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Editorial
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Mesenchymal Stem Cells: Do We Believe Their Clinical Potential?

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Editorial

Definitions and Facts

- Mesenchymal Stem Cell (MSC) is a multipotent stem cell derived from various adult tissues including bone marrow, adipose tissue, umbilical cord blood, umbilical cord, dental pulp, etc. and be able to differentiate into different cell types and culture efficiently *in vitro*.

- Multipotent stem cells are defined as adult stem cells, which committed to differentiate into specific cell types in our body.

- MSCs have emerged as valuable cell sources used in regenerative medicines due to their unique abilities in a broad range of experimental animal models and clinical applications in human, including their immunomodulatory, anti-inflammatory, immune-privilege potential, and signalling regulatory via chemokine and cytokine secretion.

Safety and Efficacy of MSC Therapy

In terms of biological perspective, the differentiation ability of MSCs is limited into certain cell types, containing chondrocytes, osteoblasts, adipocytes, myocytes (including cardiac myocytes), β-pancreatic islets cells, and potentially, neuronal cells [1]. This limited differentiation ability brings a benefit to the MSCs compared to that of Human Embryonic Stem Cells (hESCs) and Human Induced Pluripotent Stem Cells (hiPSCs). In fact, it is more difficult and time-consuming to differentiate MSCs either *in vitro* nor *in vivo* whereas both hESCs and hiPSCs are potentially able to differentiate into almost all cell types including three germ layers and more challenge in controlling their differentiation potential, especially *in vivo* model [2,3]. Also, MSCs were safely used for autologous transplantation and exhibited no toxicity or tumorigenicity following transplantation into rodents or human patients. Furthermore, the clinical uses of MSCs are safer because these cells are unable to form teratomastumour, which is a great concern of hESCs and hiPSCs. To date, no publications or records have been described cancer or tumour formations after MSC infusion both in animal models and human individuals, even in long-term studies [4-6].

Since the first discovery of MSCs by Alexander Friedenstein and colleagues in 1976, MSCs have been reported to have a broad range of clinical applications due to their abilities to regulate the immune responses in many diseases, immunomodulation, neurogenesis, neuroprotection, and aggregate clearance [7]. Various studies have illustrated that MSCs could modulate the T- and B-cell response *in vivo* by stimulating proliferation, cytokine secretion, cytotoxicity, and regulate the balance between Th1/Th2 [8-10]. Furthermore, MSCs also be able to monitor the functions of regulatory T cells (Tregs), increased B-cell activities, but also may inhibit their proliferation and ceases their cell cycle [11,12]. In addition, MSCs could affect the secretions of antibody and production of co-stimulatory molecules from B-cells, together with the inhibitory effects on the maturation, activation, and antigen presentation of dendritic cells [13,14], interleukin-2 induced natural killer cells activation [15]. Taken together, these potential activities of MSCs directly involve in the modulation of host immune system, which further enhances the safety efficacy of MSC therapy especially in autoimmunological diseases, GvHD, Asthma, allergic rhinitis, etc. About neuronal diseases, results from numerous studies illustrated the roles of MSCs in their potential differentiation into neural cell lines and secreted a wide range of factors able to promote nervous tissue repair and maintenance [16]. Interestingly, MSCs also confer the ability to migrate toward injured areas, presumably due to attraction by cytokine released from lesion areas, implying their therapeutic applications [17,18]. The neuronal differentiation capacity of MSCs has been widely accepted in both animal models and human *in vitro* works [19-21]. Emerging protocols

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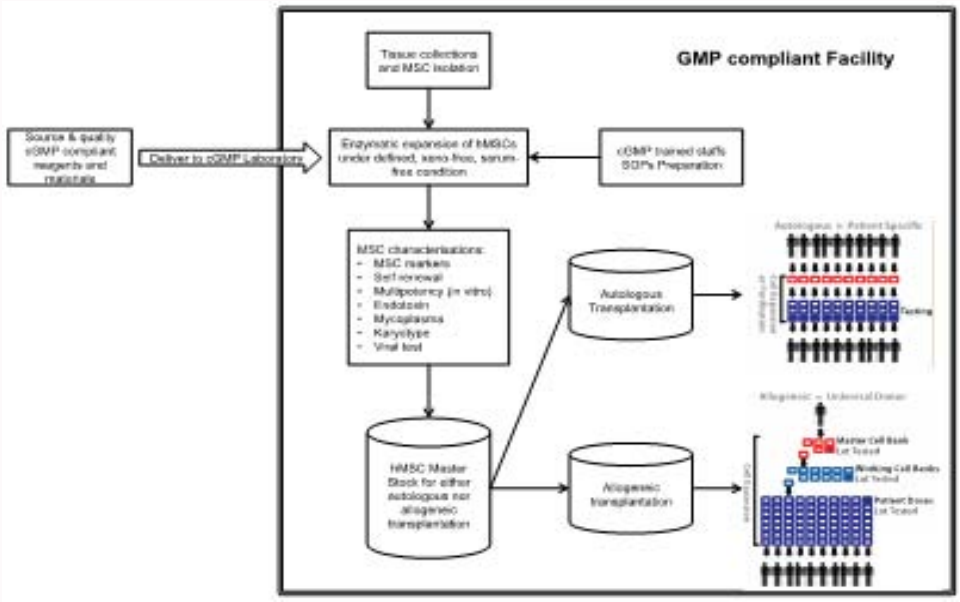

Figure 1: Establishing clinical grade hMSC manufacturing under cGMP facilities and protocols. All steps of the cell manufactory process must be defined and performed by high-skilled personnel: tissue harvesting, MSC isolation, the starting materials, cell culture medium and consumable. Cell culture process must be conducted in cGMP lab. Phenotypic analysis and characterization (QC) need to be performed in each batch. Scientific, comprehensive, and complete quality control of product needs to be performed before transfusion. Two types of biobank can be established, including autologous bank (for patient specific) and allogeneic transplantation (universal donor). Figure is adapted from https://c.ymcdn.com/sites/isctmalachite-mgmt.site.../Integrating_PPD_-_2011.pdf.

have been performed to convert MSCs into dopamine-secreting, acetylcholine-secreting cells, and neuronal-like cells [22-24]. Although transplantation of MSC-derived neuronal cells into murine brain injuries and showed a beneficial effect on brain function and recovery, it still remains unknown whether the stated recovery was indeed due to functional integration of MSC-derived cells into the existing neuronal networks [25]. In addition, the comparative study of the functional and phenotypic analysis between MSC-derived neuronal cells and primary cells has not been fully addressed, and their transdifferentiation capacity and electrophysiological functionality remain under controversy. In fact, our recent work in MSCs demonstrates safety and efficacy of stem cell therapy in the treatment of children with cerebral palsy, but the mechanism of how these stem cells could relatively improve patient outcomes remained unknown and required further investigation [26].

Due to their clinical and therapeutic advances, in a recently published article, Dr. Arnold Caplan strongly suggested for converting the term "Mesenchymal stem cells" into "medicinal signalling cells" based on the fact that the former is "immunomodulatory and tropic (regenerative) meaning that these cells make therapeutic drugs in situ that are medicinal", although the mechanisms of these therapeutic benefits are still unclear [27]. Caplan further implied that "MSCs do not function in the body as progenitors for tissue, neither in the normal steady-state nor in disease or injury circumstances; they are not stem cells". This statement challenged a current mindset about mesenchymal stem cells and overlooked decades of study and research that unequivocally demonstrates the stemness of MSCs. However, his report directly confirmed the safety and efficacy of MSCs regarding therapeutic efficacy in human patients [28,29].

Ex vivo Manufactory of MSCs Towards Clinical and Therapeutic Uses

Besides their differentiation ability, MSCs are defined by their capable of self-renewal *in vitro* as the spindle-shaped morphology, adhere to tissue culture plastics, and unique expression of surface markers (including CD29, CD44, CD49a-f, CD51, CD73, CĐ0, CD105, CD106, CD166, and Stro-1), and lack expression of definitive hematopoietic surface markers (including CD11b, CD14, CD34, and CD45) [30-32]. Upon culture *in vitro,* MSCs showed great expansion potential whiles still retaining their multipotent nature. This allows the production of high-quality cell lines, establishing these cell products as a highly efficient source for stem cell therapy. However, it is important to note that the clinical and industrial settings for MSC manufactory are different from an academic counterpart [33]. Clinical grade MSC production requires GMP standard to ensure that the "cell product" is safe, reproducible, high quality, and efficient before delivering to patients. All parts of this process must be defined: including the starting materials (tissue sources, isolation procedure, and cultivation of MSCs in serum-free, xeno-free media, characterisation, and quality control), cell culture features and medium (autologous serum or human serum, cytokines with serum-free, xeno-free, and defined media for target). To obtain the GMP standard, the cell culture facility needs to be as close to a closed system as possible (Figure 1).

Final Remarks

Taken together, the authors believe that MSCs are alternative and excellent candidates for therapeutic and clinical applications that potentially revolutionise the current cell therapy and stem cell field. Although they showed great advantages in the treatment of many diseases and improved patient outcomes, especially in immune disorder, autoimmune, neurodegenerative and brain injury patients, the significant variability derived from cell quality and quantity from different donors and tissues, inconsistent culture protocols, differences in dosages, transfusion methods, and limitations in determine patient's outcomes. To overcome these hurdles, it is important to evaluate comprehensively the differences between cell sources, more scientific data, and a better understanding of mechanisms underlying

MSC's roles in different diseases. Moreover, before applying for clinical trials, standardised protocols for isolation, cultivation, cryopreservation, and characterisation need to be investigated with a robust quality control system need to be implemented. These factors in combination with safety preconditioned and genetically modified MSCs could shed light on the development of safety and effective stem cell therapy for countless human diseases.

References

1. Gao F, Chiu SM, Motan DA, Zhang Z, Chen L, Ji HL, et al. Mesenchymal stem cells and immunomodulation: current status and future prospects. Cell Death Dis. 2016;7:e2062.
2. Simonson OE, Domogatskaya A, Volchkov P, Rodin S. The safety of human pluripotent stem cells in clinical treatment. Ann Med. 2015;47(5):370-80.
3. Andrews PW, Ben-David U, Benvenisty N, Coffey P, Eggan K, Knowles BB, et al. Assessing the Safety of Human Pluripotent Stem Cells and Their Derivatives for Clinical Applications. Stem Cell Reports. 2017;9(1):1-4.
4. Trzil JE, Masseau I, Webb TL, Chang CH, Dodam JR, Cohn LA, et al. Long-term evaluation of mesenchymal stem cell therapy in a feline model of chronic allergic asthma. Clin Exp Allergy. 2014;44(12):1546-57.
5. Bernardo ME, Zaffaroni N, Novara F, Cometa AM, Avanzini MA, Moretta A, et al. Human bone marrow derived mesenchymal stem cells do not undergo transformation after long-term in vitro culture and do not exhibit telomere maintenance mechanisms. Cancer Res. 2007;67(19):9142-9.
6. Wang D, Niu L, Feng X, Yuan X, Zhao S, Zhang H, et al. Long-term safety of umbilical cord mesenchymal stem cells transplantation for systemic lupus erythematosus: a 6-year follow-up study. Clin Exp Med. 2017;17(3):333-40.
7. Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol. 1976;4(5):267-74.
8. Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, et al. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. Br J Haematol. 2005;129(1):118-29.
9. Yañez R, Lamana ML, García-Castro J, Colmenero I, Ramírez M, Bueren JA. Adipose tissue-derived mesenchymal stem cells have in vivo immunosuppressive properties applicable for the control of the graft-versus-host disease. Stem Cells. 2006;24(11):2582-91.
10. Glennie S, Soeiro I, Dyson PJ, Lam EW, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood. 2005;105(7):2821-7.
11. Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, et al. Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4+CD25highFOXP3+ regulatory T cells. Stem Cells. 2008;26(1):212-22.
12. 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.
13. Wu J, Ji C, Cao F, Lui H, Xia B, Wang L. Bone marrow mesenchymal stem cells inhibit dendritic cells differentiation and maturation by microRNA-23b. Biosci Rep. 2017;37(2).
14. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation. 2007;83(1):71-6.
15. Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation. Blood. 2006;107(4):1484-90.
16. Black IB, Woodbury D. Adult rat and human bone marrow stromal stem cells differentiate into neurons. Blood Cells Mol Dis. 2001;27(3):632-6.
17. Sadan O, Melamed E, Offen D. Bone-marrow-derived mesenchymal stem cell therapy for neurodegenerative diseases. Expert Opin Biol Ther. 2009;9(12):1487-97.
18. Hellmann MA, Panet H, Barhum Y, Melamed E, Offen D. Increased survival and migration of engrafted mesenchymal bone marrow stem cells in 6-hydroxydopamine-lesioned rodents. Neurosci Lett. 2006;395(2):124-8.
19. Kim SS, Yoo SW, Park TS, Ahn SC, Jeong HS, Kim JW, et al. Neural induction with neurogenin1 increases the therapeutic effects of mesenchymal stem cells in the ischemic brain. Stem Cells. 2008;26(9):2217-28.
20. Dezawa M, Kanno H, Hoshino M, Cho H, Matsumoto N, Itokazu Y, et al. Specific induction of neuronal cells from bone marrow stromal cells and application for autologous transplantation. J Clin Invest. 2004;113(12):1701-10.
21. Lu J, Moochhala S, Moore XL, Ng KC, Tan MH, Lee LK, et al. Adult bone marrow cells differentiate into neural phenotypes and improve functional recovery in rats following traumatic brain injury. Neurosci Lett. 2006;398(1-2):12-7.
22. Wislet-Gendebien S, Hans G, Leprince P, Rigo JM, Moonen G, Rogister B. Plasticity of cultured mesenchymal stem cells: switch from nestin-positive to excitable neuron-like phenotype. Stem Cells. 2005;23(3):392-402.
23. Trzaska KA, Kuzhikandathil EV, Rameshwar P. Specification of a dopaminergic phenotype from adult human mesenchymal stem cells. Stem Cells. 2007;25(11):2797-808.
24. Barzilay R, Kan I, Ben-Zur T, Bulvik S, Melamed E, Offen D. Induction of human mesenchymal stem cells into dopamine-producing cells with different differentiation protocols. Stem Cells Dev. 2008;17(3):547-54.
25. Volkman R, Offen D. Concise Review: Mesenchymal Stem Cells in Neurodegenerative Diseases. Stem Cells. 2017;35(8):1867-80.
26. Nguyen LT, Nguyen AT, Vu CD, Ngo DV, Bui AV. Outcomes of autologous bone marrow mononuclear cells for cerebral palsy: an open label uncontrolled clinical trial. BMC Pediatr. 2017;17(1):104.
27. Caplan AI. Mesenchymal Stem Cells: Time to Change the Name! Stem Cells Transl Med. 2017;6(6):1445-51.
28. de Windt TS, Vonk LA, Saris DBF. Response to: Mesenchymal Stem Cells: Time to Change the Name! Stem Cells Transl Med. 2017;6(8):1747-8.
29. Boregowda SV, Booker CN, Phinney DG. Mesenchymal Stem Cells: The Moniker Fits the Science. Stem Cells. 2018;36(1):7-10.
30. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007;25(11):2739-49.
31. Haynesworth SE, Baber MA, Caplan AI. Cell surface antigens on human marrow-derived mesenchymal cells are detected by monoclonal antibodies. Bone. 1992;13(1):69-80.
32. 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.
33. Leemhuis T, Padley D, Keever-Taylor C, Niederwieser D, Teshima T, Lanza F, et al. Essential requirements for setting up a stem cell processing laboratory. Bone Marrow Transplant. 2014;49(8):1098-105.