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Adipose stromal/stem cells in regenerative medicine: Potentials and limitations

Leandra Santos Baptista

ORCID number: Leandra Santos Baptista (0000-0001-9998-8044).

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Leandra Santos Baptista, Multidisciplinary Center for Biological Research (Numpex-Bio), Federal University of Rio de Janeiro (UFRJ) Campus Duque de Caxias, Duque de Caxias, RJ 25245-390, Brazil

Leandra Santos Baptista, Post-graduate Program in Biotechnology, National Institute of Metrology, Quality and Technology (INMETRO), Duque de Caxias, RJ 25250-020, Brazil

Leandra Santos Baptista, Post-graduate Program in Translational Biomedicine (Biotrans), Unigranrio, Campus I, Duque de Caxias, Duque de Caxias, RJ 25250-020, Brazil

Leandra Santos Baptista, Laboratory of Tissue Bioengineering, Directory of Metrology Applied to Life Sciences, National Institute of Metrology, Quality and Technology (INMETRO), Duque de Caxias, RJ 25250-020, Brazil

Corresponding author: Leandra Santos Baptista, PhD, Associate Professor, Laboratory of Tissue Bioengineering, Directory of Metrology Applied to Life Sciences, National Institute of Metrology, Quality and Technology (INMETRO), Duque de Caxias, RJ 25250-020, Brazil. leandrabaptista@xerem.ufjf.br

Abstract

This article presents the stem and progenitor cells from subcutaneous adipose tissue, briefly comparing them with their bone marrow counterparts, and discussing their potential for use in regenerative medicine. Subcutaneous adipose tissue differs from other mesenchymal stromal/stem cells (MSCs) sources in that it contains a pre-adipocyte population that dwells in the adventitia of robust blood vessels. Pre-adipocytes are present both in the stromal-vascular fraction (SVF; freshly isolated cells) and in the adherent fraction of adipose stromal/stem cells (ASCs; *in vitro* expanded cells), and have an active role on the chronic inflammation environment established in obesity, likely due their monocytic-macrophage lineage identity. The SVF and ASCs have been explored in cell therapy protocols with relative success, given their paracrine and immunomodulatory effects. Importantly, the widely explored multipotentiality of ASCs has direct application in bone, cartilage and adipose tissue engineering. The aim of this editorial is to reinforce the peculiarities of the stem and progenitor cells from subcutaneous adipose tissue, revealing the spheroids as a recently described biotechnological tool for cell therapy and tissue engineering. Innovative cell culture techniques, in particular 3D scaffold-free cultures such as spheroids, are now available to increase the potential for regeneration and differentiation of mesenchymal lineages. Spheroids are being explored not only as a model for cell differentiation, but also as powerful 3D cell culture tools to maintain the stemness and expand the regenerative and differentiation capacities

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Core tip: Adipose tissue, notably subcutaneous, has a population of CD34-positive progenitor cells functionally known as pre-adipocytes. The pre-adipocytes have molecular and functional identities with the monocytic-macrophagic lineage and are altered in metabolic diseases such as obesity. To what extent will new 3D tools in cell culture, such as spheroids, be able to overcome the limitations imposed by 2D monolayer culture and unravel dormant capabilities of adipose stromal/stem cells?

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INTRODUCTION

Mesenchymal stromal/stem cells (MSCs) were first described and isolated from bone marrow as adherent colony-forming units of fibroblasts (CFU-F), and the primary role attributed to MSCs was to form niches for hematopoietic cells, supporting hematopoiesis^[1]. In 1999, Pittenger *et al*^[2] first described the *in vitro* multipotential nature of human bone marrow MSCs, introducing their use in cell therapy approaches, by delivering MSC suspensions to injury sites. The hypothesis was that MSCs were capable of tissue repair through grafting and differentiation into tissue-resident cells^[3,4]. A few years later, an adipose tissue MSC population was described that shared some properties with MSCs isolated from the bone marrow, but had important unique characteristics^[5,6].

Currently the widely accepted mechanism for tissue repair using bone marrow and adipose tissue sources (based on data from preclinical studies) is that MSCs interact with injured cells, creating tissue microenvironments or temporary niches that facilitate repair^[7]. Thus, tissue regeneration by MSC transplantation may not rely exclusively on MSC differentiation, and the potential of MSCs to differentiate into multiple lineages is yet to be confirmed *in vivo*. In regenerative medicine approaches, the paracrine activity of MSCs fits well with cellular therapy protocols, while there *in vitro* multilineage potential is beneficial for tissue engineering. Furthermore, the “stemness” of MSCs and their *in vitro* multilineage potential can be optimized by cell culture conditions. The aim of this editorial is to reinforce the peculiarities of the stem and progenitor cells from subcutaneous adipose tissue, revealing the spheroids as a recently described biotechnological tool for cell therapy and tissue engineering. Spheroids are a 3D cell culture approach where cell clusters are formed in the absence of a scaffold (scaffold-free), optimizing cell-cell and cell-extracellular matrix interactions^[8,9]. Recent studies have shown that culture as spheroids can be used to optimize the stemness and multilineage potential of MSCs^[10], unraveling unknown characteristics of these cells, as well as opening new avenues for MSC use in regenerative medicine.

REVEALING THE POTENTIAL OF STROMAL CELL POPULATIONS IN SUBCUTANEOUS ADIPOSE TISSUE

The subcutaneous adipose tissue is composed of adipocytes and of a heterogeneous “stromal-vascular fraction” (SVF). These two main cell compartments can be separated by a centrifugation approach that results in the adipocytes floating as a layer, while SVFs sediment to the bottom of the tube. Previously, the SVF was known as a compartment containing cells capable of accumulating intracytoplasmic lipids *in vitro*^[11]. Currently, the SVF is defined as a heterogeneous population containing pre-

adipocytes, endothelial mature cells, macrophages and fibroblasts. Furthermore, the SVF contains stem and progenitors cells showing different degrees of differentiation^[12]. Due to their cell heterogeneity, the SVF is a major contributor to the unique molecular identity of the different depots of adipose tissue^[13].

In 2001, Zuk *et al*^[5] first described an MSC population in human subcutaneous adipose tissue isolated from the SVF. In 2013, the International Federation for Adipose Therapeutics and Science and the International Society for Cellular Therapy established the minimal definitions for stromal cells derived from subcutaneous adipose tissue^[14]. The stromal cells within the SVF comprise heterogeneous cell types not amenable to culture *in vitro*, and a population of adherent, stromal/stem cells that can be culture *in vitro*. The latter are referred to as “adipose tissue derived stromal/stem cells” (ASCs), and this term will be used throughout this manuscript.

While ASCs were initially described as having the same *in vitro* multipotential nature, clonogenic potential (CFU-F) and similar surface markers as human bone marrow MSCs^[15], differences between bone marrow and adipose MSCs emerged in subsequent publications (Table 1). Importantly, the tissue microenvironment differs significantly between the bone marrow and white adipose tissue. In these tissues, MSCs interacts with different neighboring cells, including an osteoblastic niche in the bone marrow^[16] and cells from the more vascularized microenvironment in the white adipose tissue^[6]. Consequently, bone marrow MSCs shows an intrinsic capacity to form bone and to support hematopoiesis after *in vivo* transplantation to ectopic sites^[17], while ASCs have a superior angiogenic capacity^[18]. Intriguingly, adipose tissue is also capable of supporting hematopoiesis (in a specific form), despite the remarkable differences in tissue microenvironment relative to the bone marrow^[21]. In comparison with the MSC population derived from bone marrow after *in vitro* expansion, MSCs derived from subcutaneous adipose tissue can be distinguished by being positive for CD36 and negative for CD106^[14]. Given the differences between bone marrow MSCs and ASCs, different morphogens are required and commonly used to induce the full range of multipotential differentiation of these cells *in vitro*.

Importantly, uncultured SVFs from subcutaneous adipose tissue contain a unique cell population: The pre-adipocytes^[14]. These cells dwell in the adventitia of robust blood vessels and are identified as negative for the pan hematopoietic surface marker (CD45), the mesenchymal stem cell surface marker (CD146) and for the mature endothelial cell surface marker (CD31), being positive only for CD34^[6]. Pre-adipocytes had already been identified in adipose tissue even before the discovery of the MSC population^[11,22]. In mice, pre-adipocytes and macrophages both originate from the monocytic lineage (CD14 positive cells)^[23]. In line with this observation, pre-adipocytes share some surface markers with macrophages, as well as having the capacity to acquire certain macrophage properties^[24].

Macrophages, especially the tissue resident population (M2), have a crucial role in adipose tissue homeostasis^[22]. This role is highlighted in obesity, where chronic inflammation leads to macrophage polarization from an M2 to an M1 phenotype, disrupting adipose tissue homeostasis^[25]. This disruption also alters the behavior of pre-adipocyte, as well as increasing their frequency in early stages of obesity^[26]. In our hands, the subcutaneous adipose tissue samples from obese individuals do not present alterations in the pre-adipocyte population *per se*, but have increased frequency of mesenchymal precursors in the SVF, and ASCs with altered behavior *in vitro*^[27].

Our research group first showed that the frequency and size of blood vessels are increased in subcutaneous adipose tissue from ex-obese donors that have been subjected to bariatric surgery^[28]. In addition to blood vessels alterations, we described a significant increase in the number of pre-adipocytes cells in the SVF, together with a more heterogeneous population of ASCs, containing pre-adipocytes^[27]. The increase in pre-adipocyte frequency can be linked to the increase in the size of blood vessels, since robust vessels have the adventitia layer, where pre-adipocytes dwell^[6]. Thus, adipose tissue from ex-obese individuals appears to keep a cellular “memory” of the inflammatory microenvironment of obese tissue, despite relevant clinical improvement in obesity^[29].

Both fractions of subcutaneous adipose cells - SVF and ASCs - have been extensively used in clinical trials, mainly due their paracrine and immunomodulatory potentials; however some discrepancies between studies have emerged, mainly due donor-to-donor variability combined with differences between the protocols for cell isolation and expansion *in vitro*, highlighting the need to better characterize even the ASCs^[30]. In spite of their apparent homogeneity *in vitro*, ASCs contain a population of pre-adipocytes whose true potential has not yet been fully elucidated, especially in obese and ex-obese subcutaneous adipose tissue samples.

Table 1 Differences of mesenchymal stromal/stem cell niche, cell subpopulations, mesenchymal stromal/stem cell surface *in vitro* markers and multipotentiality between bone marrow and adipose tissue

Tissue	MSC niche	Cell subpopulations	MSC <i>in vitro</i> surface markers	Multipotentiality
Bone marrow	Subendosteal and vascular	Osteoblasts, Endothelial progenitor and mature cells, Macrophages, MSCs Hematopoietic stem and progenitor cells, lymphocytes, megakaryocytes, erythrocytes, monocytes, neutrophils, basophils, eosinophils	Positive: CD44, CD71, CD73, CD90, CD105, CD106, CD120a and CD124 Negative: CD14, CD34 and CD45	Adipogenic, Chondrogenic, and Osteogenic. Pre-committed into osteogenic lineage.
Adipose tissue	Vascular	Adipocytes SVF: Pre-adipocytes, endothelial progenitor and mature cells, macrophages, fibroblasts, MSCs	Positive: CD13, CD29, CD44, CD73, CD34, CD36, CD90 and CD105 Negative: CD31, CD45, CD235a and CD106	Adipogenic, Chondrogenic, and Osteogenic. Pre-committed into adipogenic lineage.

MSCs: Mesenchymal stromal/stem cells; SVF: Stromal-vascular fraction.

ARE MULTIPOTENTIALITY AND PLURIPOTENTIALITY DEPENDENT ON CELL CULTURE CONDITIONS?

ASCs has been extensively described in the scientific literature as having their embryonic origin in a mesodermal progenitor population^[31]. As a consequence, the typical multilineage capacity of ASCs represents their ability to form adipose tissue, bone and cartilage *in vitro*^[14]. The multilineage capacity of ASCs has been extensively explored in tissue engineering, mainly by scaffold-based approaches. Recently, non-classical, scaffold-free approaches to tissue engineering have emerged that often rely on the production of 3D cell clusters called "spheroids"^[32]. Spheroids mimic the embryonic stages of tissue development, optimizing the multilineage differentiation capacity of ASCs and MSCs (Figure 1). Moreover, spheroids are currently used not only as 3D culture models of cell differentiation *in vitro*, but also as a powerful cell culture tool to maintain the stemness and increase the regenerative, anti-inflammatory and angiogenic potentials of ASCs and MSCs^[33]. The increase in the stemness of ASC and MSC spheroids (compared with 2D culture) is indicated by their higher multilineage potential, increased expression of pluripotency genes and late senescence^[10], which reflect the cytoskeletal reorganization and expressive changes in cell morphology observed in spheroids^[34]. However, the limitations of ASC and MSC spheroids comprise the low proliferation rate, causing *in vitro* cell expansion to still occur by monolayer culture. Furthermore, part of tissue engineering approaches intends to repair tissue critical-sized defects, requiring a scaffold.

Embryonic development in mammals starts with a cluster of epiblast stem cells^[35]. Therefore, *in vitro* culture as spheroid-like cell clusters is used not only for embryonic stem cells, which are isolated from the early blastocyst stage, but also for induced pluripotent stem cells (iPSC) obtained by "reprogramming" adult somatic cells. Recapitulating embryogenesis, iPSCs initially form cell clusters that eventually become 3D cell aggregates representing spheroids.

A population of cells recently isolated from mesenchymal human tissue, named multilineage-differentiating stress enduring cells (Muse), is capable of forming pluripotent spheroid-like cell clusters^[36] in the absence of *in vivo* tumorigenic capacity^[37]. The differentiation of Muse cells for non-mesenchymal lineages relies on cell culture as clusters or spheroids, as well as on the use of a lower percentage of serum (or even on serum deprivation) during cell culture^[38]. Human ASCs cultured in early passage under a lower percentage of autologous serum formed floating 3D spheroid-like cell clusters spontaneously^[39]. Adipose-Muse cells differentiate into mesodermal, ectodermal and endodermal lineages, without teratoma formation^[40].

The capacity of mature adipocytes to dedifferentiate and to differentiate into multiple cell lineages was already described before the identification of Adipose-

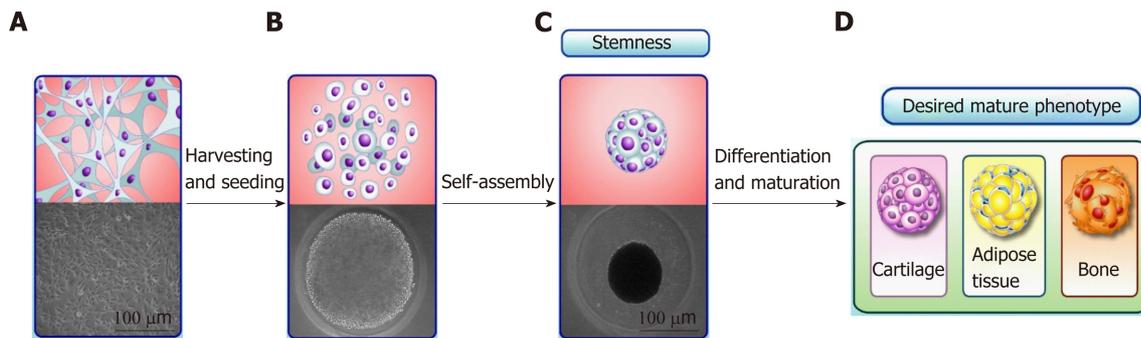


Figure 1 Spheroids mimic the embryonic stages of tissue development, optimizing the multilineage differentiation capacity of Adipose stromal/stem cells and mesenchymal stromal/stem cells. A: Adipose stromal/stem cells (ASCs) and mesenchymal stromal/stem cells (MSCs) can be harvested from monolayer and seeded into 3D culture plate dishes; B: The cell suspension starts to establish cell-cell interaction in a process known as self-assembly; C: The resulting spheroids containing cells and extracellular matrix components, are described for optimizing the stemness; D: Multilineage differentiation capacity of ASCs and MSCs under appropriate morphogens.

Muse cells^[41,42], with some signs of pluripotency^[36]. Accordingly, it is not surprising that spheroid-based culture, which is known to increase the stemness capacity of cells, may increase the potential of ASC differentiation beyond that expected for mesenchymal lineage cells. The major advantage in exploring the pluripotency of ASC spheroids will be their safety in regenerative medicine protocols, since some studies show the absence of teratoma formation after Adipose-Muse transplantation^[40].

CONCLUDING REMARKS

In 2001, ASCs emerged as an accessible source of adult multipotent stem cells, showing high angiogenic and regenerative potential. The *in vitro* expansion of ASCs as monolayers may mask the multipotency and anti-inflammatory capacities of ASCs from obese and ex-obese donors. Embryonic development is marked by the formation of spheroid-like cell clusters, which can be mimicked *in vitro* by 3D culture as spheroids. Spheroid culture promises to reveal features of ASCs that were masked by culture in monolayers, including their pluripotency. In conclusion, ASC spheroids can be delivered into the injury site in an undifferentiated state due their regenerative potential or even as a tissue engineered construct, while allowing the use of obese and ex-obese ASCs in regenerative medicine protocols.

FUTURE DIRECTIONS

The transition from 2D monolayer culture of ASCs to 3D culture as spheroids brought previously unimaginable advantages. The next step is to translate the advantages of spheroid culture into novel therapeutic uses of ASCs in tissue regeneration and tissue engineering.

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