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Adipose Mesenchymal Stem Cells: Could be the Future in Regenerative Medicine?

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Human Mesenchymal Stem Cells (MSC's) are known to constitute a heterogeneous population of cells and their properties and functionality depend on the environmental characteristics. MSC's can be expanded in culture where they give rise to fibroblastic colonies (CFU-F). However the cultures of MSC's are not completely explored. Former studies claimed that MSC's isolated from bone marrow comprise a single phenotypic population forming symmetric, spindle-shaped colonies (homology up to 98%).

MSC's differentiated in a variety of cell lineages, such as, osteoblasts, chondrocytes, adipocytes, fibroblasts, myoblasts and cardiomyocytes, hepatocytes, tenocytes, cenocytes, and even neurons. This differentiation potential may differ in the relation to the source of MSC's with many pros as well as cons [1, 2].

The multilineage potential of embryonic stem cells and adult stem cells from the bone marrow has been characterized extensively. Although embryonic stem cell potential is enormous, many ethical and political issues accompany their use. Therefore, adult stem cells from the bone marrow stroma (i.e. mesenchymal stem cells) have been proposed as an alternative source. Originally identified as a source of osteoprogenitor cells, MSC's differentiate into adipocytes, chondrocytes, osteoblasts, and myoblasts in vitro, making these stem cells promising candidates for mesodermal defect repair and disease management. However, the clinical use of MSC's has presented problems, including pain, morbidity, and low cell number upon harvest. This has led many researchers to investigate alternate sources for MSC's [2, 3].

In 1960 Rodbell et al. introduced the initial method for isolating cells from adipose tissue. Adipose tissue has been reported as a source of adult stem cells. A high yield of Adipose-Derived Mesenchymal Stem Cells (ADSC's) can be obtained with minimal discomfort under local anesthesia. Many studies have examined their characteristics, plasticity, and inducibility [4].

Abundant numbers of ADSC can be derived from lipoaspirate, the waste product of liposuction surgery. Processing 300 mL of lipoaspirate routinely yields between 1 x 10^7 and 6 x 10^8 ADSC cells with >90% cell viability. The yield compares favorably with a bone marrow aspirate. Compared with bone marrow stromal cells (BMSC'S), ADSC cells are more easily cultured and grow more rapidly. They can also be cultured for longer than BMSC cells before becoming senescent. All of these qualities make ADSC cell a useful source of mesenchymal stem cells [5].

The proliferation capacity of ADSC's seems to be greater than that of bone marrow-derived MSC's.

ADSC's are generally considered to be stable throughout long-term culture and have practical advantages in clinical medicine and their use has become more realistic because adipose tissue, the primary source of ADSC's, is abundant and easy to obtain (from human lipoaspirate)with less donor site morbidity [6, 7].

Those cells are adherent in vitro, maintaining their mesenchymal phenotype and plasticity toward the mesenchymal lineage after many passages in culture. They have been molecularly characterized using a panel of multiple mesenchymal differentiation markers such as CD9, CD10, CD13, CD29, CD44, CD49, CD54, CD55, CD59, CD73, CD90, CD105, CD106, CD146, CD166, CD271, CD11b, CD14, CD19, CD31, CD34, CD45, CD79, CD80, CD117, CD133 and CD144.

The following criteria may be used to characterize the positivity and negativity of ADSC's:

•**Positive markers**: Cells must show >95% positivity for expression of cell-surface antigens CD9, CD10, CD13, CD29, CD44, CD49, CD54, CD55, CD59, CD73, CD90, CD105, CD106, CD146, CD166, CD271.

•**Negative markers**: Cells must show <2% positivity for expression of cell-surface antigens CD11b, CD14, CD19, CD31, CD34, CD45, CD79, CD80, CD117, CD133, CD144.

They could also differentiate into multiple cell types in vitro, including adipocytes, chondrocytes, osteoblasts, cardiomyocytes, and vascular endothelial cells. As a result, ADSC's express positive effects on patients with graft-versus-host disease occurring after bone marrow transplantation, suggesting an immunomodulatory function [8, 9].

The specific characteristics of ADSC's make them an attractive tool in regenerative medicine. They possess the capacity to engraft into various tissues and organs when infused systematically, and this engraftment has been shown to be stable in the long term. Even more, when they infused to the peripheral circulation have the ability to migrate to a specific site of injury. They have been also proposed to be an excellent potential tool for gene therapies. One of the fields for their use in regenerative medicine is the treatment of bone defects. The results, however, were not completely satisfying because the amount and the quality of regenerated bone remained disappointing [10].

The treatment of wound healing is a complex process that involves the coordinated efforts of many types of cells and the release of their cytokines. A new option for treating difficult wounds has provided by understanding the roles of ADSC's in wound healing and tissue regeneration. The concept of cell-assisted lipotransfer by adding ADSC's has been successfully used in the clinic for soft tissue augmentation in a number of patients [11].

Allergic diseases, autoimmune diseases, and Graft-Versus-Host Disease (GVHD) are another potential application of ADSC's which involves the harnessing of their immunomodulatory effects to treat those conditions. It has been shown by many researchers that ADSC's can ameliorate steroid-resistant severe GVHD after hematopoietic stem cell transplantation, but further studies are needed in that area to examine the mechanism by which this occurs and to determine the long-term effects of such treatment [12].

The leading causes of mortality worldwide are various cardiovascular diseases. The injection of ADSC's is growing evidence which indicates the improved cardiac function via the differentiation into cardiomyocytes and vascular cells and through paracrine pathways. By injected ADSC's, paracrine factors secreted and enhance angiogenesis, reduce cell apoptosis rates, and promote neuron sprouts in damaged myocardium. These findings suggest important implications for the design of future cell therapy strategies for cardiac repair [13].

In the field of neurodegenerative diseases, we have various stem cell types under investigation because they are able to differentiate into neurons and glial cells. Similarly, ADSC's have been known to have a differentiation potential and also

by the secretion of some nerve growth factors are capable of promoting neuronal healing. The ADSC's express nestin, a marker for neural progenitor cells, in a significantly high proportion. ADSC's can secrete Vascular Endothelial Growth Factor (VEGF) which is an angiogenetic factor and insulin-like growth factor 1 which is a neuroprotective factor: the major factor that mediates protection against serum and potassium deprivation-induced apoptosis of cerebellar granule neurons. At this point there are many limitations in protocols worldwide in order to establish homogeneous populations of neural progenitors and stem cells and must be resolved before we can talk for effective therapy in neurodegenerative diseases like Alzheimer's, multiple sclerosis, and Parkinson's disease [14 -16].

The use of ADSC's is currently increasing in clinical fields because of their ability to harvest in large numbers and also shown evidence of safety and efficacy. So far, relatively few clinical trials in a limited number of research areas have been conducted to assess the therapeutic potential of ADSC's compared with the large number of published preclinical studies [17].

In addition, there are several points that remain unclear and must be considered prior to use of ADSC's:

- There is evidence that the differentiation potential of ADSC's may depend on the anatomic location of the fat and the donor's gender and age,
- The key molecular events and transcription factors that initially allocate the ADSC's to a specific lineage are still unknown, although their lineage-specific differentiation into cells of mesodermal origin is well understood at the molecular level.

Despite these limitations, ADSC's have practical advantages in clinical medicine and their use has become more realistic because of adipose tissue, the primary source of ADSC's, is abundant and easy to obtain with less donor site morbidity [18, 19].

As concluded remarks, the use of ADSC constitutes a potential powerful tool in regenerative medicine and in gene therapy in vitro and in vivo.

They have an extensive proliferative potential and are able to differentiate into various cell lineages such as adipocytes, osteoblasts, cardiomyocytes, vascular endothelial cells, pancreatic b-cells, and hepatocytes. Due to these important features their use in clinical trials has been increased.

It has been documented that the cells engraft successfully in patients and cause beneficial effects. ADSC extraction is easily obtained in comparison to BMSC's cells. The procedure is safe and minimally invasive.

Last, there is no risk of immune rejection with autologous cells in comparison with embryonic stem cells or induced pluripotent stem cells (iPSC's). Therefore, ADSC's are a useful tool in the field of regenerative medicine.

However, it will be a while before using those cells as a routinely applied therapy in clinics. Further preclinical and clinical studies are needed to determine whether ADSC's therapies can fulfill the expectations and if they can be used successfully to treat disorders for which current medical and surgical therapies are either impractical or ineffective.

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