



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 teratoma, 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 autoimmune 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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Received Date: 08 Feb 2018

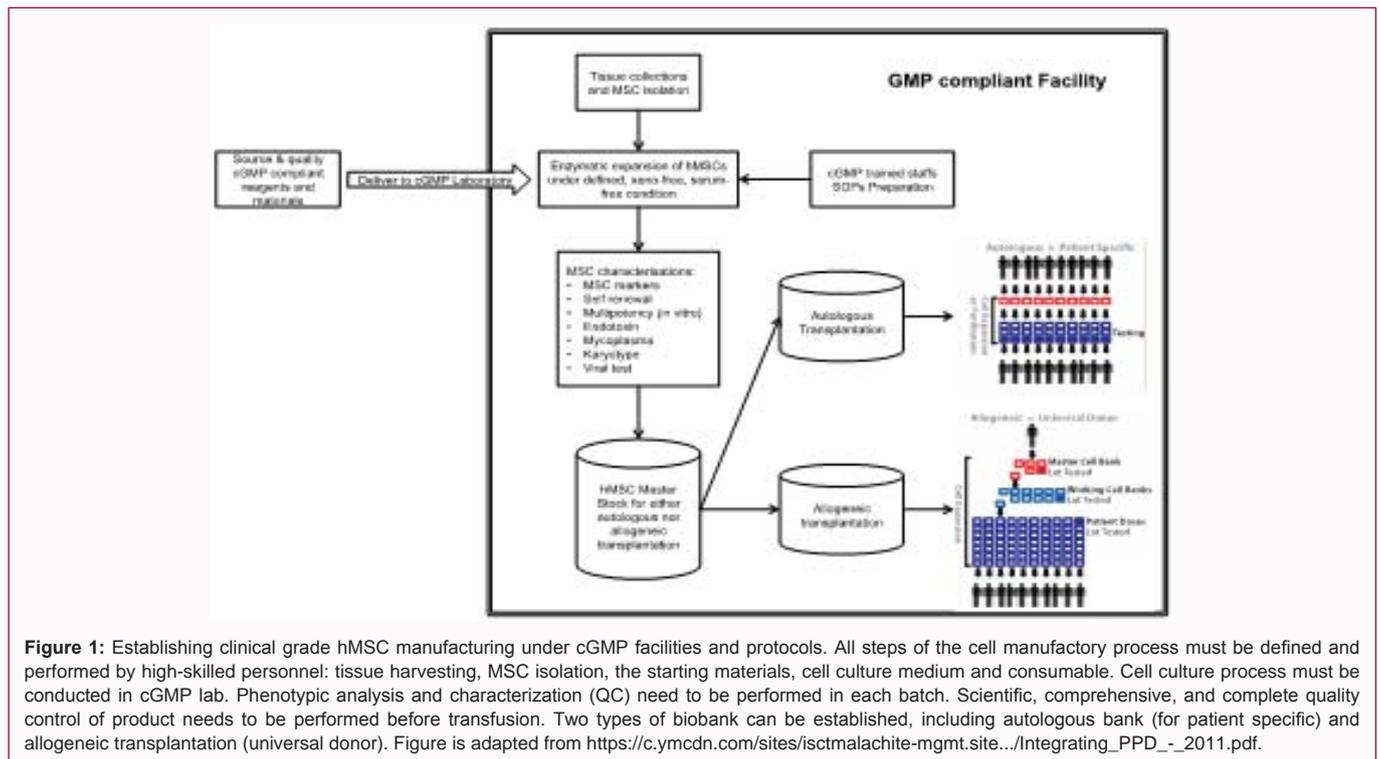
Accepted Date: 20 Feb 2018

Published Date: 26 Feb 2018

Citation:

Hoang MD, Nguyen LT. Mesenchymal Stem Cells: Do We Believe Their Clinical Potential?. *Ann Stem Cell Res Ther.* 2018; 2(1): 1009.

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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, CD90, 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 while 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.

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