Journal of Cancer and Tumor International

Volume 13, Issue 3-4, Page 78-84, 2023; Article no.JCTI.114584
ISSN: 2454-7360

The Role of Adipose-derived Stem Cell in Breast Reconstruction with Fat Grafting: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author JWS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AP and IA managed the analyses of the study. Author IA managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2023/v13i3-4245

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/114584

Review Article

Received: 24/10/2023
Accepted: 29/12/2023
Published: 31/12/2023

ABSTRACT

Adipose-derived stem cells (ADSC) are a biological development that provides new hope regarding tissue engineering and regenerative therapy. Due to its potential paracrine activity, compounding, paracrine activity and immunomodulatory function, ADSC-based cell-assisted lipotransfer has emerged as a promising cell therapy technology and significantly improves fat graft retention. Initially used for breast augmentation as a cosmetic function, currently ADSC-based cell-assisted lipotransfer has potential utility for breast reconstruction in breast cancer patients. Post-fat grafting complications of 10.9% were reported and considered major, including hematoma, seroma, fat necrosis, dermatitis, cellulitis, and infection. In this review, we summarize the latest research and aim to provide an overview of ADSC in fat grafting, so that in the future research can be found to avoid post-fat grafting complications in breast reconstruction and provide satisfactory breast reconstruction results.

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Keywords: Angiogenesis; adipose-derived stem cells; fat grafting; breast reconstruction.

1. INTRODUCTION

"Adipose Derived Stem Cells are part of the Stromal Vascular Fraction of subcutaneous adipose tissue, which has various collections of heterogeneous mesenchymal cells" [1]. Stromal Vascular Fraction can be obtained by separating lipoaspiration mechanically or enzymatically. The stromal vascular fraction consists of the non-adipocyte fat fraction and consists of mesenchymal stromal cells, stromal cells, fibroblasts and blood vessel cells in the smooth muscle and endothelium. Stromal cells produce and maintain the extracellular matrix that adheres to and supports cells in the Stromal Vascular Fraction. An intraoperative mechanical isolation procedure has been developed to produce tissue-derived stromal vascular fraction (tSVF) with more feasible clinical applications than enzymatic isolated Stromal Vascular Fraction [2]. There are 10.9% complications after fat grafting that have been reported and are considered serious, including hematoma, seroma, fat necrosis, dermatitis, cellulitis, and infection [3]. In this review we summarize the latest research and aim to provide an overview of ADSC angiogenesis in fat grafting, so that in the future research can be found that can avoid complications after fat grafting in breast reconstruction and provide satisfactory breast reconstruction results.

2. CHARACTERISTICS OF ADIPOSE-DERIVED STEM CELLS

Adipose-derived stem cells has abilities including self-regeneration, asymmetric division, and pluripotency. Further differentiation of SVF into various cellular populations has been reported based on CD31/CD34 and CD146 markers for mature endothelial cells (CD31+/CD34−), endothelial stem cells (CD31+/CD34+), ASCs (CD31−/CD34+) and pericytes (CD146+/CD31−/CD34−) [4]. Cellular markers of ASCs and their subpopulations, as well as their location close to blood vessels contribute to their characteristics as previously described. The stromal vascular fraction components are summarized in Fig. 1 [5]. In addition, adipose-derived stem cells does not express Major Histocompatibility Complex-II and thus it can be concluded that ASC has potential immunomodulatory functions that benefit post-transplant recipients [1,4].

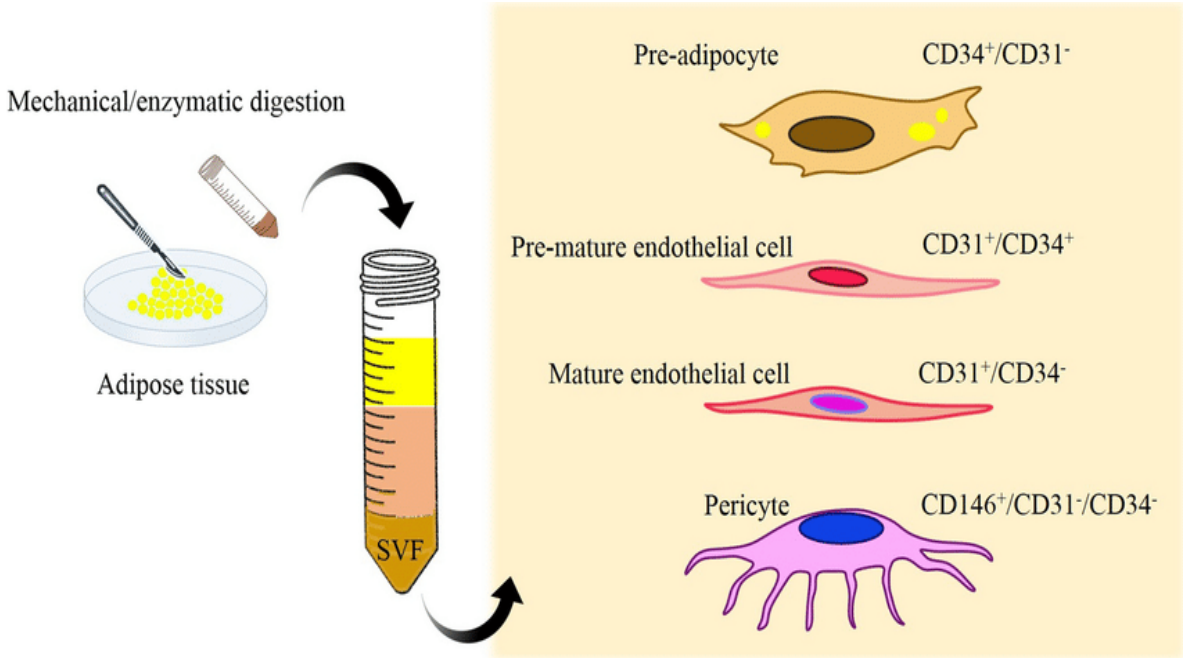

Fig. 1. Cellular component of the stromal vascular fraction (SVF). Four cell populations with their surface markers

3. FAT GRAFTING IN BREAST RECONSTRUCTION

"Fat grafting has been widely used in breast reconstruction by reconstructive plastic surgeons. Fat grafting has the advantages of being biocompatible, easy access, minimal complications, cost-effective, and minimal risk of injury to the donor site" [6]. "Adipose-derived stem cells originate from the stromal components of adipose tissue, and have the potential to proliferate and differentiate into various cell lineages such as adipogenic, myogenic, osteogenic, chondrogenic, and vascular endothelial cell types" [7]. "In addition, adipose-derived stem cells collection is easy to perform, has a low donor site morbidity rate and it has been proven that adipose tissue aspirates contain a much higher concentration of stem cells compared to bone marrow. This evidence, makes this adipose-derived stem cells a tool that improves long-term survival of fat grafts. Preclinical studies also show that adipose-derived stem cells can contribute to adipose tissue regeneration and maintain graft viability by promoting angiogenesis" [7].

"In addition, two concerns have emerged regarding the application of stem cell-based techniques in breast reconstruction surgery including graft contamination during extracorporeal stem cell enrichment procedures and the alleged crosstalk between stem cells and breast carcinogenesis" [4,7]. "It has been suggested that stem cells can induce molecular cascades and changes in the breast microenvironment that can promote de novo carcinogenesis, proliferation of residual cancer cells and metastasis" [4,7]. "Clinical studies have not reported an increased risk of recurrence although results from preclinical models support the theory" [4]. "The number of stem cells transplanted is also believed to be no match observed. However, important threshold values cannot be determined with the existing evidence" [7].

"Advances in the technical aspects of autologous fat grafting have reduced the incidence of complications. The total complication rate was lower (8.4%, 95% CI 7.6–9.1) compared with other breast reconstruction procedures" [4].

4. ADIPOSE-DERIVED STEM CELLS ANGIOGENESIS IN FAT GRAFTING

Adipose-derived mesenchymal stem/stromal cells can induce angiogenesis (Fig. 2), and they exert their pro-angiogenic effects mainly through paracrine secretion [8]. "The hASC secretome is rich in several growth factors and cytokines, many of which are known to be pro-angiogenic. These include VEGF, fibroblast growth factor 2 (FGF-2, also known as basic fibroblast growth factor), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β) and hepatocyte growth factor (HGF)" [7]. The abundance of these growth factors makes ASCs attractive because they can influence many different pathways and mechanisms of angiogenesis.

"ASCs express β-1 integrin (CD29) which participates in angiogenesis and CD44 hyaluronate and osteopontin receptors, which are essential in the development of the extracellular matrix and pathological processes such as neoplasia" [3]. "In vitro and in vivo research show that ASCs are often found lining the outside of microvessels, and they have a stabilizing role by differentiating into pericytes and by expressing common pericyte surface proteins such as the smooth muscle late pericyte marker α-actin (α-SMA), neuronal/glial antigen 2 (NG2) or platelet-derived growth factor receptor β (PDGFRβ)" [8]. IGF-1 upregulates α-SMA in ASCs, indicating that it can induce ASC differentiation toward pericyte-like cells (Fig. 3).

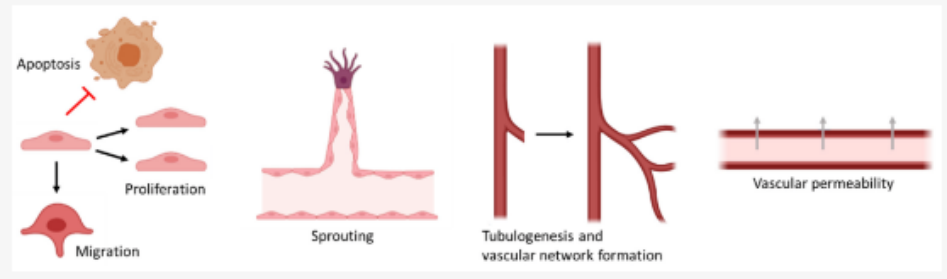

Fig. 2. Mechanisms of angiogenesis induced by adipose-derived mesenchymal stem/stromal cells (ASCs)

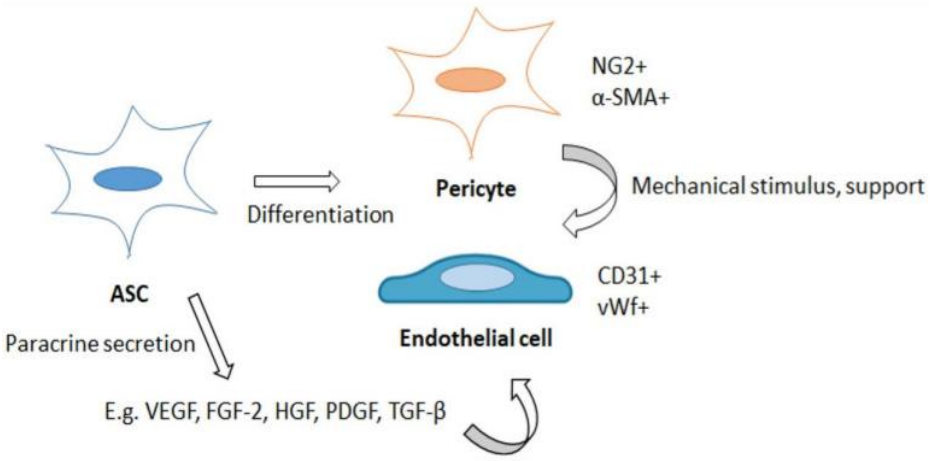

Fig. 3. ASCs induce angiogenesis through the secretion of paracrine growth factors that regulate endothelial cells, and by differentiating into EC expression

"In another study, EPCs or HUVECs were combined with ASCs in a fibrin matrix and implanted in the chorioallantois membrane (CAM) of fertilized chicken eggs. The results showed that ASCs induced the migration of blood vessels into the fibrin structure either independently or when administered together with EPCs or HUVECs" [9]. "In ASC-HUVEC implants there were much more capillary-like structures and blood vessel perfusion was observed compared to ASC-EPC implants. No blood vessels or only a few blood vessels were observed when EPCs or HUVECs were transplanted independently. Based on these results, it suggests that the potential reason for vascularization is influenced by EC. Mature EC serves as a stronger alternative to EPC or ECFC. On the other hand, after EC transplantation alone when implanted subcutaneously using scaffold material it was found that no significant vascular structure formation occurred. Meanwhile, ASCs induce angiogenesis even when simply transplanted. It has been suggested that the scaffold matrix is not required for vasculogenesis after co-transplantation because cells delivered in media induce similar CD31-positive functional vasculature compared with cells transplanted in collagen-fibronectin gel" [10]. "It is possible that ASCs provide support for ECs to facilitate angiogenesis. In several studies, the role of ASCs as a type of perivascular cell after co-transplantation has been demonstrated" [11].

5. POTENTIAL EVIDENCE OF ADSC FOR BREAST RECONSTRUCTION

In vitro and in vivo studies, ADSCs in breast cancer have a proven role in the potential to affects breast cancer cell behavior due to the adipokines they secrete and their affects in tumor microenvironment [12]. Adipokines play a role in increasing the invasion of human and mouse breast cancer cells characterized by excessive expression of proteases, including proinflammatory cytokines (IL-6, IL-1β) and MMP-11 when co-cultured with adipocytes. Research shows that ADSCs increase the motility of MCF-7 breast cancer cells in vitro through the secretion of the chemokine CCL5 [13].

"However, the statement that ADSC only promotes the growth and development of active breast cancer cells and does not activate the remaining inactive breast cancer cells. Therefore, the use of ADSC regenerative therapy should be postponed until there is no evidence of active cancer cells" [14].

6. CLINICAL AND EXPERIMENTAL TRIALS

Research on adipose-derived stem cells in breast reconstruction using animal models has provided satisfactory results, however the use of adipose-derived stem cells in human breast reconstruction is still controversial. In a study, ADSCs (2 × 107 cells/ml) with 30 ml were mixed with adipose tissue in vitro and implanted under the skin of the upper extremities of healthy subjects [15] showed "the results that the survival of fat in the ADSC-enriched tissue group was significantly greater. higher than the control group (80.9% vs 16.3%, $P < 0.0001$) at 121 days after surgery, and no side effects occurred". "Gentile et al.'s research. also supported the

benefits of ADSC-based cell-assisted lipotransfer where SVF significantly improved autologous fat graft survival (63% vs. 39%, P < 0.0001) at 1 year after surgery" [16].

In contrast, research by Wang et al. [17] and Peltoniem et al. [18] completely contradicts "the statement that there was no increase in fat survival in 10 and 12 patients undergoing breast reconstruction, and the fat reabsorption rate was approximately 50% at 6 months after surgery". Many factors contribute to variations in results from different studies, including age of the fat donor [19], blood supply to the recipient site, density of SVF or ADSC, ADSC isolation technique, surgical process of fat transplantation, and skill of the surgeon. "This showed that approximately 90% of ADSCs remained viable within 1 hour of isolation, while only 6% remained active after 6–8 hours" [20]. Therefore, isolation of ADSCs from adipose tissue should be performed as soon as possible and surgery performed carefully.

7. FUTURE DIRECTION

"Progress in adipose tissue engineering has made significant progress, but there are several unresolved issues that need to be addressed before adipose tissue engineering can be applied clinically. Basically, the isolation technique used to produce lipoaspirate still requires refinement to optimize cell survival and viability. It is currently believed that high-speed centrifugation may pose a risk to lipoaspiration and that washing adipose tissue to separate it from blood and infiltration solution may improve results" [21]. "However, to date, there is no consensus regarding protocols regarding lipoaspirate isolation techniques" [22]. Adipose depots are The optimal source also needs to be identified, as the source of the greatest ADSC cell yield and as an oncologically safe source. As previously discussed, several genes involved in cell growth, ECM deposition, or remodeling and angiogenesis were expressed at higher levels in local breast ADSCs compared with genes isolated from adipose tissue or bone marrow, suggesting that the breast adipose depot plays a role which is more important in breasts. cancer development.

The exact oncological safety of ADSC still requires investigation. The role of ADSCs in stromal support for tumors also requires careful study in future trials. Patient factors will also influence the oncological safety of ADSC. And there are still questions that need to be answered, are there other patient characteristics that place them at greater risk of recurrence?

Determining the timing of reconstruction with ADSC also still requires careful consideration. There is an opinion that ADSC only promotes the growth and development of active breast cancer cells and not the remaining inactive breast cancer cells. Therefore, should the use of ADSC regenerative therapy be postponed until there is no evidence of active cancer cells, and what is the optimal time after curative surgery for reconstruction with ADSC technology to prevent recurrence?

8. CONCLUSION

Adipose-derived mesenchymal stem/stromal cells have been studied extensively in the last two decades. Mesenchymal stem/stromal cells have the ability to modulate the immune system and participate in tissue regeneration. Because these cells can be easily harvested from adipose tissue, their low donor site morbidity makes them a better choice than bone marrow-derived mesenchymal stem cells. Basic studies in co-culture with endothelial cells have demonstrated pro-angiogenic effects of ASC through paracrine secretion or through direct cell contact where ASC supports the formation of tube-like structures. Supplementation of IGF-1 in culture media promotes the expression of growth factors in ECs and ASCs that are important for angiogenesis via the PI3K/AKT signaling pathway.

In addition, activation of PDGFRβ promotes the formation of blood vessel tissue in vitro, while activin A, which is secreted by ASC, plays a role in inhibiting the formation of blood vessel tissue. ASCs can differentiate into endothelial cells, especially under three-dimensional culture conditions. FGF-2 and activation of the PI3K/AKT signaling pathway are critical in ASC endothelial differentiation. Additionally, ASCs can participate in the stabilization of microvessels by differentiating into pericytes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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