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Superior Proliferative and Tissue Regeneration Potential of Adipose Tissue-Derived Mesenchymal Stem Cells Compared to Bone Marrow: A Review

Omar MMS*

Histology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

***Corresponding author:** Omar MMS, Histology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, Tel: 00201001428289; E-mail: Saharhistology@gmail.com

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Abstract

Adipose tissue is an abundant source of mesenchymal stem cells. The liposuction procedure to harvest adipose tissue is less invasive and produces less donor site morbidity than bone marrow aspirations. The current review outlines the potency advantage of Adipose tissue derived mesenchymal stem cells (AT-MSCs) compared to bone marrow derived mesenchymal stem cells (BM-MSCs). Including higher proliferative potential, more immunotolerance capabilities, anti-inflammatory and immunosuppressant activity and angiogenesis and vascularization during tissue regeneration. Adipose tissue derived mesenchymal stem cells, proliferative potential, tissue regeneration & angiogenesis.

Keywords: Tissue Regeneration; Stem Cells; Angiogenesis; Regenerative Medicine

Introduction

Bone marrow (BM) has been extensively investigated as a source of adult stem cells. Because BM-MSCs are multipotent and readily expandable *in vitro*, these cells have already been employed in early clinical studies, including the treatment of human myocardial infarction, osteogenesis imperfecta, and graft versus host disease [1]. However, mesenchymal stem cells (MSCs) constitute only a small proportion of the cells in BM (0.01-0.001% of nucleated cells) and their number, frequency and differentiation capacity correlate inversely with age. In addition to the high morbidity including pain and high degree of viral contamination upon harvest [2]. Adipose tissue (AT) is emerging as a source of stem cells that can be obtained by a less invasive method and in larger quantities than from BM. These cells can be isolated from human lipoaspirates and, like MSCs, can differentiate toward osteogenic, adipogenic, myogenic, chondrogenic, and especially neurogenic lineages [3]. Recent advances in cosmetic surgery add to its advantage with huge amount of available fatty tissue. It may have a further advantage where, the rapid expansion of cells is of utmost importance especially at cell therapy strategies [4].

Characterization and localization

AT-MSCs express the mesenchymal stem cell markers Cluster of Differentiation 10 (CD10), CD13, CD29, CD34, CD44, CD54, CD71, CD90, CD105, CD106, CD117, and STRO-1. They are negative for the hematopoietic lineage markers CD45, CD14, CD16, CD56, CD61, CD62E, CD104, and CD106 and for the endothelial cell (EC) markers CD31, CD144, and vonWillebrand factor [5]. Morphologically, they are fibroblast-like and preserve their shape after expansion *in vitro* [6]. Adipose tissue (like the bone marrow) is derived from the embryonic mesenchyme and contains a stroma that is easily isolated. Several workers have identified a stem cell population within the adipose stromal compartment [7]. Current studies have suggested that the niche for the AT-MSCs is the vasculature of adipose tissue [8]. Other researchers have gone so far as to identify the AT-MSCs to be located in the outer adventitial ring of the vasculature [9]. The migration of AT-MSCs to areas surrounding blood vessels after reinjection into adipose tissue supports this theory [10]. Additionally, the expression of CD146 by AT-MSCs, together with the expression of 3G5-a pericyte marker, has led others to suggest that the AT-MSCs may actually be pericytes located within the adipose vasculature [11]. However, there still remains slight disagreement as the absence of smooth muscle actin (a pericyte marker) in the majority of isolated AT-MSCs populations might also argue against its classification as a pericyte [12]. Whether these differences are due to isolation and/or expansion techniques remains unknown. Moreover, adipogenesis and angiogenesis are known to be intimately linked and since adipose tissue is a highly vascularized tissue, it would yield a good supply of pericytes upon harvest [13]. Finally, numerous *in vitro* studies have described the *in vitro* differentiation of AT-MSCs into endothelium-a specialized epithelial tissue. Using simple *in vitro* induction conditions involving exposure to VEGF, AT-MSCs express typical markers of endothelial cells, such as vonWillebrand Factor (vWF) and function as endothelial cells, forming tubular structures on

Matrigel substrates and taking up acetylated Low Density Lipoprotein (LDL) [14]. Fisher and colleagues also confirm tubule formation by human ASCs, but suggest that functional LDL uptake and CD31 expression by the AT-MSCs can only be seen upon their exposure to shear stress [15].

Proliferative potential

The population doubling time of cells depends upon many factors including the specific cell source, the supplementary factors that are necessary for cell adhesion and the number of passages [16]. The proliferation capacity and senescence of stem cells have been analyzed by many scientists over the last few years. The proliferation capacity of stem cells is of great importance determining their application in cell therapy and tissue engineering. It was formally demonstrated that AT-MSCs exhibited a higher proliferation capacity than BM-MSCs [17]. Similarly, a population doubling times of 45.2 h for AT-MSC and 61.2 h for BM-MSC was also recorded [18]. On the other hand, it should be noted that differences in the doubling times of AT-MSCs originating from different regions of the body have been reported by many authors as well [19,20]. It was also recorded that AT-MSCs from the subcutaneous adipose tissue region proliferated faster (doubling time, 4 ± 1 days) than those from the omental region (doubling time, 5 ± 1 days) [21]. In addition to the origin of the cells, the cultivation conditions and various medium supplements may have an effect on doubling times of the AT-MSCs. It was found that AT-MSCs display a cell doubling time of 2 to 4 days, depending on the culture medium and passage number [17]. Recent work directly comparing AT-MSCs and BM-MSCs has measured tenfold more CFU-F units following an AT-MSCs harvest [22]. Moreover, it was estimated that one gram of the adipose tissue could produce 500 fold more MSCs than one gram bone marrow [23]. As such, the AT-MSCs may be a more suitable stem cell than the BM-MSCs for eventual clinical application. Although conventional wisdom used to suggest that once a progenitor cell had committed to its specific lineage, it remained committed. However, studies suggest that this may not be the case regarding adipose tissue, as mature adipocytes was found to be dedifferentiated back to a more primitive progenitor population that may be an AT-MSCs or may, at the least, share many similarities with the AT-MSCs [24-26]. In support of this, dedifferentiated fat cells have the same CD profile as AT-MSCs. Therefore, it appears that the mature adipocyte may retain some of its potency despite having committed to the adipogenic lineage. This finding may now make not only the stromal vascular fraction of adipose tissue a source of AT-MSCs but also the adipose tissue itself, greatly increasing the potential number of multipotent (or pluripotent) cells available for eventual clinical application [27-29].

Immunotolerance capabilities

In comparison to bone marrow, an adipose tissue harvest not only yields significantly more stem cells, but also has more immunotolerance upon transplantation. One cell surface marker that has received significant attention in the stem cell field is the HLA class of cell surface antigens. Of particular interest is the HLA/MHC class II protein, which is found on the surface of antigen-presenting cells and plays critical roles in immunotolerance and transplantation [30,31]. Immunophenotyping of AT-MSCs has confirmed the absence of the HLA-class II antigen on the AT-MSCs surface and the absence of this HLA protein may allow the AT-MSCs to evade the host's immune surveillance machinery. This may make it possible to use AT-MSCs in xenogeneic model systems of tissue regeneration [32]. Of additional interest, recent studies denote that human AT-MSCs have lower susceptibility to natural killer (NK) cell mediated lysis in comparison to BM-MSCs. This finding may be part of the reason for xenogeneic tolerance of AT-MSCs in that NK-AT-MSCs crosstalk does not result in immediate recognition of MSCs as foreign cells.

Paracrine signaling

Is tissue regeneration by AT-MSCs a direct result of their differentiation into the desired cell type or does the AT-MSCs direct the host's ability to heal itself through paracrine signaling mechanisms? An increasing number of studies suggest that tissue regeneration is the result of AT-MSCs-secreted soluble factors that either induce vascularization, tissue protection or suppress the host's inflammatory pathways. In support of this, AT-MSCs are known to secrete multiple growth factors, including Vascular endothelial growth factor (VEGF), Hepatocyte growth factor (HGF), Nerve growth factor (NGF) and Brain-derived neurotrophic factor (BDNF) and numerous interleukins [33,34]. Therefore, the AT-MSCs possess a unique "secretome" that may have powerful paracrine effects on the health, repair, and function of a tissue and has resulted in an exciting, new theory that proposes the AT-MSCs as a mediator of tissue regeneration through the secretion of specific soluble factors. However, whether direct or indirect participation may be the root cause of AT-MSCs-mediated tissue regeneration is unclear and it may be possible that the AT-MSCs uses both approaches to ensure tissue healing and health [35]. Autologous AT-MSCs have also been found to favour epidermal healing in porcine models of cutaneous radiation injury [36] and the effects of AT-MSCs-conditioned media on aged fibroblasts have been studied as a means of developing antiaging strategies [37]. Finally, implantation of 3D skin "rafts" made from adult skin explanted onto dermal tissues containing fibroblasts and human AT-MSCs form completely healed multilayered epidermis upon implantation into skin injuries, whereas rafts without AT-MSCs still show significant areas of injury [38]. What paracrine factors are involved in these studies of epidermal/dermal formation remain unknown but possible paracrine factors may include HGF, VEGF, Transforming growth factor beta (TGF1), TGF3, Granulocyte-colony stimulating factor (G-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF), IL6, and IL8 [39]. In support of this, it was reported that conditioned medium from AT-MSCs can increase hyaluronic acid synthesis by human dermal fibroblasts and that neutralizing antibodies to TGF1 can abolish this effect [40].

Vascularization potential

It has long been known that vascularization is critical to tissue healing. The *in vitro* AT-MSCs differentiation of to endothelial cells is not under dispute as they quickly and easily form vessel-like structures in Matrigel substrates that assume endothelial function [41]. Consistent with this, vessel formation has been observed in several AT-MSCs models of cardiac infarct treatment, epithelial regeneration, and neural tissue healing. In addition, multiple studies of ischemia describe increased vascularization following AT-MSCs administration [42]. Hemodynamic abnormalities in pulmonary arterial hypertension may be reversed using AT-MSCs-owing to their capabilities to induce angiogenesis and increase formation of small, pulmonary arteries [43]. Increased capillary densities and higher blood flow have been reported in several studies using AT-MSCs for the healing of skin wounds and improvement of skin flap survival [44]. At the cosmetic level, adipose grafts, transplanted with AT-MSCs survive at higher levels, are 35% larger and show increased neoangiogenesis when compared to grafts transplanted without these stem cells [45]. Finally, there are numerous studies detailing the use of AT-MSCs in the treatment of ischemia/reperfusion injury.

Immunosuppressant potential

For a stem cell to be ideal for regenerative medical applications, it should meet several criteria. It should be found in abundant quantities (millions to billions of cells) and it should be harvested by a minimally invasive procedure. Besides, it should be differentiated along multiple cell lineage pathways and can be safely and effectively transplanted to either an autologous or allogeneic host [46]. Successful tissue regeneration is also reliant upon control of inflammation. Multiple *in vitro* and in vivo studies suggest that bone marrow MSCs possess anti-inflammatory properties that may mediate the host's immune response [47], thus making these cells a therapeutic approach for mediating inflammatory responses, including tissue regeneration and transplantation [48]. In light of the numerous similarities found between bone marrow MSCs and AT-MSCs, it may be that AT-MSCs are also capable of modulating host immunity through immunosuppression. Consistent with this, early *in vitro* work identifies numerous inflammatory mediators secreted from human AT-MSCs, including IL6, IL8, G- Cerebrospinal fluid (CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF), and Monocyte Chemoattractant Protein-1 (MCP-1)[49]. Furthermore, AT-MSCs-mediated immunosuppression has been observed in numerous *in vitro* experiments utilizing the gold-standard mixed lymphocyte reaction (MLR) system [50]. More recently, dendritic cells cocultured with AT-MSCs and then cultured with CD4+ T cells have been found to inhibit T cell activation, suggesting that the dendritic cells' ability to mediate immunity has been altered through its exposure to AT-MSCs [51]. *In vitro*, AT-MSCs inhibit the proliferation of activated lymphocytes via cell-cell binding and paracrine signaling. AT-MSCs can also attenuate autoimmune arthritis in Collagen antibody-induced arthritis. They induce the expression of inhibitory Fc gamma receptor on macrophages and inhibit the secretion of proinflammatory cytokines without affecting the serum levels of pro-inflammatory adipokines [52]. AT-MSCs-ameliorated allergic airway inflammation and improved lung function through the inhibition of regulatory cytokines expansion. AT-MSCs may be a promising candidate for a novel cell-free therapy for allergic airway diseases that has many advantages in overcoming the limitations and risks associated with the cell-based therapeutics [53].

Conclusion

Since its first appearance in the literature in 2001, the AT-MSCs has made quite an impact on the fields of adult stem cells and regenerative medicine. It is remarkable to see how many researchers around the world have adopted the AT-MSCs as their stem cell of choice. AT-MSCs can thus be a promising alternative source to BM- MSCs, which can be obtained by a less invasive method and harvested in larger quantities than from bone marrow sources. The easy and repeatable access to subcutaneous adipose provides a clear advantage over other types of cells. Their isolation and culture techniques are also easier to perform than bone marrow. Further pre-clinical and clinical studies need to be performed so these cells can fulfill expectations and can be successfully used to treat disorders for which the present medical and surgical therapies are either ineffective orimpractical.

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