REVIEWS

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Adipose Tissue-Derived Stem Cell Therapy for Post-Surgical Breast Reconstruction – More Light than Shadows*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Breast cancer remains the most common tumor in women, and new techniques for post- surgical breast reconstruction have been recently introduced. These new procedures include autologous fat grafting with or without the enrichment with autologous stromal vascular fraction (SVF), platelet-derived growth factors and insulin. The reported improvement of fat graft viability with these techniques likely depends on the presence in the SVF of multipotent resident adipose derived-stem cells (ASCs). The clinical advantage derives from the plasticity of ASCs and their ability to generate new functional adipose tissue and vessels. However, there is an ongoing debate regarding the possible interplay between breast tumor cells and resident or transplanted ASCs for their capacity to locally secrete growth factors. Most of the data in the literature concerning ASCs is derived from *in vitro* models, whereas the knowledge of ASC behavior *in vivo* remains scarce. Recent reports concerning SVF/ASC enrichment of fat graft did not describe any significant worsening of prognosis for patients undergoing those procedures. However, further studies and longer follow-ups are needed to specifically define technical procedures and to confirm the safety of procedures of SVF/ASC enrichment during post-surgical breast reconstruction (**Adv Clin Exp Med 2015, 24, 3, 545–548**).

Key words: ASCs, breast reconstruction, fat grafting, SVF.

Breast cancer remains the most common tumor in women but the scars and deformities following its surgical removal could give rise to psychological problems [1]. Recently, plastic surgery procedures for the treatment of deformities following breast cancer or tissue defects include autologous fat grafting with or without the enrichment with enzimatically-obtained stromal vascular fraction (SVF), platelet-derived growth factors and hormones including insulin [2, 3]. Ameliorated transplanted fat viability is critically regulated by the presence of resident adipose derived-stem cells (ASCs). The latter can be isolated by cultures of the enzymatically-obtained SVF from aspirate subcutaneous adipose tissue [4]. ASCs displays a capacity of differentiation similar to bone marrow mesenchymal stem cells (MSCs) and showed *in vivo* the expression of stem cell markers, such as CD44 (Fig. 1) [5]. ASCs are readily responsive to platelet-derived growth factors and insulin, through the activation of complex receptor-mediated pathways stimulating proliferation and differentiation [6]. Several studies reported that the use of autologous fat graft, enriched with SVF, increases the viability of the fat graft, likely due to the creation of new blood vessels and the promotion of cell turn-over [7, 8]. SVF/ASCs, because of their ability to differentiate into various cell lineages

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apart from adipocytes, have been proposed to increase autologous fat graft viability for regenerative purpose [4]. More recently, in a randomized placebo-controlled trial, the enrichment with *ex vivo* expanded ASCs improved fat graft viability, so opening new prospective to their selective use in reconstructive surgery [9]. Unfortunately, the safety of the procedure of stem cells enrichment remains unclear in the field of reconstructive surgery after mastectomy, where the full clinical potential of ASCs needs deeper investigation.

Adipose Derived Stem Cells and Breast Cancer Progression

Recent studies demonstrated the increase of efficacy of autologous fat grafting when associated to SVF enrichment, in particular in the treatment of lower extremity ulcers [10]. In response to damage or ischemia, circulating and resident stem cells promote angiogenesis through secretion of growth factor, such as VEGF, while collagen synthesis contributes to tissue remodelling following acute and chronic damages [11–13]. Actually, major attention has been focused in order to clarify if the transfer of ASCs-containing SVF may increase the risk of breast cancer development or relapse [14]. Tumor microenvironment consists in a complex signaling network which influences the behavior of both resident stem cells and tumor cells [15]. Angiogenesis is one of the crucial events for cancer development and growth, and VEGF secretion plays a pivotal role in this process, thereby becoming a main target for antitumor strategies [16, 17]. ASCs may contribute to stromal support for cancer cells by the local delivering of inflammatory cytokines and/or growth factors including VEGF, thus facilitating the recruitment of migratory cancer cells, tumor growth and metastasis [18]. In fact, a large number of myofibroblasts is present in the stromal compartment of invasive breast cancer [19–21] and SVF-derived ASCs express high levels of alpha-smooth muscle actin, a myofibroblastic marker also expressed from mesenchymal tumor cells [22]. Similarly to circulatory stem cells, resident or seeded ASCs may favor cancer growth by supporting myofibroblast differentiation, the formation of new vessels, the synthesis or deposition of extracellular matrix and the release of metalloproteinases responsible of extracellular matrix remodeling [23–26]. Recent data suggests that soluble factors secreted from breast cancer cells inhibit adipogenic differentiation and increase the proliferation, pro-angiogenic factor secretion and myofibroblastic differentiation of ASCs [27–29]. A stable population of engrafted stem cells may contribute to a inflammatory/growth factor-driven of residual breast cancer cells, a potential risk parallel to the aesthetic advantage [29, 30]. Nevertheless, the role of resident or engrafted stem cells in breast cancer progression is still controversial. Several studies document that ASCs influence variably the growth of active and dormant cancer cells [31]. ASCs transplantation or co-injection into mouse breast cancer models had an inhibitory

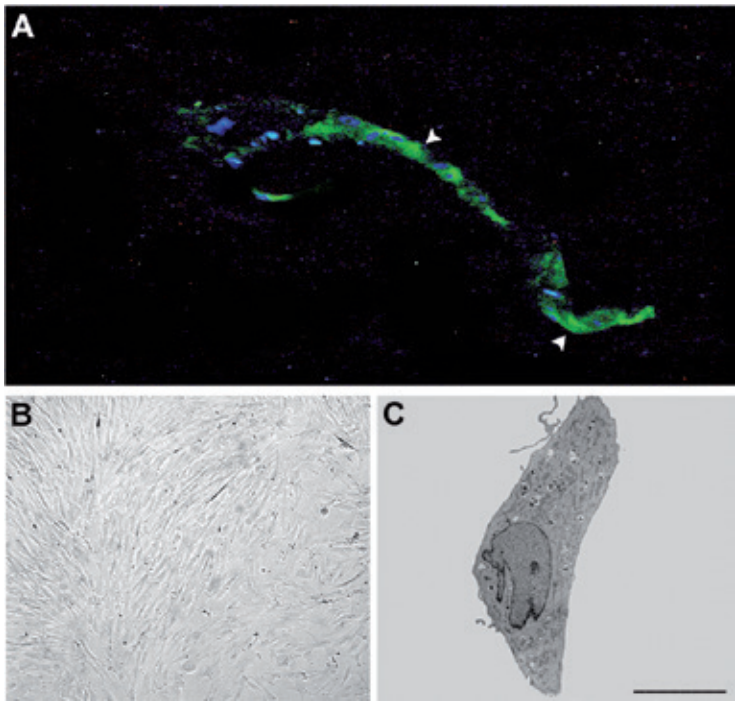

Fig. 1. Morphology and stem phenotype of adipose-derived stem cells *in vivo* and *in vitro*.
A) Immunofluorescence staining reveals the strong expression of CD44 stromal stem cell marker in the perivascular cells of *in vivo* breast adipose tissue (arrow heads, green fluorescence). Hoechst nuclear are staining. Scale bar, 100 μm.
B) Phase contrast micrograph shows the typical elongated shape of adipose-derived stem cells cultured in the presence of 10% FBS. Original magnification, X200.
C) Transmission electron microscopy displays the ultrastructural appearance of an adipose tissue-derived stem cell cultured *in vitro* in presence of serum, with rare intracytoplasmic lipid droplets accumulation. Scale bar, 10 μm

effect on tumor growth, likely due to the activity of ASC-dependent Poly ADP ribose polymerase cleavage inducing cancer cell apoptosis [32]. Nevertheless, many receptor-mediated pathways involved in breast cancer growth, including those related to ErbB, FGFR and EGFR, are also involved in adipogenic differentiation of ASCs [4]. This is why further studies are needed to clarify how growth factors and cytokines differently stimulate resident stem and cancer cells and to can address cancer cell differentiation without stimulatory proliferation.

In conclusion, follow-up studies did not prove any significant difference in relapse when patients treated with fat grafting were compared with untreated ones, so at least for the presence of resident ASCs, fat grafting in post-surgical breast reconstruction appears safe. However, in relation to reconstructive therapy utilizing fat graft enrichment with SVF or expanded ASCs, further studies with optimization of preclinical procedures and longer follow-up are required; at the present, the literature suggests that SVF/ASC enrichment should be postponed until there is no evidence of active disease.

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