Human adipose tissue-derived stem cells in breast reconstruction following surgery for cancer: A controversial issue

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ABSTRACT

Breast cancer is the most common cancer in women. Patients, in particular young women, after surgical removal of the tumor have a poorer quality of life and psychological problems. The use of lumpectomy and adjuvant radiation as surgical approach has contributed to ameliorate cosmetic and functional outcomes. In addition, ameliorated plastic surgery procedures for breast reconstruction, including autologous fat grafting, concur to reduce cosmetic and psychological problems. The maintenance of the transplanted fat is partially due to the presence of adipose derived-stem cells (ASCs). The latter can be isolated from the stromal vascular fraction (SVF) after digestion and centrifugation of residual subcutaneous adipose tissue. Intraoperatory SVF/ASC enrichment has been proposed to stabilize and optimize autologous fat engraftment for breast reconstructive surgery after mastectomy, but the safety of these procedures is still uncertain. Although the literature offers contrasting opinions concerning the effects of ASCs on cancer growth according to the tumor type, at the present time ASC implementation for regenerative medicine therapies should be carefully considered in patients previously treated for breast cancer. At the present, reconstructive therapy utilizing ASC-enriched fat grafting should be postponed until there is no evidence of active disease.

Keywords: Human Adipose-Derived Stem Cells; Breast Cancer; Breast Reconstruction; Fat Grafting

1. INTRODUCTION

Breast cancer is the most common cancer in women.
2. ADIPOSE DERIVED STEM CELLS AND BREAST RECONSTRUCTION

Whilst there has been no direct evidence linking fat grafting in the breast to an increased risk of cancer progression, recent scientific attention has turned to whether the transfer of ASCs-containing SVF could favour an increased risk of breast cancer development or recurrence [6]. The first evidence of interplay between adipose tissue and cancer cells was reported by Manabe et al. [8]; they demonstrated that rat mature adipocytes and preadipocytes stimulated proliferation of oestrogen receptor positive breast cancer cell lines in 3D collagen matrices [8]. Successive studies confirmed that ASCs increased proliferation and invasive potential of breast cancer cells [9,10]. Human ASCs co-cultured with MCF7 breast cancer cells secreted transforming growth factor-β1 and regulated the establishment of extracellular matrix [11]. These findings suggest that ASCs may promote cancer diffusion by stimulating the extracellular matrix assembly process. As concerning the role of ASCs in non-breast cancer progression, data are contradictory. Findings similar to those obtained with breast cancer cells were documented with osteosarcoma cells with or without murine mesenchymal stem cells [12]. Opposite conclusions have been made for prostate cancer. ASCs were found to be nontumorigenic and capable to variably reduce tumor growth and prostate tumor establishment in two prostate cancer xenograft models in vivo, as well using a soft agar assay in vitro [13]. Recent studies indicate that soluble factors from breast cancer cells inhibit adipogenic differentiation while increase proliferation, pro-angiogenic factor secretion, and myofibroblastic differentiation of ASCs [14]. Extracellular matrix deposition increased stiffness and, in turn, facilitated changes in ASC behaviour [14]. The potential concern of autologous fat transfer is that enrichment with ASCs may contribute to stromal support for cancer cells and to deliver locally inflammatory cytokines and/or growth factors, thus facilitating potential residual cancer cell survival and growth. Recent data suggest that a small subpopulation of cancer stem cells is responsible for tumor dedifferentiation, metastasis and chemotherapy resistance. Moreover, malignant cells can reprogram and de-differentiate, so acquiring a stemness phenotype. Inflammatory signals, such as TGF-β, TNF-α, and NF-κB, induce the expression of specific molecules. Transglutaminase 2, is an extracellular matrix molecule that plays a relevant role in TGF-β-driven osteocartilaginous tissue remodeling [15]. Transglutaminase 2 has been recently recognized to drive the ovarian tumor cell phenotypic conversion sustaining the epithelial-mesenchymal transition and stemness appearance [16]. A potentially less stable population of engrafted mesenchymal stem cells likely contribute to inflammatory/growth factor-driven residual breast cancer growth, so representing an undetermined or too high potential risk compared to the aesthetic advantage [17]. Nevertheless, in an interesting study, Zimmerlin et al. [18] tested tumorigenesis of tumor cells from metastatic pleural effusion from breast cancer patients in ASC co-cultures. The Authors provided convincing evidence that ASCs enhanced the growth of active, but not resting tumor cells and concluded that reconstructive therapy utilizing ASC-augmented whole fat should be postponed until there is no evidence of active disease [18].

3. CONCLUSION

Current scientific evidence suggests that ASC implementation for regenerative medicine therapies should be carefully considered in patients previously treated for breast cancer. Reconstructive therapy utilizing SVF/ASC-enriched fat grafting should be postponed until there is convincing clinical and anamnestic evidence of absence of active disease.

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