myocytes	[29]
9	MSCs	Tenocytes	[30]
10	BM-SCs	Retinal cells	[31]
11	BM-MSCs	Neural cells	[32]

12	PMCs	Astrocytes	[33]
13	MSCs	Hepatocytes	[34]
14	MSCs	Hematopoietic Supporting stroma	[35]
15	BM-MSCs	Pancreatic cells	[36]

Abbreviations: BM-MPCs (bone marrow mesenchymal progenitor cells), BMCs (bone marrow cells), Ad-MSCs (adipose derived mesenchymal stem cells), BM-MFbs (bone marrow derived myofibroblasts), SM-MSCs (synovial membrane derived mesenchymal stem cells), BM-SCs (bone marrow derived stem cells), PMCs (primitive mesenchymal cells)

Clinical Applications of MSCs:

MSCs are receiving increased attentions from all over the world by researchers for their clinical purposes due to their various properties e.g. easy proliferation, multi-lineage differentiation potential, immunomodulation and paracrine effects [1, 2, 37-40]. Their immune privileged characteristics are due to the major histocompatibility (MHC) I positive and MHC II negative. They also lack the co-stimulatory molecules like CD40, CD80, and CD86. Their little immune response is due to the low levels expression of MHC I antigens which may activate T cells but these cells lack co-stimulatory molecules which are responsible for secondary signals and result in reduced immune surveillance [41]. Their multipotent differentiation capacity and unique immunological properties, have made them potential agent in regenerative medicine and have gained the interest of researchers in cell-based therapies. Moreover, they are easy to obtain, can readily be harvested from cryopreserved, and expanded many times *in vitro* [42]. MSCs also have shown some trophic effects and produce number of growth factors and cytokines [43] which make them ideal candidates in cell replacement therapies, tissue repairing and regeneration, immunomodulation and disease modelling studies.

MSCs in Wound Healing:

Cell therapy or cultured epithelial cell grafts is a common practice for burn and traumatic wound healing in hospitals using the cells derived from cadaver skin. This method has numerous problems, such as limited availability of cells, graft rejection etc. In the quest for alternative cells, to heal cutaneous or non-healing wounds, MSCs have shown an attracted clinical response [44-47]. MSCs also have been applied in clinics using combinatorial approaches to heal the diabetic ulcers [46, 48], non-healing acute and chronic wounds [49]. Site specific injection of *in vitro* expanded MSCs have also shown very positive results in both preclinical and clinical studies for burn wounds [50, 51].

MSCs in Cancer Therapy:

Cancer therapy is the application of different methodologies to treat cancer. In cancer, cells lose their regular cell cycle checkpoints and start dividing uncontrolled [52]. Up to now, there is no accurate or recommended treatment for cancer and past decades have witnessed the huge number of ideas targeting cancer and recently it has been finalized that cancer is caused by some unknown mutations in human genetic makeups [53, 54]. Cell therapy or stem cell therapy has been proposed as one of the most promising targeted therapies to treat cancer. T-cells and MSCs have been considered as the most promising agents for cancer therapy after having hundreds of successful clinical trials [55]. Mesenchymal stem cells are the main agents of epithelial-mesenchymal transition (EMT), creating tumor microenvironments. A very strong relationship has been found in the role of EMT microenvironment leading to tumor development [56, 57] and it has been found that, EMT microenvironment may arise cancer stem cells becoming abnormal or losing their cell cycle checkpoints [58]. A number of epigenetic or

environmental factors may be the reasons to create tumor microenvironments [59, 60]. Obesity has also been termed as one of these factors and it has been described that Adipose Cells play an important role in the creation of tumor microenvironments [61]. Studies have shown that MSCs are very responsive as a part of cell therapy against tumor that may be due to the paracrine effect of normal cells to recognize and apoptosis the tumor cells [62-66].

Conclusion:

Stem cell therapy has become an integrated part of medicine as a modern approach to treat diseases. MSCs have been called as most reliable cells, applied in stem cell therapy because of their versatile properties. MSCs have shown the capability to treat numerous diseases e.g. injured tissue such as bone and cartilage etc [67]. A number of opinions have been given so far regarding methods, timing and cell sources to transplant MSCs for clinical purposes which have received many recommendations [65].

Their immunomodulatory potential in regenerative medicine, paracrine effects and cell survival after transplantation have been followed in a number of pre-clinical and clinical trials of various diseases such as osteo-diseases, and cardiovascular diseases etc. Clinical and pre-clinical studies are still in progress to assess their regenerating potentials, which are going to become an important tool defining the future of regenerative medicine [68].

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Conflict of Interest:

There is no any conflict of interest with any person or organization regarding this manuscript.

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