American Journal of Pharmacology

Review Article
Published: 24 Sep, 2018

Sources of Mesenchymal Stromal Cells: An Overview

Soysa NS[1]* and Alles NA[2]

[1]*Department of Oral Medicine and Periodontology, University of Peradeniya, Sri Lanka*

[2]*Department of Biochemistry, University of Peradeniya, Sri Lanka*

Abstract

Cell based therapy has become the center of attention in developing novel treatment strategies to many disease conditions. Especially stem cells have gathered much attention due to their self-renewal ability and clonogenicity. Hematopoitic Stem Cell (HSC) therapy is commonly employed in managing many cancers and conditions involving blood and immune system. With the discovery of mesenchymal stem cells which are found co-localized with HSCs in bone marrow, they have become more popular in past few decades due to their multitude of attractive biological features which make these cells the most attractive cell in regenerative medicine and dentistry. Tissue repair properties, ability to secrete paracrine factor, differentiation ability, immunomodulation and immune-privileged properties make them more amenable to treat many disease conditions like bone diseases, diabetes, strokes, myocardial infarction, etc. Most importantly the ability to isolate these cells from various tissues could overcome the many problems related to cell based therapies.

Introduction

Mesenchymal Stem Cells/Mesenchymal Stromal Cells (MSCs) are non-hematopoietic, multipotent fibroblastoid like cells with self-renew abilities. MSCs are characterized by their trilineage differentiation potential into bone, cartilage and fat tissue. Though the osteogenic potential of certain cells in bone marrow had been identified in late 1860's MSCs have been first isolated in bone marrow by Friedenstein et al., [1]. These findings were substantiated by the similar works done by Pittenger et al., [2] which ultimately led to the recognition of this discrete stem cells in bone marrow stroma. MSCs constitute 0.001% to 0.01% of the total nucleated cells in the heterogeneous cell population in marrow. Though the concept of MSCs actually attributed to Bone Marrow derived Mesenchymal Stem Cells (BM-MSCs) however, at present time it encompasses cells from other sources such as adipose tissue, umbilical cord blood, umbilical cord, peripheral blood, dental tissues, nasal mucosa, salivary glands etc. and *de facto* almost from any postnatal tissue compartment [3]. MSCs are characterized by other properties such as adherence to plastic in culture and many cell surface markers they express as assessed by flow cytometry. It has been demonstrated that depend on the type of tissue the panel of antigens might differ but still they should express the more defining cell surface antigens such as CD73, CD90 and CD105. Bone marrow MSC niches include both endosteal and perivascular niches (Figure 1). In the bone marrow, MSCs are important in development and maintenance of the hematopoiesis by providing many soluble factors such as cytokines and growth factors. In addition, MSCs directly interact with the adjacent neighboring cells including HSCs and extracellular matrix *via* adhesion molecules and extracellular matrix proteins including integrins, ICAMs and selectins. There is a plethora of reports to show that MSCs are involved in immunoregulation by interacting with both myeloid and lymphoid cells of innate and adaptive immune systems. Immunoregulatory effects exerted by MSCs are *via* direct cell-to-cell interaction as well as by secreting soluble factors such as cytokines. MSCS mainly exert immunosuppressive effects on T cells, B cells and DCs [4-7]. However, interestingly immunoenhancing effects have been observed with B cells when co-cultured with MSCs suggesting that the cultural microenvironment may have some role for this conflicting observation [8]. MSCs have been demonstrated to exert tissue repair by homing to the injury site guided by chemokines released as a result of tissue damage and then differentiate into organ specific mature cells and exert their trophic effects at the injured tissue mimicking the leukocyte migration to sites of inflammation (Figure 2). MSCs home to the injured tissue from the circulation by rolling on the endothelium, adhesion, trans-endothelial migration, extravasation, and then migration towards the injured tissue (Figure 2). Given the lineage conversion ability of MSCs, their hematopoiesis support, and their immunoregulatory capabilities have led these multipotent cells to gain wide popularity in the field of stem cell biology and is considered a potential therapeutic target in ameliorating many skeletal

OPEN ACCESS

****Correspondence:***

Soysa NS, Department of Oral Medicine and Periodontology, Faculty of Dental Sciences, Pharmacology, University of Peradeniya, Sri Lanka, Tel: 0094- 81-2397470, 0768818205, 0718502120; Fax: 0094-81- 2388948; E-mail: niroshanis@pdn.ac.lk

Received Date: *22 Aug 2018*

Accepted Date: *20 Sep 2018*

Published Date: *24 Sep 2018*

Citation:

Soysa NS, Alles NA. Sources of Mesenchymal Stromal Cells: An Overview. Am J Pharmacol. 2018; 1(1): 1007.

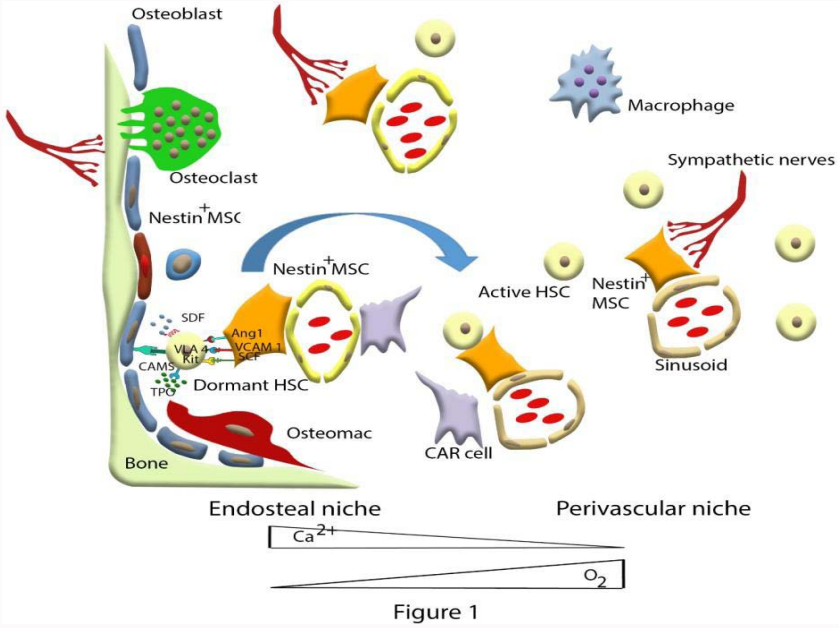

Figure 1

Figure 1: Haematopoietic-support provide by MSCs in trabecular bone.
In the bone marrow Haematopoietic Stem Cells (HSCs) reside in two niches. HSCs in the endosteal niche are quiescent and nestin$^+$ MSCs along with osteoblasts, maintain the quiescent state of HSCs via factors such as CXCL12, VCAM-1, Ang-1 and SCF. In addition, MSCs differentiate into tri-leange cells giving rise to osteoblasts, adipocytes and chondrocytes. In the perivascular niche, netin$^+$ MSCs along with CAR cells and sinusoidal endothelial cells provide the HSC maintenance.

and non-skeletal disease conditions.

Characterization of MSCs

The current understanding on MSCs is that they are derived from pericyte fraction in vessel [9,10]. Pericytes are cells which surround the endothelial cells in capillaries and micro vessels in multiple organs and important in stabilizing blood vessels. The observation that made them to come to that conclusion is that cells with MSC markers also express pericyte markers. This relationship is further emphasized by using cell sorting for pericytes (CD146+, CD34-, CD45-, CD56-) and subsequent in vitro expansion into cells of multipotent lineages (osteogenic, chondrogenic, adipogenic, and myogenic) which express MSCs markers suggesting that pericytes may act as the reservoir of precursor cells capable of giving rise to multiple lineages [9,11]. A recent report has shown that adventitial cells (cells lining the outermost layer of all blood vessels except capillaries) as precursor of MSCs, suggesting that both pericytes and adventitial cells have the potential to be the precursors of MSCs which is an indication that the marrow stem/progenitor cell system might not be a highly ordered hierarchy and that more evidence is required to resolve as to exactly what cells are the precursors of MSCs [12].

Due to the ambiguity arose as a result of isolation of MSCs from varying sources using diverse procedures and different approaches to characterize the cells, among other reasons, the International Society for Cell Therapy (ISCT) proposed three criteria for human cells to be considered as MSCs [13].

1. Plastic-adherence in culture.

2. Ability to tri-lineage differentiation *in vitro* into osteoblasts (bone), adipocytes (fat) and chondroblasts (cartilage) under appropriate culture conditions.

3. Expression of certain surface markers by flow cytometry; the expression of SH-4/4 (CD73), Thy-1 (CD90), SH-2/endoglin (CD 105) in greater than 95% of the culture and their lack of expression of markers including macrophage antigen CD 11b, monocyte and macrophage antigen CD14, B-lymphocyte antigens CD19 and CD79α, leukocyte antigens CD34 and CD45 and MHC class II antigen HLA-DR in greater than 95% of the culture.

Presently the panel of MSC markers is growing rapidly. In the pursuit of cell surface markers to best identify the MSCs has led to the identification of several markers such as CD146 (Melanoma Cell Adhesion Molecule- MCAM), CD271 (Low Affinity Nerve Growth Factor Receptor-LNGFR), Stro I and, so on [14-16]. Tormin et al., [17] showed that all CFU-Fs in human bone marrow are contained in the $CD271^+/CD45^-/CD146^{-/low}$ and the $CD271^+/CD45^-/CD146^+$ fraction, and since all human BM-CFU are found in the CD271, this has the potential to be the most appropriate marker in MSC enrichment [17]. Delorme et al., [18] found that CD200, a new marker for MSCs is not expressed in BM hematopoietic cells and appeared to be one of the most efficient markers to reproducibly purify native MSCs. In addition, the *in vitro* adipogenic, osteogenic, and chondrogenic potentials of $CD200^+$ cells were similar to that observed for cells separated by plastic adherence or selected by CD146 expression, suggesting that CD200, a new marker for MSCs not expressed on BM hematopoietic cells have the potential to be one of the most appropriate markers to maximally purify native MSCs. Therefore, the antigens that give the highest CFU-F enrichment score when the MSCs are cultured should be directed against CD105, CD73, CD146 and CD200 [19].

Types of Mesenchymal Stem Cells

The vast accumulated knowledge and current understanding on MSCs have come from studies carried out on MSCs derived from BM. BM-derived MSCs (BM-MSCs) are usually obtained from the tissues such as iliac crest or sternum and then they are either directly plated or obtained by density gradient isolation. Culturing of cells for 12 days to 14 days in growth medium containing Dulbecco's modified

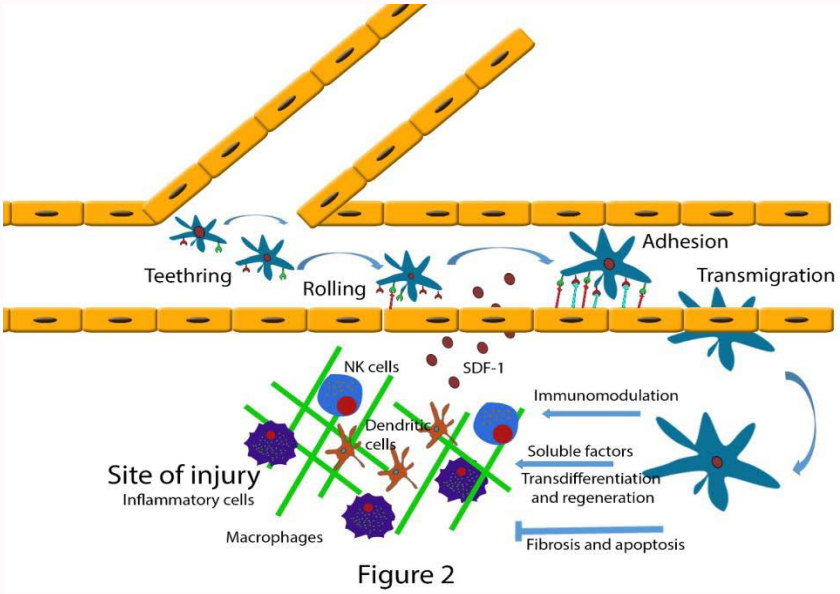

Figure 2: MSCs move from their niche in the BM into the circulation (mobilization) and then home to the injured tissue. Homing involves multi-step processes including rolling of cells on the endothelium, adhesion, transendothelial migration and extravasation. In the injured tissue MSCs by direct cell-to-cell contact and *via* secretion of trophic factors try to rejuvenate the tissue and bring back it to an acceptable functional level. In addition, MSCs differentiate and transdifferentiate into the organ-specific cells.

essential medium with fetal bovine serum and antibiotic solution usually give rise to fibroblastic like MSCs depleted of HSCs. There are plethora of reports showing other sources of tissues having cells with the features of MSCs and include amniotic fluid, umbilical cord blood, peripheral blood, muscle, adipose tissue and many organs including brain, spleen and, so on [20]. It has been observed that once MSCs occupy various other organs and tissues they exert multitude of organ specific functions in them. However, given their different sources of origin, the functional characteristics of these MSCs might vary between each other [21].

Adipose tissue

Adipose Tissue (AT) is found in many areas in the human body including visceral and subcutaneous fat pads and hip area. AT is commonly obtained by lipoaspirate following cosmetic liposuction or lipectomy procedures. AT-derived MSCs or Adipose Stem Cells (ASCs) share the similar characteristics pertaining to BM-MSCs but have the advantage of easy isolation in large quantities and greater expansile property unlike BM-MSCs. Unlike the low CFU-F number of BM-MSCs (0.001% to 0.01%), ASCs are found to be about 3% of nucleated cells in adipose stroma. Adipose stroma consists of heterogeneous cells including pre-adipocytes, fibroblasts, cells of vasculature such as endothelial and leukocytes and nervous tissue. Adipocyte precursor cells are found in Stromal Vascular Fraction (SVF) of AT. Analysis of SVF by flow cytometry has revealed that two cell populations can be identified based on CD31 and CD34 expression and ASCs are found to be localized mainly within capillaries while a small fraction is found in the lumen of small vasculature [22]. However, the physiological roles of endogenous ASCs are not clarified yet. Though surface marker expression of ASCs is very much similar to BM-MSCs. ASCs express CD34 which reduce in culture, but not CD106 as BM-MSCs suggesting that both cells types share a related but distinct phenotypes [22-24]. There is clear line of evidence to show that while ASCs are more prone to differentiate towards adipocyte lineage, BM-MSCs are more inclined towards osteogenic and chondrogenic lineages [25,26]. ASCs have been shown to secrete pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF) and, so on, making them more promising candidates in ameliorating conditions such as myocardial infarction [27,28]. Zuk et al., [29] showed that once Processed Lipoaspirate (PLA) include cells of mesenchymal nature with minute number of cells belonging to endothelial and pericyte fractions. Interestingly, the cells thus derived were able to grow continuously in culture giving rise to steady population expansions.

Amniotic fluid

Stem cells derived from Amniotic Fluid (AFS) following routine amniocentesis show cells with the features of MSCs with the ability to differentiate into cells of all three germ line lineages under specific culture conditions [30]. In addition, AFS cells show positivity to stage-specific embryonic antigen (SSEA)-4 [31].

Umbilical cord blood

Cord blood consists of varied type of stem cells, including hematopoietic stem cells, MSCs and monocyte-derived fibroblast-like macrophages with the ability to differentiate to endothelial and insulin-secreting cells (with regard to latter cells) [32-35]. Umbilical Cord blood (UCB) is considered one of the sources of stem cells with little or no whatsoever adverse effect on the baby or mother since harvesting stem cells from UCB is non-invasive and produce abundant yield due to their higher proliferative capacity and is frequently used in HSC transplantations [36]. Despite the reduced frequency of MSCs compared to BM-MSCs, the generation of progeny from a single colony is greater than BM-MSCs with 20 population doublings after eight passages, suggesting that UCB-MSCs hold promise as an alternative source of MSCs for regenerative therapy [32]. Interestingly UCB-MSCs share some of the surface antigens common to human ES cells and hematopoietic cells such as Oct-4, nanog, SSEA-4 for former and CD45 for latter cells, respectively [35,37].When these cells were sorted and enriched for $CXCR4^+$, $Oct\text{-}4^+$, $SSEA\text{-}1^+$, $Sca\text{-}1^+$, lin^-, $CD45^-$ they give rise to pluripotent Very Small Embryonic-Like (VESL) stem cells which were similar in nature to that isolated in BM by the same

group [35].

Umbilical cord/Wharton's jelly

Umbilical cord consists of vessels embedded in mucoid matrix named Wharton's jelly. Wharton's jelly contains cells such as fibroblasts, collagen and hyaluronic acid forming extracellular matrix. Umbilical Cord-derived MSCs (UC-MSCS) are similar in phenotype and biological characteristics pertaining to BM-MSCs [38,39]. UC-MSCs are another good candidate as a substitute to BM-MSCs due to the ease of accessibility, lack of painful procedures, greater proliferative potential, less risk of contamination and hypo-immunogenicity. The other attractive advantage of UC-MSCs is their ability to cryopreserve following the delivery of baby and use them in future purposes [40].

When cells from Wharton's jelly are cultured in low-serum media containing Fibroblast Growth Factor (FGF), Butylated Hydroxyanisole (BHA) and Dimethylsulfoxide (DMSO), the cells attain a neural stem cell phenotype which express neural stem cell markers such as Neuron-Specific Enolase (NSE) and neural proteins including NeuN and neurofilament M suggesting that given the appropriate culture conditions the UC-MSCS are capable of transdifferentiation into other cell types [41,42]. The ability of UC-MSCS to differentiate into dopaminergic neurons indicate that the cells are a promising target in ameliorating certain neurological disorders such as Parkinson's disease [43,44]. Moreover, these cells are able to transdifferentiate into cardiomyocytes under appropriate conditions in addition to their ability to differentiate into mesodermal lineages [45].

Peripheral blood

HSCs continuously supply mature and immature cells into the circulation from the BM while maintaining the undifferentiated stem cell population in the BM. Very modest number of MSCs also has been isolated from the Peripheral Blood (PB) in healthy volunteers as well as in patients having malignancies such as breast cancer [46]. The fresh PB usually contains cells of hematopoietic origin which express CD45 but not the mesenchymal marker CD90. When isolated by plastic adherence the cells give rise to non-fibroblast like cells mimicking monocytes/macrophages. Though the number of MSCs in PB (PB-MSCs) is very low, blood mobilization of MSCs by injecting GM-CSF could yield a 0.35% to 0.5% of MSCs by using Fibrin Microbeads (FMB) [46]. PB-MSCs are capable of self-renewal and differentiation into osteoblasts, chondroblasts and adipocytes similar to that of BM-MSCs [47]. A study done by Trivanović et al., [48] using UC-MSCs and PB-MSCs demonstrated that both cell types form less colonies in culture but colony formation is observed when $CD133^+$ cells were selected suggesting that in addition to HSCs $CD133^+$ cell fraction also has MSCs. In addition, in the presence of condition medium of BM-MSCs both UC-MSCs and PB-MSCs showed more colony formation. Moreover, UC-MSCs showed greater CFU-F and markers of pluripotent ES such as Sox2, Nanog than PB-MSCs though they have similar tri-lineage differentiation versatility and morphology.

Dental/oral tissues

MSCs have been isolated from dental tissues such as dental follicle of developing tooth, dental pulp of permanent teeth (DPSC), exfoliated deciduous teeth (SHED), periodontal ligament (PDLSC), gingival, and apical papilla of developing root (SCAP) [49-55]. Stem cells derived from the dental tissues have also been considered one of the potential candidates for regenerative medicine since they have been employed in regeneration of dental (including dentin, cementum, dental pulp and periodontal ligament) as well as non-dental tissues such as bone and nerves [56-58]. Except for DPSC which shows moderate proliferative capacity other aforementioned types show high proliferation rates [59]. *Ex vivo* expansion of PDLSCs on biocompatible scaffolds in mineralization medium for 4 weeks have clearly shown the osteogenic potential of PDLSC indicating that MSCs have a big role to play in regenerative dentistry [60]. Though MSCs from dental/oral tissues share the common features pertaining to MSCs, due to their heterogeneity and their different roles in the particular niches, the genotypic pattern may differ among each other [61]. In addition, SCAP and DFPC being developing tissues have the broadest differentiation versatility than other cells [59]. Using viral vectors, Yan et al., [62] successfully reprogrammed MSCs of SHED, SCAP and DPSCs into induced Pleuripotent Stem Cells (iPSCs) suggesting that dental tissue derived MSCs form an additional source to produce iPSCs.

Cancer Stem Cells

Cancer Stem Cells (CSCs), also known as tumor-initiating cells constitute a small fraction of cells capable of differentiation and self-renewal are found in most cancers including hematological malignancies such as acute myeloid leukemia, cancers of breast, brain, lung, ovarian, prostates, testis, liver, esophagus, colon, and melanomas. These cells are shown to have the ability of tumor initiation, self-renewal, unrestricted proliferation, metastasis and exert more resistance to chemotherapy. Once injected the cells regenerate a phenocopy of the original tumor in immune deficient mice. Some of the techniques employed in isolating CSCs include long term cell culture, Magnetic Cell Sorting (MACS) and flow cytometry. Surface markers used in isolation or identification depend on the type of cancers.

Stem cells and CSCs have some common characteristics including dormancy, DNA-repair machinery, to name a few. In addition, they show resistance to drug-induced apoptosis by up-regulating antiapoptotic proteins Bcl-2 and Bcl-xL *via* secreting cytokines such as IL-4 and IL-10 [63]. CSCs employ several mechanism to escape cell destruction by radiotherapy and chemotherapy including prevention of entry of chemicals into the cell, synthesize of enzymes to withstand radiation-induced ROS and increased DNA damage repair, multidrug chemo resistance *via* transporters, dysregulation of cell renewal pathways such as Notch, BMI1 and Wnt, interfering biotransformation of drugs and escaping programmed cell death or apoptosis [64]. Furthermore, CSCs enhance angiogenesis via secretion of proangiogenic factors such as VEGF which is further enhanced under hypoxic conditions [65]. Several studies have shown that CD133 of CSCs confers resistance to radiation and enhances tumour recurrence after therapy [64,66].

In cancer conditions, MSCs seem to migrate to sites of tumorigenesis as well as colonize other sites without any tumor cells, such as lung, liver kidney, or spleen. However the tumor specific migration is attributed to the several growth factors including PDGF, VEGF, EGF, SCF/c-Kit and stromal cell–derived factor-1/CXCR4. Given the fact that MSCs are capable of homing to active tumor sites, studies are currently carried out to seek the feasibility of using MSCs as cellular vehicles for anti-cancer drug delivery [67].

The effect of MSCs on tumor growth and development is

controversial. Several studies have shown that MSCs co-injected with tumor cells can inhibit the tumor growth in many cancer animal models [68-70]. Contrary to these findings, MSCs also have been shown to increase tumor mass along with necrosis and angiogenesis [71]. This could be due to immunosuppressive effect as well as the upregulation of Stat-3 by secreting IL-6 [72]. There are several lines of studies which suggest that MSCs could spontaneously transform, however, this should be fully elucidated as duration of culture expansion could play a major role in this phenomenon.

MSCs Culture for Regenerative Medicine

Embryonic Stem Cells (ESC) are pluripotent and have the ability to differentiate into any lineage. Though it has been shown that reprogramming of somatic cells give rise to iPSC, due to the ethical issues surrounding the procurement of ESC, MSCs become more popular cellular-based therapy in regenerative medicine. The ideal properties of stem cells required for regenerative medicine include the ability to harvest abundantly using a minimum invasive method. In addition, the cells should be able to regulate into different cell lineages reproducibly by following Good Manufacturing Practice guidelines so that they can undergo autologous transplantation or to a different host by allogeneic transplantation [73].

MSCs have a pivotal role in regenerative medicine due to their attractive biological properties and immunomodulation and unique in comparison to other treatment modalities used so far which could only either alleviates the symptoms and signs or halts further progression of the disease. Most importantly the paracrine effects they show on the resident cells to repair the effete tissue and restore its function make these cells more appealing in regenerative medicine.

MSCs from bone marrow, the primary source of MSCs for clinical applications is commonly obtained by harvesting iliac crest. Unlike HSCs which can be obtained directly from marrow, bone marrow should be first plated and amplified to obtain MSCs [19]. MSC enrichment from total cells can be done by using plastic adherence technique or by immune selection [15]. *In vitro* expansion is necessary to obtain adequate number of cells for clinical application. Among other factors culture medium, cell plating density, passage, O_2 tension, influence the expansion rate. Fatal Calf Serum (FCS) enriched with FGF-2 and PDGF or even platelet rich plasma derived products are known to promote MSCs expansion [74].

It has been shown that cells plated at low density ($<1.5 \times 10^5$ cells/cm^2) gives the highest proliferation rate [75]. Prolonged *in vitro* culturing reduces differentiation potential of MSCs. Therefore for the clinical application the recommended is 1-2 passages to prevent changes in the phenotype and expression of adhesion and other molecules necessary for effective migration and homing of cells to injured tissues. More importantly since MSCs thrive in hypoxic niches the low levels of O_2 (2% O_2) seem to induce higher proliferation and differentiation, whereas the usual normoxic conditions of 20% O_2 is thought to cause oxidative stress on MSCs [76].

Conclusion

MSCs are derived from various sources such as bone marrow, adipose tissue, umbilical cord, blood and so on. However, the yield varies depend on the tissue and they have been successfully used in therapy. However, depend on the source of MSCs; the differentiation versatility and functional equivalence of each type of cells are different indicating that there is no global stem cell type which can be used in all the disease conditions. Therefore, depending on the disease condition, the appropriate stem cell type should be carefully selected before applying in regenerative therapy.

References

1. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet. 1970;3(4):393-403.
2. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284(5411):143-7.
3. Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell. 2008;2(4):313-9.
4. Glennie S, Soeiro I, Dyson PJ, W-F Lam E, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood. 2005;105(7):2821-7.
5. Krampera M, Glennie S, Dyson J, Scott D, Laylor R, Simpson E, et al. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood. 2003;101(9):3722-9.
6. Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, Cazzanti F, et al. Human mesenchymal stem cells modulate B-cell functions. Blood. 2006;107(1):367-72.
7. Zhang W, Ge W, Li C, You S, Liao L, Han Q, et al. Effects of mesenchymal stem cells on differentiation, maturation, and function of human monocyte-derived dendritic cells. Stem Cells Dev. 2004;13(3):263-71.
8. Traggiai E, Volpi S, Schena F, Gattorno M, Ferlito F, Moretta L, et al. Bone marrow-derived mesenchymal stem cells induce both polyclonal expansion and differentiation of B cells isolated from healthy donors and systemic lupus erythematosus patients. Stem Cells. 2008;26(2):562-9.
9. Doherty MJ, Ashton BA, Walsh S, Beresford JN, Grant ME, Canfield AE. Vascular pericytes express osteogenic potential in vitro and in vivo. J Bone Miner Res. 1998;13(5):828-38.
10. Caplan AI. All MSCs are pericytes? Cell Stem Cell. 2008;3(3):229-30.
11. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. J Cell Physiol. 2007;213(2):341-7.
12. Corselli M, Chen CW, Sun B, Yap S, Rubin JP, Péault B. The tunica adventitia of human arteries and veins as a source of mesenchymal stem cells. Stem Cells Dev. 2012;21(8):1299-308.
13. Dominici M, Blanc KL, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-7.
14. Sacchetti B, Funari A, Michienzi S, Cesare SD, Piersanti S, Saggio I, et al. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. Cell. 2007;131(2):324-36.
15. Quirici N, Soligo D, Bossolasco P, Servida F, Lumini C, Deliliers GL. Isolation of bone marrow mesenchymal stem cells by anti-nerve growth factor receptor antibodies. Exp Hematol. 2002;30(7):783-91.
16. Simmons PJ, Torok-Storb B. Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. Blood. 1991;78(1):55-62.
17. Tormin A, Li O, Brune JC, Walsh S, Schütz B, Ehinger M, et al. CD146 expression on primary nonhematopoietic bone marrow stem cells is correlated with in situ localization. Blood. 2011;117(19):5067-77.
18. Delorme B, Ringe J, Gallay N, Vern YL, Kerboeuf D, Jorgensen C, et al. Specific plasma membrane protein phenotype of culture-amplified and native human bone marrow mesenchymal stem cells. Blood.

2008;111(5):2631-5.

19. JF Stoltz, Ed. Regenerative medicine and cell therapy. Amsterdam? Washington, DC: IOS Press. 2012.

20. da Silva Meirelles L, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J Cell Sci. 2006;119(Pt 11):2204-13.

21. Keyser KA, Beagles KE, Kiem HP. Comparison of mesenchymal stem cells from different tissues to suppress T-cell activation. Cell Transplant. 2007;16(5):555-62.

22. Maumus M, Peyrafitte JA, Angelo RD, Fournier-Wirth C, Bouloumié A, Casteilla L, et al. Native human adipose stromal cells: localization, morphology and phenotype. Int J Obes. 2005;35(9):1141-53.

23. Noël D, Caton D, Roche S, Bony C, Lehmann S, Casteilla L, et al. Cell specific differences between human adipose-derived and mesenchymal-stromal cells despite similar differentiation potentials. Exp Cell Res. 2008;314(7):1575-84.

24. Kern S, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006;24(5):1294-301.

25. Huang JI, Kazmi N, Durbhakula MM, Hering TM, Yoo JU, Johnstone B. Chondrogenic potential of progenitor cells derived from human bone marrow and adipose tissue: a patient-matched comparison. J Orthop Res. 2005;23(6):1383-9.

26. Vishnubalaji R, Al-Nbaheen M, Kadalmani B, Aldahmash A, Ramesh T. Comparative investigation of the differentiation capability of bone-marrow- and adipose-derived mesenchymal stem cells by qualitative and quantitative analysis. Cell Tissue Res. 2012;347(2):419-27.

27. S Kachgal, AJ Putnam. Mesenchymal stem cells from adipose and bone marrow promote angiogenesis via distinct cytokine and protease expression mechanisms. Angiogenesis. 2011;14(1):47-59.

28. Hsiao ST, Asgari A, Lokmic Z, Sinclair R, Dusting GJ, Lim SY, et al. Comparative analysis of paracrine factor expression in human adult mesenchymal stem cells derived from bone marrow, adipose, and dermal tissue. Stem Cells Dev. 2012;21(12):2189-203.

29. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001;7(2):211-28.

30. In 't Anker PS, Scherjon SA, Kleijburg-van der Keur C, Noort WA, Claas FH, Willemze R, et al. Amniotic fluid as a novel source of mesenchymal stem cells for therapeutic transplantation. Blood. 2003;102(4):1548-9.

31. De Coppi P, Bartsch G Jr, Siddiqui MM, Xu T, Santos CC, Perin L, et al. Isolation of amniotic stem cell lines with potential for therapy. Nat Biotechnol. 2007;25(1):100-6.

32. Bieback K, Kern S, Klüter H, Eichler H. Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood. Stem Cells. 2004;22(4):625-34.

33. EJ Gang, Hong SH, Jeong JA, Hwang SH, Kim SW, Yang IH, et al. In vitro mesengenic potential of human umbilical cord blood-derived mesenchymal stem cells. Biochem. Biophys Res Commun. 2004;321(1):102-8.

34. Kögler G, Sensken S, Airey JA, Trapp T, Müschen M, Feldhahn N, et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med. 2004;200(2):123-35.

35. Zhao Y, Wang H, Mazzone T. Identification of stem cells from human umbilical cord blood with embryonic and hematopoietic characteristics. Exp Cell Res. 2006;312(13):2454-64.

36. Pipes BL, Tsang T, Peng SX, Fiederlein R, Graham M, Harris DT. Telomere length changes after umbilical cord blood transplant. Transfusion. 2006;46(6):1038-43.

37. Kucia M, Halasa M, Wysoczynski M, Baskiewicz-Masiuk M, Moldenhawer S, Zuba-Surma E, et al. Morphological and molecular characterization of novel population of CXCR4+ SSEA-4+ Oct-4+ very small embryonic-like cells purified from human cord blood: preliminary report. Leukemia. 2007;21(2):297-303.

38. Lu LL, Liu YJ, Yang SG, Zhao QJ, Wang X, Gong W, et al. Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. Haematologica. 2006;91(8):1017-26.

39. Baksh D, Yao R, Tuan RS. Comparison of proliferative and multiline age differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem Cells. 2007;25(6):1384-92.

40. Arien-Zakay H, Lazarovici P, Nagler A. Tissue regeneration potential in human umbilical cord blood. Best Pract Res Clin Haematol. 2010;23(2):291-303.

41. Mitchell KE, Weiss ML, Mitchell BM, Martin P, Davis D, Morales L, et al. Matrix cells from Wharton's jelly form neurons and glia. Stem Cells. 2003;21(1):50-60.

42. Fu YS, Shih YT, Cheng YC, Min MY. Transformation of human umbilical mesenchymal cells into neurons in vitro. J Biomed Sci. 2004;11(5):652-60.

43. Fu YS, Cheng YC, Lin MY, Cheng H, Chu PM, Chou SC, et al. Conversion of human umbilical cord mesenchymal stem cells in Wharton's jelly to dopaminergic neurons in vitro: potential therapeutic application for Parkinsonism. Stem Cells. 2006;24(1):115-24.

44. Weiss ML, Medicetty S, Bledsoe AR, Rachakatla RS, Choi M, Merchav S, et al. Human umbilical cord matrix stem cells: preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease. Stem Cells. 2006;24(3):781-92.

45. Wang HS, Hung SC, Peng ST, Huang CC, Wei HM, Guo YJ, et al. Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord. Stem Cells. 2004;22(7):1330-7.

46. Kassis I, Zangi L, Rivkin R, Levdansky L, Samuel S, Marx G, et al. Isolation of mesenchymal stem cells from G-CSF-mobilized human peripheral blood using fibrin Microbeads. Bone Marrow Transplant. 2006;37(10):967-76.

47. Chong PP, Selvaratnam L, Abbas AA, Kamarul T. Human peripheral blood derived mesenchymal stem cells demonstrate similar characteristics and chondrogenic differentiation potential to bone marrow derived mesenchymal stem cells. J Orthop Res. 2012;30(4):634-42.

48. Trivanović D, Kocić J, Mojsilović S, Krstić A, Ilić V, Djordjević IO, et al. Mesenchymal stem cells isolated from peripheral blood and umbilical cord Wharton's jelly. Srp Arh Celok Lek. 2013;141(3-4):178-86.

49. Morsczeck C, Völlner F, Saugspier M, Brandl C, Reichert TE, Driemel O, et al. Comparison of human dental follicle cells (DFCs) and stem cells from human exfoliated deciduous teeth (SHED) after neural differentiation in vitro. Clin. Oral Investig. 2010;14(4):433-40.

50. Morsczeck C, Petersen J, Völlner F, Driemel O, Reichert T, Beck HC. Proteomic analysis of osteogenic differentiation of dental follicle precursor cells. Electrophoresis. 2009;30(7):1175-84.

51. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U S A. 2000;97(25):13625-30.

52. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, et al. SHED: stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci U S A. 2003;100(10):5807-12.

53. Zhang Q, Shi S, Liu Y, Uyanne J, Shi Y, Shi S, et al. Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis. J Immunol. 2009;183(12):7787-98.

54. Tomar GB, Srivastava RK, Gupta N, Barhanpurkar AP, Pote ST, Jhaveri

HM, et al. Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. Biochem Biophys Res Commun. 2010;393(3):377-83.

55. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. J Endod. 2008;34(2):166-71.

56. Demarco FF, Conde MC, Cavalcanti BN, Casagrande L, Sakai VT, Nör JE. Dental pulp tissue engineering. Braz Dent J. 2011;22(1):3-13.

57. Nör JE. Tooth regeneration in operative dentistry. Oper Dent. 2006;31(6):633-42.

58. Seo BM, Sonoyama W, Yamaza T, Coppe C, Kikuiri T, Akiyama K, et al. SHED repair critical-size calvarial defects in mice. Oral Dis. 2008;14(5):428-34.

59. Estrela C, Alencar AH, Kitten GT, Vencio EF, Gava E. Mesenchymal stem cells in the dental tissues: perspectives for tissue regeneration. Braz Dent J. 2011;22(2):91-8.

60. Trubiani O, Orsini G, Zini N, Di Iorio D, Piccirilli M, Piattelli A, et al. Regenerative potential of human periodontal ligament derived stem cells on three-dimensional biomaterials: a morphological report. J Biomed Mater Res A. 2008;87(4):986-93.

61. Waddington RJ, Youde SJ, Lee CP, Sloan AJ. Isolation of distinct progenitor stem cell populations from dental pulp. Cells Tissues Organs. 2009;189(1-4):268-74.

62. Yan X, Qin H, Qu C, Tuan RS, Shi S, Huang GT. iPS cells reprogrammed from human mesenchymal-like stem/progenitor cells of dental tissue origin. Stem Cells Dev. 2010;19(4):469-80.

63. Stassi G, Todaro M, Zerilli M, Ricci-Vitiani L, Di Liberto D, Patti M, et al. Thyroid cancer resistance to chemotherapeutic drugs via autocrine production of interleukin-4 and interleukin-10. Cancer Res. 2003;63(20):6784-90.

64. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006;444(7120):756-60.

65. Bao S, Wu Q, Sathornsumetee S, Hao Y, Li Z, Hjelmeland AB, et al. Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. Cancer Res. 2006;66(16):7843-8.

66. Chiou SH, Kao CL, Chen YW, Chien CS, Hung SC, Lo JF, et al. Identification of CD133-positive radioresistant cells in atypical teratoid/rhabdoid tumor. PloS One. 2008;3(5):e2090.

67. Lazennec G, Jorgensen C. Concise review: adult multipotent stromal cells and cancer: risk or benefit? Stem Cells. 2008;26(6):1387-94.

68. Maestroni GJ, Hertens E, Galli P. Factor(s) from nonmacrophage bone marrow stromal cells inhibit Lewis lung carcinoma and B16 melanoma growth in mice. Cell Mol Life Sci. 1999;55(4):663-7.

69. Ohlsson LB, Varas L, Kjellman C, Edvardsen K, Lindvall M. Mesenchymal progenitor cell-mediated inhibition of tumor growth in vivo and in vitro in gelatin matrix. Exp Mol Pathol. 2003;75(3):248-55.

70. Nakamura K, Ito Y, Kawano Y, Kurozumi K, Kobune M, Tsuda H, et al. Antitumor effect of genetically engineered mesenchymal stem cells in a rat glioma model. Gene Ther. 2004;11(14):1155-64.

71. Zhu W, Xu W, Jiang R, Qian H, Chen M, Hu J, et al. Mesenchymal stem cells derived from bone marrow favor tumor cell growth in vivo. Exp Mol Pathol. 2006;80(3):267-74.

72. Sasser AK, Sullivan NJ, Studebaker AW, Hendey LF, Axel AE, Hall BM. Interleukin-6 is a potent growth factor for ER-alpha-positive human breast cancer. FASEB J. 2007;21(13):3763-70.

73. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. Circ Res. 2007;100(9):1249-60.

74. Doucet C, Ernou I, Zhang Y, Llense JR, Begot L, Holy X, et al. Platelet lysates promote mesenchymal stem cell expansion: a safety substitute for animal serum in cell-based therapy applications. J Cell Physiol. 2005;205(2):228-36.

75. Sekiya I, Larson BL, Smith JR, Pochampally R, Cui JG, Prockop DJ. Expansion of human adult stem cells from bone marrow stroma: conditions that maximize the yields of early progenitors and evaluate their quality. Stem Cells. 2002;20(6):530-41.

76. Grayson WL, Zhao F, Izadpanah R, Bunnell B, Ma T. Effects of hypoxia on human mesenchymal stem cell expansion and plasticity in 3D constructs. J Cell Physiol. 2006;207(2):331-9.