APMB - Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Medico Biologiche
Vol. 114 (1) 2026

ISSN 1828-6550

DOI: 10.13129 / 1828-6550 / APMB.114.1.2026.SD4

Scholarly Dialog SD4 (1-6)

An overview of Mesenchymal stromal cells: biology, functional role and therapeutic potential

Alessandra Pelagalli

Dipartimento di Scienze Biomediche Avanzate, Università degli Studi di Napoli Federico II, Naples, Italy

Abstract

Mesenchymal stromal cells (MSCs) are multipotent non-hematopoietic cells able to auto-renewal and differentiate into mesodermal cell lineages. The cells have been attracted for their potential therapeutic roles in different diseases possessing broad spectrum of activities (immunomodulatory, trophic, anti-inflammatory and migratory). Thus, MSCs represent optimal biological “tool" for tissue regeneration approaches both in human and animals. MSCs firstly isolated from bone marrow (BM) (Friedenstein, 1970) can be obtained from different sources and organs in adults like, adipose tissue (AT), Wharton’s jelly, dental pulp, peripheral blood, etc. Upon isolation, MSCs can be characterized by their ability to grow and expand on plastic plates and can differentiate into multiple lineages like osteocytes, chondrocytes, myocytes, adipocytes, and express certain cell surface markers like cluster of differentiation (CD) CD90, CD105, CD73 and are negative for markers like CD45, CD34, CD14, CD11b, CD19. In addition, they express low level of major histocompatibility complex (MHC) class I, CD40, CD80, CD86 and do not express MHC class II molecules, which make these cells immune privileged and an ideal candidate for allogenic transplantation in diseased patients.
Recent studies demonstrating the reduced MSCs engraftment revealed that their beneficial regenerative effects primarily derive from paracrine activity (secretome release) rather than differentiation capacity.
Today, MSCs are at the forefront of regenerative medicine, offering potential treatments for a wide range of diseases (in primis musculo-skeletal, neurodegenerative and auto-immune) for which MSCs act by reducing inflammation and pain, and promoting the development of hyaline cartilage.
Future research is directed towards new and important objectives (optimization of MSC sources and dosage, use of MSC exosomes and/or in combination with other substances/cells) that can allow us to enhance knowledge and increase the number of clinical studies.

Key words: Mesenchymal stromal cells (MSCs); tissue regeneration; immunomodulation; secretome self-renewal and differentiation.

Corresponding Author: Alessandra Pelagalli - alessandra.pelagalli@unina.it

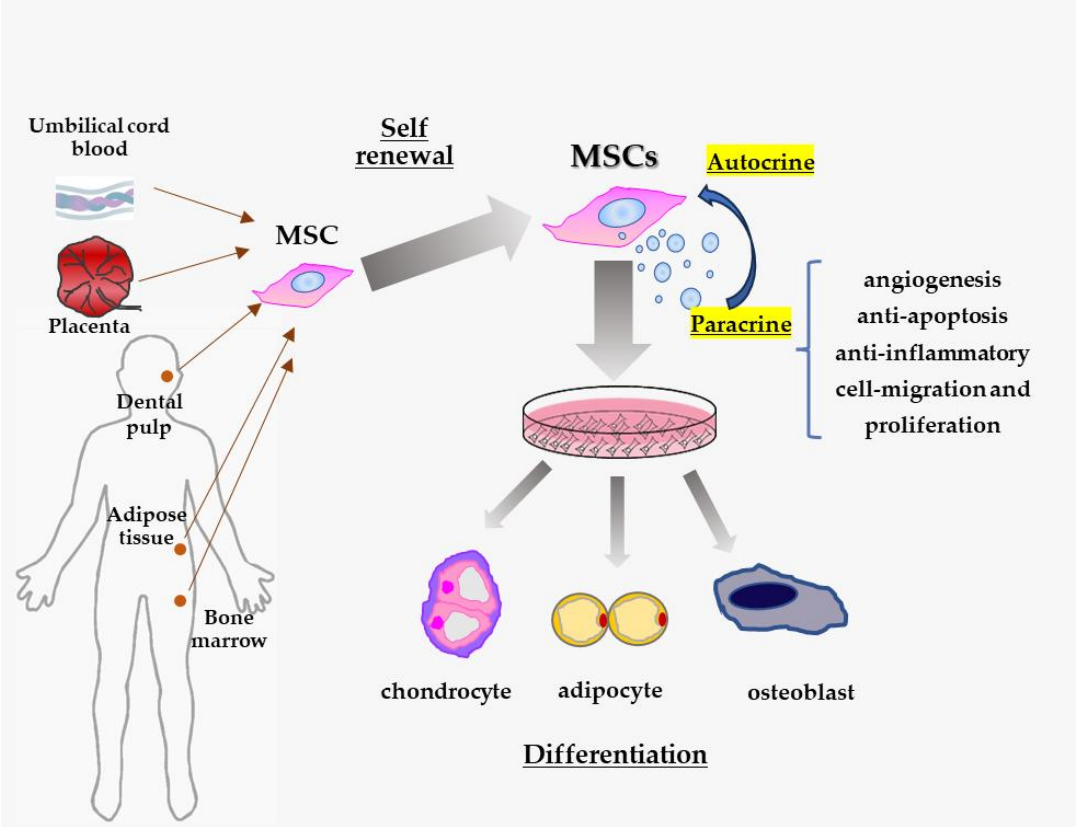
Introducing Member: Esterina Fazio

Introduction

Mesenchymal stromal cells (MSCs)

In the last years, regenerative medicine has made numerous progresses and therapies which involve adult mesenchymal stromal cells (MSC) represent a good alternative. MSCs are undifferentiated multipotent cells firstly identified as stromal or support cells for the hematopoietic stem cells in bone marrow (Fiedenstein, 1970) (1). The main characteristics of MSCs are self-renewal and the differentiation into a limited number of cell types (primarily forming bone, cartilage and fat) derived from mesoderm (Figure 1) (2,3).

Fig.1 Various isolation sites and properties of MSCs. Bone marrow, adipose tissue, umbilical cord blood and placenta are common sites for MSC extraction. MSCs can either enhance their self-renewal, differentiation, and proliferation through the autocrine effects or or secretion of trophic factors that acting through a paracrine effect. (Figure modified by Zannetti A. et al., Cells 2020, 9, 2678; doi:10.3390/cells9122678)



The self-renewal gives MSCs the possibility to create a reservoir of stem cells to promote tissue regeneration. This unique property is fundamental to repair throughout the organism's life, although it undergoes a progressive decline with age (4). Other than in bone marrow, MSCs can also be found in other postnatal organs and tissues (adipose tissue, muscle, placenta, umbilical cord, etc.) (Figure 1) in considerable concentrations to be used further for cell therapy. Notably, MSC biological characteristics, including proteome, transcriptome, and surfactome profiles, can differ according to the different cell-sources (heterogeneity of MSCs) (5,6). MSCs have been extensively investigated and characterized for their identification criteria and biological roles. According to International Society for Cellular Therapy (ISCT) (2006) MSCs must possess n. 3 minimal fundamental prerequisite: 1. ability to adhere on plastic dishes when cultured *in vitro;* 2. positive expression of CD105, CD73, CD105 (95% of MSC population) and negative expression (98 %) of CD34 (hematopoietic progenitors and endothelial cells), CD45 (pan-leucocytes), CD14 or CD11b (monocyte/macrophages), and CD19 or CD79a (lymphocyte B) (7,8). Additionally, the 98% of MSCs is negative for HLA-DR (human leucocyte) antigen-DR isotype, an MHC (major histocompatibility complex) class II cell surface receptor, if not stimulated by interferon-gamma (IFN-g) (7,8); 3. Ability to differentiate in three cell lineages of mesodermal origin: osteocyte, adipocyte and chondrocyte.

MSCs in tissue repair and regeneration

Research results focused on the MSCs roles in tissue regeneration showed different and important activities among which trophic, migratory and immunomodulation are fundamental for the therapeutic role (9,10). In fact, in a condition of tissue damage, through different direct and indirect mechanisms, MSCs target the cells implied in innate immunity: mastocytes, monocytes/macrophages, immature dendritic cells, natural killer cells, and natural T-killer cells (11,12). Moreover, MSCs act on adaptative immunity. This immunomodulatory role of MSCs need to be primed by inflammatory cytokines to be exerted (13).

However, in consideration of no engraftment of MSCs in significant numbers in damaged tissue to satisfy their therapeutic role after their administration in damaged tissue (14), other studies have been performed. Therapeutic value of MSCs has been attributed to their paracrine effects (secretome) (Figure 1) via soluble factors (growth factors, cytokines, and hormones) and extracellular vesicles (EVs) including especially exosomes that contain reparative peptides/proteins, mRNA, and microRNAs (14). Exosomes have been characterized and isolated in MSCs from different animal species showing significant advantages for that obtained from dog considered the most appropriate model for human diseases (15). Notably, canine exosomes demonstrated potential therapeutic activity against a variety of diseases (in particular osteoarticular and gastrointestinal) by not only acting as bilipid membrane particles, but also as carriers, transporting various substances to specific targets, thereby promoting their enhanced beneficial abilities (16).

However, other that paracrine activity of MSCs altering nearby surrounding cells, an autocrine role has been attributed to the conditionated medium. It acts enhancing their own migration, wound healing closure and thus suggesting its role as modulator of MSC behaviour in tissue repair (Figure 1) (16). Indeed, the secretome could be a promising alternative to stem cell therapy, offering numerous advantages in terms of safety and efficacy, compared to the direct application of MSCs.

MSCs and main clinical applications

The therapeutic potential of MSCs is extensively increased along the last decades pointing towards new diseases to potentially treat. Many studies demonstrated the efficacy of MSCs in pre-clinical models of musculoskeletal, nervous, cardiovascular, and immune diseases showing a particular activity for osteoarthritis (OA). Several findings demonstrate that intra-articular injection of MSCs in damaged tissue improved the clinical condition accompanied by pain reduction and enhanced functional capacity (17). In this condition, exosomes from MSCs seem to act predominantly mitigating inflammation and enhancing tissue regeneration through stimulating

the shift of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages and reducing expression of IL-1β, TNF-α, and IL-6 (pro-inflammatory cytokines). Additionally, it has been shown that exosomes increase the expression of IL-10 chondrogenic genes SOX9 and enhance the proliferation and migration of chondrocytes, as well as diminish chondrocyte apoptosis (18). Similar therapeutic results have been demonstrated in domestic animals (horse and dog) affected by OA for which an improved joint function complemented by pain and inflammation reduction was shown (19).

Recently mostly attention has paid to MSCs employed in cardiovascular sciences for which an interesting activity in neovascularization and cardiac function improvement following myocardial infarction was demonstrated (20). In addition, in pre-clinical approaches, bone marrow and adipose MSCs have been used for the treatment of chronic ischemic heart disease revealing enhanced cardiac function, reduced infarct size, and improved angiogenesis (21). Recent, new clinical trials are assessing the safety and efficacy of allogeneic MSC therapy in patients with several cardiac diseases (including acute myocardial infarction, chronic ischemic and non-ischemic cardiomyopathy). Encouraging results obtained suggest continuing for the development of allogeneic cell-based regenerative therapies for structural and functional disorders of the myocardium. However, many challenges remain, such as addressing long-term safety, serial stem cell injections, and optimal cell type, dose, and delivery route (22).

Furthermore, the beneficial effects of MSCs enhancing neuronal repair in neurodegenerative diseases including spinal cord injury and stroke have been shown (23). In particular, the neuroprotective role exerted by MSCs seem to be mediated by the production of various trophic factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF),, and insulin-like growth factor-1 (IGF-1), which contribute to recovering neurobehavioral function and stimulating endogenous regeneration (24).

Clinical applications of autologous and allogeneic MSCs are already available for treating a range of diseases or conditions albeit both of them have their own advantages and disadvantages in their medical practice. In addition, heterogeneity of MSCs in term of individuals, tissue source, and biological potential impacts their therapeutic potency.

Conclusions

In conclusion, the results emerging from published papers on a series of a Special Issue by International Journal of Molecular Sciences (“Novel MSC Perspectives: From Cell Regulation to Tissue Regeneration”, 2019-2024, guest editor Alessandra Pelagalli) paint a picture of an orchestrated web of signals and interactions that can be modulated to impact advances in MSC translation to reach the goal of using MSC in routine clinical practice (25). Currently, the

available data point to the need for stem cell precision medicine in relation to several factors (donor characteristics, specific culture conditions, and specific therapeutic applications) also suggesting that MSC therapy warrants further investigation in large-scale trials (25).

Conflicts of Interest: the Author declares no conflict of interest

References

1. Friedenstein, A.J., Chailakhjan, R.K., Lalykina, K.S. (1970). The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet, 3, 393-403. doi: 10.1111/j.1365-2184.1970.tb00347.x.
2. Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., Horwitz, E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy, 8, 315-317. doi: 10.1080/14653240600855905.
3. Păunescu, V., Deak, E., Herman, D., Siska, I.R., Tănasie, G., Bunu, C., Anghel, S., Tatu, C.A., Oprea, T.I., Henschler, R., Rüster, B., Bistrian, R., Seifriedet, E. (2007). In vitro differentiation of human mesenchymal stem cells to epithelial lineage. J Cell Mol Med, 11, 502-508. doi: 10.1111/j.1582-4934.2007.00041.x.
4. Yang. Y.H.K. (2018) Aging of mesenchymal stem cells: Implication in regenerative medicine. Regen Ther, 9, 120-122. doi: 10.1016/j.reth.2018.09.002. eCollection 2018 Dec.
5. Chen, J.Y., Mou, X.Z., Du, X.C., Xiang, C. (2015). Comparative analysis of biological characteristics of adult mesenchymal stem cells with different tissue origins. Asian Pac J Trop Med, 8, 739–746. doi: 10.1016/j.apjtm.2015.07.022. Epub 2015 Jul 29.
6. Kwon, A., Kim, Y., Kim, M., Kim, J., Choi, H., Jekarl, W.D., Lee, S., Kim, J.M., Shin, J.C., Park, I.N. (2016). Tissue-specific differentiation potency of mesenchymal stromal cells from perinatal tissues. Sci Rep, 6, 23544. doi: 10.1038/srep23544.
7. Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., Horwitz, E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 8, 315e7. doi: 10.1080/14653240600855905.
8. Boxall, S.A., Jones, E. (2012). Markers for characterization of bone marrow multipotential stromal cells. Stem Cell Int, 2012, 975871. doi: 10.1155/2012/975871.975871.
9. Fu, X., Liu, G., Halim, A., Ju, Y., Luo, Q., Song, G. (2019). Mesenchymal stem cell migration and tissue repair. Cells, 8, 784. doi: 10.3390/cells8080784.
10. Zannetti, A., Benga, G., Brunetti, A., Napolitano, F., Avallone, L., Pelagalli, A. (2020). Role of aquaporins in the physiological functions of mesenchymal stem cells. Cells, 9, 2678. doi: 10.3390/cells9122678.
11. Zachar, L., Bačenková, D., Rosocha, J. (2016). Activation, homing, and role of the mesenchymal stem cells in the inflammatory environment. J Inflamm Res, 9, 231-240. doi: 10.2147/JIR.S121994. eCollection 2016.
12. Regulski, M.J. (2017). Mesenchymal stem cells: “guardians of inflammation.” Wounds, 29, 20-27.
Krampera, M. (2011). Mesenchymal stromal cell 'licensing': a multistep process. Leukemia, 25, 1408-1414. doi: 10.1038/leu.2011.108. Epub 2011 May 27.
13. Spees, J.L., Lee, R.H., Gregory. C.A. (2016) Mechanisms of mesenchymal stem/stromal cell function. Stem Cell Res Therap, 7, 125. doi: 10.1186/s13287-016-0363-7.
14. Saba, E., Sandhu, M.A., Pelagalli, A. (2024). Canine mesenchymal stromal cell exosomes: state-of-the-art characterization, functional analysis and applications in various diseases. Vet Sci, 11, 187. doi: 10.3390/vetsci11050187.
15. Pelagalli, A., Nardelli, A., Lucarelli, E., Zannetti, A., Brunetti, A. (2018). Autocrine signals increase ovine mesenchymal stem cells migration through Aquaporin-1 and CXCR4 overexpression. J Cell Physiol, 233, 6241-6249. doi: 10.1002/jcp.26493. Epub 2018 Mar 1.
16. Sun, H., Zhai, H., Han, K., Ma, H., Tan, Y., Li, S., Liu, Z., Cheng, L., Lu, Q., Zhou, L., Liu, P. (2024). Clinical outcomes of autologous adipose-derived mesenchymal stem cell combined with high tibial osteotomy for knee osteoarthritis are correlated with stem cell stemness and senescence. J Transl Med, 22, 1039. doi: 10.1186/s12967-024-05814-3.

17. Vonk, L.A., van Dooremalen, S.F.J., Liv, N., Klumperman, J., Coffer, P.J., Saris, D.B.F., Lorenowicz, M.J. (2018). Mesenchymal stromal/stem cell-derived extracellular vesicles promote human cartilage regeneration in vitro. Theranostics, 8, 906-920 (2018). doi: 10.7150/thno.20746. eCollection 2018.
18. Brondeel, C., Pauwelyn, G., de Bakker, E., Saunders, J., Samoy, Y., Spaas, J.H. (2021). Review: Mesenchymal Stem Cell Therapy in Canine Osteoarthritis Research: "Experientia Docet" (Experience Will Teach Us). Front Vet Sci, 8, 668881. doi: 10.3389/fvets.2021.668881. eCollection 2021.
19. Shi, W., Xin, Q., Yuan, R., Yuan, Y., Cong, W., Chen, K. (2021). Neovascularization: The main mechanism of MSCs in ischemic heart disease therapy. Front Cardiovasc Med, 8, 633300. doi: 10.3389/fcvm.2021.633300.
20. Bagno, L., Hatzistergos, K.E., Balkan, W., Hare, J.M. (2018). Mesenchymal stem cell-based therapy for cardiovascular disease: progress and challenges. Mol Ther 25, 26, 1610-1623. doi: 10.1016/j.ymthe.2018.05.009.
21. Fernandez-Aviles, F., Sanz-Ruiz, R., Climent, A.M., Badimon, L., Bolli, R., Charron, D., Fuster, V., Janssens, S., Kastrup, J., Kim, H.S., Lüscher, T.F., Martin, J.F., Menasché, P., Simari, R.D., Stone, G.W.,e Terzic, A., Willerson, J.T., Wu, J.C. (2017). Global position paper on cardiovascular regenerative medicine. Eur Heart J, 38, 2532-2546. doi: 10.1093/eurheartj/ehx248.
22. Sadatpoor, S.O., Salehi, Z., Rahban, D., Salimi, A. (2021). Manipulated mesenchymal stem cells applications in neurodegenerative diseases. Int J Stem Cells, 13, 24-45. doi: 10.15283/ijsc19031.
23. Paul, G., Anisimov, S.V. (2013). The secretome of mesenchymal stem cells: potential implications for neuroregeneration. Biochimie, 95, 2246-2256. doi: 10.1016/j.biochi.2013. 07.013
24. Abdelrazik, H., Pelagalli, A. (2023). Novel MSC Perspectives: From cell regulation to tissue regeneration. Int J Mol Sci, 24, 13392. doi: 10.3390/ijms241713392.

Received February 12, 2026, accepted March 21, 2026, published on line June 11, 2026