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Mini Review

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Adherent or non-adherent mesenchymal stem cell; which one is more applicable for clinical study?

Abstract

Regenerative or reparative medicine is a new term which emerged in medicine to refer to renewing of damaged organs by stem cells. Mesenchymal stem cells are multipotent progenitor cells that have the capacity to differentiate into all lineages of mesodermal origin. Mesenchymal stem cells (MSCs) have a good potential for inducing anti-inflammatory responses in inflamed tissues, hence they are used as therapy in auto-inflammatory disease. Due to their differentiation, proliferation and self- renewing characteristics, have received attentions with regard to their potential use as therapeutic agent. This promising area of science is leading scientists to investigate the possibility of cell-based therapies to treat different kinds of diseases, e.g., GVHD, Multiple sclerosis, diabetes and etc. There are two population of cells in the bone marrow that can be differentiated to MSCs *in vitro*. Mesenchymal stem cells derived from the non-adherent cell population of human bone marrow cell cultures had similar cell proliferation rates *in vitro* when compared with the MSCs derived from the primary adherent cell population. While there are different methods for isolation and preparation of MSCs from different tissues, but none of them are completely standard. All these methods need additional manipulations of cells, which may affect their differentiation potentials as well as increasing the risk of contamination of cultures. Therefore, there is a need to compare these populations from different aspects. We hypothesize that non adherent MSCs population are more applicable than adherent one, therefore, culturing and manipulating of non-adherent MSCs population is easier than adherent MSCs. In addition, non-adherent MSCs culturing is a cost-effective way as well as increasing the number of cells and shortening the time of the cell culture.

Keywords: mesenchymal stem cell, adherent, non-adherent, cell culture, regenerative or reparative medicine, embryonic stem cells

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Abbreviations: MSCs, mesenchymal stem cells; iNOS, inducible nitric oxide synthase; COX, cyclooxygenases; PGE2, metabolite prostaglandin e2

Introduction

It has been many years since scientists desired to regenerate damaged tissues and give them another chance to live. Stem cells are fundamental cells which have the capacity to self-renew and to give rise to cells of various lineages. "Regenerative or reparative medicine" is almost new term which has been entered in medicine refer to renewing of damaged organs by stem cells.[1] Overall, there are two kinds of stem cells in human body; embryonic stem cells and adult stem cells. One type of adult stem cells is mesenchymal stem cells (MSCs). Mesenchymal stem cells are multipotent progenitor cells that have the capacity to differentiating into all lineages of mesodermal origin, e.g., fabricate bone, cartilage, adipose, tendon, muscle, and other connective tissues.[2,3] After the discovery and isolation of adherent mesenchymal stem cells by Friedenstein in 1968,[4] a gleam of hope appeared which motivate scientist to do more studies on this cell and its biological function. Furthermore, it was discovered that MSCs could be isolated from other tissues such as an adipose tissue, peripheral blood, umbilical cord and placenta which make it more applicable for clinical usage[5] MSCs are easily isolated from bone marrow and adipose tissue and are expanded *in vivo*.[6] MSCs are immune evasive cells which can been transplanted between individuals of the same species which after administration, will migrate to inflamed tissue and by releasing antigenic and trophic substrates, will help to regeneration of damaged tissue.[7–9] In other hand, significant trait of MSCs is their immunomodulatory effect which is proceded by secretion of anti-inflammatory cytokine such as IL-10 and TGF-b.[10,11] In fact, a lot of investigations have revealed that MSC therapy is a worthwhile strategy to down-regulate pathogenic immune responses in graft-versus-host and autoimmune diseases.[12] Interestingly, some scientific literatures suggested that MSCs are categorized in two groups in bone marrow; non-adherent MSC[13] and adherent MSC. From the beginning, it was acclaimed that non adherent MSCs have similar proliferation and differentiation potentials as the adherent MSCs.[14] This mini-review will provide an overview of the recent findings related to adherent-MSCs and non-adherent MSCs application in clinical therapy.

Discussion

In 2006, the International Society of Cellular Therapy defined MSCs by different criteria which make it characterization easier.[15] These criteria are; (1) adherent to plastic under standard tissue culture conditions; (2) expressing certain cell surface markers such as CD73, CD90, and CD105, and lack of expression in other markers, including CD45, CD34, CD14, or CD11b, CD79alpha or CD19 and HLA-DR surface molecules and have the capacity to differentiate into osteoblasts, adipocytes, and chondroblasts under vitro conditions.[3] There are four Biological characteristics of MSCs associated with their therapeutic effects. These are; Capacity to migrate and engraft, Differentiation, Secreting multiple bioactive molecules and

Immunomodulatory functions.[16,17] The therapeutic efficacy of MSCs which is greatly dependent on their ability to produce paracrine factors, will not be effective until they are delivered to site of injury, this process is termed "homing". Migration and homing to the tissue of injury is influenced by multiple factors including age and passage number of the cells, culture conditions, and the administration method. We here provide a review of the literature demonstrating the effect of various factors on migration of MSCs. Former studies have shown that administrated MSCs could migrate to inflamed sites by chemotaxis.[18,19] These mean that MSCs will arrive to the target site just because of their chemokine receptor such as CCR2, CCR3, CCR4 or CCL5.[20,21] After arriving of MSC in damaged tissue, they can have differentiated into other cells, such as muscle cells, epithelial cell, fibroblast and etc.[22] The process which leads to MSCs differentiation is not completely known, but what expected is that various substances and different signals in target place will lead to this differentiation and proliferation. Another significant role of MSCs is their abilities to secrete different molecules which help the remission of inflammation.[23,24] Contrast immunomodulatory effect of MSCs is most due to it soluble factor which release by inflammatory microenvironment stimuli.[25] These factors are including; indoleamine 2,3-dioxygenase (IDO), inducible nitric oxide synthase (iNOS), cyclooxygenases (COX), metabolite prostaglandin E2 (PGE2), tumor necrosis factor α-induced protein 6 (TSG6), transforming growth factor β (TGF-β), soluble form of HLA-G5 and IL-10[26–29] studies have shown that MSc by realizing anti-inflammatory cytokine could prevent autoimmunity responses.[30,31] By this, MSCs can reduce the activity of T helper cells,[32] B cells[33] and NK cells[34] which are the key players in autoimmunity disease. The immunomodulatory effects of MSCs have also been examined in animal models of immune diseases.

The first clinical trial using culture-expanded MSCs was performed in 1995 on 15 patients whom were treated with autologous stem cells.[35] Clinical applications of MSCs are evolving with the ambitious goals of improving hematopoietic engraftment rate and pace, ameliorating or preventing GVHD,[36] correcting inborn metabolic errors and delivering a variety of therapeutic genes and regeneration of damage tissue in different organ in diverse situation such as IBD.[37,38] As evidences show, most of the studies on allogenic or autogenic MSCs in trials are Phase I studies, Phase II, and a combination of Phase I/II studies. Only a small number of these trials are in Phase III or Phase II/III (comparing a newer treatment to the standard or best known treatment). Nevertheless, adherent MSCs are a wonderful candidate for disease treatment but there is some obstacle in the way of its clinical usage. For instance, isolation and culturing of adherent MSCs is a costly procedure. After isolation, cells should be centrifuged and transferred to a flask and every 2-3 days its medium culture should be changed until the desired number of MSCs are gained (about 19-21 days).[39] It has also shown that the number of adherent MSCs in bone marrow is too low, about 1 in 10,000 nucleated cells, thus it means we need more amount of bone marrow cells and subsequently more culture medium, more damage to bone and finally more rate of infection by doing procedures. Additionally, we know that culturing and sub culturing processes are susceptive to bacterial contamination. If we take a precise look at it, we will find out that all of these will impose more charge to the patient. Zhang and et al shows that, non-adherent MSCs are another type of mesenchymal stem cell progenitors which however couldn't attach to plastic while can differentiate to divers lineage such as chondrocytic and adipocytes and etc.[14] By pour-off', non-adherent MSCs methods it is feasible to show that non-adherent MSCs are present in bone marrow. Studies show that, non-adherent MSCs have a potential therapeutic effect on the hematopoietic system regeneration and damaged tissue repairing.[14] Mesenchymal stem cells derived from the non-adherent cell population of human bone marrow cell cultures had similar cell proliferation rates *in vitro* when compared with the MSCs derived from the primary adherent cell population. It has been suggested that the transformation from non-adherent mesenchymal to adherent phenotype might be involved in the actions of bone anabolic drugs such prostaglandin E2 and parathyroid hormone.[40,41] In other study, Stephan Fricke et al demonstrated that non-adherent mesenchymal triggered endogenous hematopoiesis and induced faster recovery compared to bone marrow controls.[42]

Conclusion

From three decades ago when Friedenstein discovered MSCs in bone marrow specimen, usage of culture-expanded marrow derived MSCs in the fields of tissue engineering, cell therapy, and gene therapy has become popular and widely accepted. Therefore, it needs to use, the safe, effective, and standardized full-scale methods to isolate and culturing MSCs. While there are different methods for isolation and preparation of MSCs from different tissues, but none of them are completely standard. All these methods need additional manipulations of cells, which may affect their differentiation potentials as well as increasing the risk of contamination of cultures. As studies show, the number of non-adherent MSCs in the primary sample of bone marrow is more than adherent MSCs which make it easier for culturing and manipulating. In conclusion, this mini review established that using non adherent MSCs is easier and cost-effective way as well as increasing the number of cells and shortening the time of the cell culture.

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Conflict of interest

The author declares no conflict of interest.

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