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LETTER TO THE EDITOR

Insight into generation of induced mesenchymal stem cells from induced pluripotent cells

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Abstract

Mesenchymal stem cells (MSCs) have the potential for use in cell-based regenerative therapies. Currently, hundreds of clinical trials are using MSCs for the treatment of various diseases. However, MSCs are low in number in adult tissues; they show heterogeneity depending upon the cell source and exhibit limited proliferative potential and early senescence in *in vitro* cultures. These factors negatively impact the regenerative potential of MSCs and therefore restrict their use for clinical applications. As a result, novel methods to generate induced MSCs (iMSCs) from induced pluripotent stem cells have been explored. The development and optimization of protocols for generation of iMSCs from induced pluripotent stem cells is necessary to evaluate their regenerative potential *in vivo* and *in vitro*. In addition, it is important to compare iMSCs with primary MSCs (isolated from adult tissues) in terms of their safety and efficacy. Careful investigation of the properties of iMSCs *in vitro* and their long term behavior in animals is important for their translation from bench to bedside.

Key Words: Induced mesenchymal stem cells; Induced pluripotent stem cells; Regenerative potential; Pluripotent; Multipotent; Clinical studies

Core Tip: Regenerative potential of mesenchymal stem cells (MSCs) have been

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explored in a number of preclinical and clinical studies for the treatment of various diseases and disorders. However, factors such as low number of MSCs in donor tissues, heterogeneity, limited *in vitro* proliferative potential and early senescence in *in vitro* cultures restrict MSC use clinically. Novel methods to generate induced MSCs from induced pluripotent stem cells have been explored. Development and optimization of such protocols is necessary to evaluate the regenerative potential of induced MSCs *in vivo* and *in vitro*.

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TO THE EDITOR

An interesting article was recently published by Dupuis and Oltra[1] in the "*World Journal of Stem Cells*" about the generation of induced mesenchymal stem cells (iMSCs) from induced pluripotent stem cells (iPSCs). The authors highlighted the importance of production of iMSCs to overcome the problems related to primary MSCs derived from adult tissues. In this regard, they summarized the protocols of iMSC generation from iPSCs. In addition, they discussed the common and method-specific culture components and materials required for iMSC generation. We appreciate the idea of discussion of the current protocols for iMSC generation specifically dividing the available protocols into categories such as MSC switch method, embryoid body formation method, specific differentiation method, pathway inhibitor method and platelet lysate method. However, certain points especially the terminology used, and the information provided is arguable.

MSCs are one the best characterized types of adult stem cells. MSCs can be isolated easily from various adult autologous tissues (such as adipose tissue, bone marrow, *etc.*) as well as neonatal tissues (such as umbilical cord tissue, umbilical cord blood, *etc.*). Due to their regenerative potential, MSCs are currently the focus of cell-based therapy for various diseases and disorders. As a result, a significant number of clinical trials have been registered using MSCs to evaluate their safety and efficacy for future clinical use in myocardial infarction, stroke, meniscus injury, limb ischemia, graft-versus-host disease, skin diseases and autoimmune disorders as well as for wound healing and aesthetic applications (www.clinicaltrials.gov).

The factors such as low number of MSCs in adult tissues, age and donor-related heterogeneity, limited proliferative potential and early senescence in *in vitro* cultures restrict MSC use for research as well for clinical applications[2]. As a result, there has been a great interest in generating MSCs from alternative sources. One such novel alternative method is to generate MSCs (iMSCs) from iPSCs[3,4]. iPSCs are a well-characterized source of pluripotent cells. iPSCs are derived by genetic reprogramming of various types of adult somatic cells to an embryonic stem cell-like state. Forced expression of pluripotent genes (such as *OCT3/4*, *Sox2*, *Klf4*, *c-myc*) convert somatic cells into pluripotent cells. Theoretically, iPSCs have unlimited proliferative potential and ability to differentiate into large numbers of tissues. The generation of iPSCs from mouse fibroblasts was first reported by Takahashi and Yamanaka[5] in 2006. Later, human iPSCs were independently generated by Takahashi *et al*[6] from human fibroblasts[6]. iPSCs are an ideal source of cells for generation of patient specific cells without any ethical and legal concern. Development and optimization of protocols to generate iMSCs from iPSCs is important to overcome the problems associated with primary MSCs isolated from adult tissues. In addition, it is necessary to evaluate regenerative potential of iMSCs *in vivo* and *in vitro* before their clinical applications. Careful investigation of the biological properties of iMSCs *in vitro* and their long term behavior in animals is imperative for their translation from bench to bedside.

The manuscript by Dupuis and Oltra[1] used the term "adult pluripotent stem cells" for MSCs, which is debatable and requires attention. MSCs are multipotent stem cells, although very few studies have identified a subpopulation of very small embryonic-like stem cells (pluripotent) in MSC cultures[7]. In addition, the use of the term "multipotent" for iPSCs may be a typo error. Furthermore, the authors have frequently

used the term "differentiation" for conversion of iPSCs into iMSCs. We are in the view that the use of such terminology may create confusion for readers especially for those who are not the subject specialist. The term differentiation (*i.e.* differentiation of iPSC into iMSCs) is somewhat misleading, as MSCs (iMSCs) are "stem cells," undifferentiated cells with the potential to differentiate into other types of cells. Therefore, appropriate terminology such as conversion, derivation or production seems more suitable for description of iMSCs when obtained from iPSCs.

The authors in the study[1] have only discussed iMSCs based on the cell surface markers. The International Society for Cellular Therapy[8] has recommended the minimum criteria for defining MSCs. According to the International Society for Cellular Therapy, MSCs must exhibit the following attributes: (1) Plastic adherent growth when maintained in standard culture conditions; (2) Positive expression of CD105, CD73 and CD90; (3) Negative expression of hematopoietic lineage surface markers (CD45, CD34, CD14 or CD11b, CD79α or CD19) and HLA-DR; and (4) *In vitro* tri-lineage (osteoblasts, adipocytes, chondroblasts) differentiation capability. To make their review article more comprehensive and for better understanding of iMSCs, more relevant information about other MSC attributes (especially tri-lineage differentiation) suggested by the International Society for Cellular Therapy is desirable.

In addition, the study by Dupuis and Oltra[1] discussed the factors associated with restricted use of MSCs for clinical applications. However, there is no discussion of how the use of iMSCs will overcome these problems. From the rationale of the study, it was expected that there will be proper information showing suitability of iMSC use for patients.

iPSCs are derived from various tissues as described in the study. Do iMSCs derived from different iPSCs lines show the same characteristics? What is the behavior of iMSCs in long-term cultures? Furthermore, the protocols described in the review manipulate the cell culture environment, and therefore their safety for clinical use is questionable. The discussion of relevant challenges in the use of iMSCs and future perspectives could possibly highlight the importance of careful research and use in patients.

iMSCs are a next generation alternative source of stem cells with potential therapeutic applications in regenerative medicine[3,4,9]. iPSC-derived iMSCs could significantly elevate the therapeutic values for clinical applications. However, there are a number of challenges ahead that need to be addressed before their clinical use. One such challenge is their proper characterization and development and optimization of reliable and efficient protocols for consistent production of a homogenous population of iMSCs. The behavior of iMSCs in *in vitro* cultures especially in long-term cultures and *in vivo* in animal studies needs to be addressed for better understanding of their safety. In addition, it is important to compare iMSCs with MSCs (isolated from adult tissues) in terms of their safety and efficacy in preclinical and clinical studies. Overall, the search for suitable alternative sources of MSCs are the focus of current research to minimize associated problems. However, careful investigation of new methods for development of MSCs (iMSCs) is the key for successful translation of clinical research from bench to bedside.

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