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Review

Fat grafting and stem cell enhanced fat grafting to the breast under oncological aspects – Recommendations for patient selection

Anna Krumboeck, Pietro Giovanoli, Jan A. Plock*

Division of Plastic and Hand Surgery, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

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ABSTRACT

Reconstructive and aesthetic fat grafting has been introduced to the breast level over the last years. The safety of such procedures has so far not been completely clarified. The concept has now been refined to stem cell enhanced fat grafting. However beside the promise of using adult stem cells in terms of tissue rejuvenation and augmentation, scar treatment and reconstruction, the variance of adipose stem cell function – including angiogenetic, antiapoptotic, immunomodulatory, chemotactic and anti-scarring potential – raises new scepsis about oncological safety.

Herein we reviewed experimental and clinical data on fat grafting and stem cell enhanced fat grafting addressing surgical promise and oncological concerns. Based on these data we suggest clinical criteria for patient selection undergoing fat grafting for aesthetic or reconstructive reasons based on their individual breast cancer risk.

Introduction

Restoration of healthy body contour and function is a major aim after cancer surgery. Currently reconstructive plastic surgery offers specialized surgical techniques utilizing tissue transfer and artificial materials (e.g. silicone implants, injectable fillers) to achieve this goal. Although these procedures are safe and the results are satisfying, multiple co-morbidities like obesity and diabetes impair the success overall rate. Additionally, the perioperative risk is increased and enormous care costs are produced for the sequelae of these pathological conditions. Consequently appropriate and safe adjuncts or appealing alternatives to the present surgical concepts are of utmost socioeconomic interest.

In aesthetic surgery breast augmentation is one of the most frequently requested operations. The safety and low risk of state-of-the-art silicone prosthesis breast augmentation has been demonstrated in several studies.[1,2] However, about 10–20% of the patients are prone to long-term complications such as capsular contraction, which necessitate further operations on the long-term.

Given these circumstances autologous fat grafting is thought to be a promising strategy in reconstructive and aesthetic breast surgery. Several authors have promoted the issue, as the whole concept is sound and has been proven to be feasible on a pioneer basis.[3,4] An increasing number of surgeons are using lipoaspirates for additional or corrective contouring after completion of breast surgery. However, comprehensive data is rarely discussed and personal reports with low evidence level seem to overweigh scientific data. Fat grafting as a technique has been described already 150 years ago, but was re-popularized in the 1980s and especially with the beginning of the 21st century. Safety of fat grafting has been a major issue especially on the breast level over the past years. Recent reviews have addressed the topic based on biological and clinical data.[5–8] The newest prospective of the technique relies on the detection of adult stem cells in adipose tissue. These adipose derived stem cells (ASCs) are mesenchymal stem cells (MSCs) and share multipotency of differentiation and homing with MSCs from different origin like bone marrow.[9–14] Adult stem cells are undifferentiated cells found in adult specific tissues or organs. They are self-renewing and capable of differentiating into specialized cell types to maintain the integrity and repair of the tissue in which they are found.[15,16] These abilities together with the capacity to proliferate and to return to its original stem cell phenotype are summarized as stem cell plasticity.[17] The breast itself has rarely been investigated as stem cell source for engineering or reconstruction purposes.[14,18,19] Adipose tissue as a stem cell niche has been shown to be an easy available and accessible source with high yield of adult stem cells up to advanced age in humans.

* Corresponding author.
E-mail address: jan.plock@usz.ch (J.A. Plock).

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Meanwhile autologous fat transfer is a recognized method to the extent of usage as an adjunct to established reconstructive techniques in breast reconstruction clinically.[20] Recently aesthetic breast augmentation through autologous fat grafting has also been promoted.[21,22] While some authors enduringly claim safety and efficacy for fat grafting from lipoaspirates to the breast,[3,22] others are concerned about long-term safety, predictability of results and efficacy.[23] Also national societies of plastic surgery in Europe and the United States have been critical about the technique on the breast level until evidence from scientific data is available.

Very recently now the concept of fat grafting has been further developed to stem cell enhanced fat grafting.[24–29] Latest overview recommendations have however included the possibilities of adding this procedure to the breast surgery armamentarium,[30,31] which again raises the question of safety if the stem cell yield in a fat graft to the breast is increased. The more so as the great variance of mesenchymal stem cell function beside the potential to differentiate is becoming more and more deplored and MSCs have been demonstrated to have angiogenetic, antiapoptotic, immunomodulatory, chemotactic and anti-scarring potential in multiple applications.[32]

This review is aiming at giving an overview of present scientific data on the basics of stem cell enhanced fat grafting, its clinical promise and the oncological concerns. We suggest easy to use clinical criteria for patient selection undergoing fat grafting for aesthetic or reconstructive reasons based on their individual breast cancer risk.

Fat – adipose stem cells

Over the past decade increasing knowledge has emerged postulating that adult stem cells or progenitor cells may also be involved in tissue regeneration in adult tissue. Clinically the late side effects of radiation therapy could be countered by adipose derived adult stem cell treatment, which included MSCs.[33] Although not purified, cultured or differentiated into any specific cell line, lipoaspirates and its stromal fractions show great potential to create viable natural tissue not only in damaged tissue.[33–35] Tremendous efforts have been made to utilize stem cells for tissue engineering purposes. In humans especially the subcutaneous fat has been identified as easy accessible resource. Several strategies have been developed: Scaffold guided[14,36] and injectable systems containing stem cells, growth factors or both[37–41] showed promising results. Fat grafting from lipoaspirates is now an encouraging strategy, as it results in regenerative effects to the recipient tissue. Outstanding results in animal models and preliminary results in humans, the first reconstructive concepts advocated for adipose derived stem cell transplantation for breast reconstruction and also in breast augmentation.[3,4,21,33,42] The technical feasibility has been proven for these procedures. Clinical results seem to be promising, but predictability and stability of the graft take are limited so far.

Current grafting techniques separate the destructed detritus and oil as well as blood and supernatant fluid.[43] The final result is a cellular graft, which is an unpurified pool of various cells including adipocytes, preadipocytes, resident tissue cells and stromal stem cells, which include mesenchymal stem cells. The number of stem cells varies individually and dependent on the technique for liposuction, processing and grafting. Some authors are seeking to increase the stem cell fraction before grafting by additional *in vitro* steps for improved outcome,[25–28] which has now also been tried on the breast level clinically.[42,44]

Adipose derived stem cells are meanwhile well characterized,[45,46] but little is known on how the transplanted or differentiated cells will react on a long-term or in cell–cell interaction with highly reproductive tissue or residual tumor cells.[47]

Experimental studies

In vitro studies

The mammary gland itself is source of a quiescent, self-renewing population of stem cells, which are capable of differentiating to ductal, alveolar and myo-epithelial cells.[19,48] These stem cells have been suspected to endorse breast cancer development.[49–51] Growth and progression of breast tumor cells depend also on the microenvironment. The breast consists not only of mammary gland cells but also of a great amount of mammary fat tissue. Recently first studies were performed on the signaling components in breast adipose tissue exhibiting a large variety of signaling molecules, cytokines and growth factors.[18] FGFs, interleukins, IGFBP, PDGF, RANTES, TGF-β, TNF-α, VEGF and numerous factors involved in stem cell mobilization and homing like G-CSF, SDF-1 have been found in a population of high risk breast cancer patients.[18] All these factors are commonly known to play a significant role in tissue regeneration, neo-vascularization, carcinogenesis and tumor progression. Interestingly MSCs and ASCs also express a variety of these factors. Simultaneously migration of MSCs to tumors is an evident process during tumor progression.[52,53] Epithelial to mesenchymal transition in breast cancer cells was facilitated in the presence of MSCs, which advocates a role in metastatic spread.[54] The levels of chemokines secreted through MSC differentiation and in presence of cancer cells might also play a role in breast cancer progression.[55,56] SDF-1, which is known for stem cell recruitment and homing has been demonstrated to have antiapoptotic effects on mammary tumors, whereas its receptor CXCR-4 showed to promote large breast cancer formation and propagation of distant organ metastasis.[57–60] ASCs themselves have been found to express not only cytokines, but also chemokines and growth factors with synergistic proliferative effects on breast cancer cell lines.[61] However these findings are not new and have been shown for preadipocytes and breast cancer[62] already in the beginning of adipose stem cell research. The same group could show that tumor promotion is dependent on the cancer cell type.[62] Newest findings specify that ASCs do not necessarily activate resting cancer cells and transform into active cancer growth, but might promote residual active cancer cells (Fig. 1).[63]

In vivo studies

In a review article about the use of ASCs as filler Moseley et al.[28] concluded that the limitations of fat grafting exceptionally the

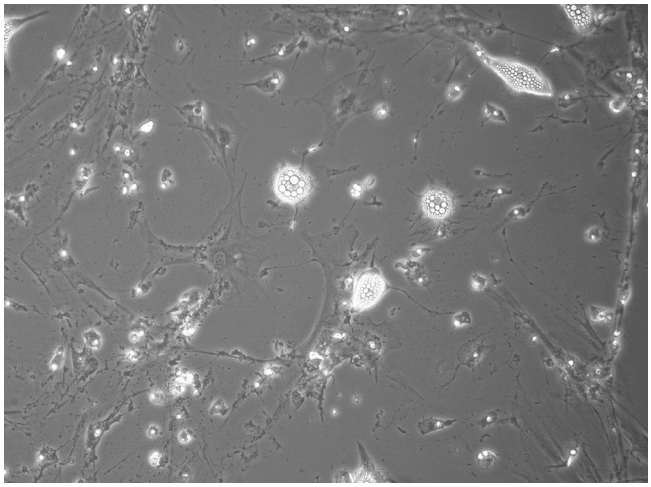

Fig. 1. Adipogenic differentiation of adipose derived stem cells under the influence of differentiation medium *in vitro*.