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The safety of autologous fat transfer in breast cancer: Lessons from stem cell biology

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Summary

Autologous fat grafting is versatile tool in plastic surgery and is increasing used for reconstruction following breast conserving surgery for breast cancer. Part of the reconstructive qualities of the transferred fat may be due to the presence of adipose derived mesenchymal stem cells (ADMSC) playing an angiogenic and an adipogenic role.

In this context it must be considered if autologously engrafted fat tissue could contribute to carcinogenesis following breast conserving surgery. In this article we review the current stem cell biology evidence on engraftment, transdifferentiation and potential carcinogenic contribution in the breast and other solid organ stem cell niches in an attempt to highlight possible areas of concern.

Keywords

Fat grafting; Breast reconstruction; Stem cells

Introduction

Autologous fat transfer is widely used in plastic surgery for both reconstructive and aesthetic purposes.[1] Its role as a natural filler is commonly used in the face[2–5] but is also increasingly utilized to restore contour, increase volume and improve irradiated skin in the breast.[5–7] Further applications in the hands, gluteal region and throughout the body have been well described.[4,8,9] Increasingly, it is employed by breast reconstructive surgeons following cancer treatment, particularly in the realms of breast conserving surgery.[9,10]

Whilst resorption of transferred fat often mean several treatments are required for lasting results,[7] the complications of fat grafting, including fat necrosis, cyst formation and calcification are well recognized and rarely cause significant morbidity.[11] Previous concerns that post operative calcification following fat grafting to the breast might compromise breast

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cancer screening, have largely been allayed with several studies concluding there is no clear evidence that autologous fat transfer affects the efficacy of breast cancer screening, nor results in delay of breast cancer diagnosis.[7,10,12–14] Moreover, recent radiological advances have made differentiating benign and malignant calcification on mammogram far more consistent. The American Society of Plastic Surgeons (ASPS) Fat Graft Task Force states that, whilst more studies are needed, on the current available data “there appears to be no interference with breast cancer detection”.[11]

However, fat is not an inert filler akin to a silicone breast implant. On the contrary, it is a metabolically active tissue, secreting an abundance of hormones, cytokines and growth factors. This must be recognized by the surgeon who recruits fat grafting to his armoury of reconstructive techniques as it has far reaching potential implications. The particular situation of most potential concern is paradoxically the one in which fat transfer appears to demonstrate the most exciting possibilities, namely addressing defects resulting from wide local excision and adjuvant radiotherapy in breast cancer treatment.

Part of the restorative and reconstructive qualities of autologous fat grafting has been attributed to the presence of adipose derived mesenchymal stem cells (ADMSC) within the transferred fat,[6,7] probably through a process of adipogenesis and angiogenesis.[15,16] Whilst there has been no direct evidence linking fat grafting in the breast to an increased risk of cancer, recent scientific attention has turned to whether the transfer of adipose derived stem cells contained within fat could potentially convey an increased risk of breast cancer or cancer recurrence.

Can autologously engrafted fat tissue contribute to carcinogenesis following breast conserving surgery? In this article we ask a series of questions to review current stem cell biology evidence on engraftment, transdifferentiation and potential carcinogenic contribution in the breast and other solid organ stem cell niches in an attempt to highlight possible areas of concern.

Are there stem cells in adipose tissue?

Adipose tissue is an abundant source of mesenchymal stem cells (Adipose derived mesenchymal stem cells - ADMSC) which, under appropriate conditions, can differentiate into a range of cell types (e.g. chondrocytes, myocytes, osteoblasts) and secrete angiogenic factors such as vascular endothelial growth factor (VEGF).[17,18] The presence of ADMSC in transferred fat has also been shown to play a key role in fat graft survival.[19,20] The influence of the paracrine attributes of adipose tissue and ADMSC is illustrated when considering their influence on angiogenesis. Whilst this has exciting possibilities in areas such as wound healing, the pro-angiogenic role of the transplanted adipose tissue has more worrisome implications in oncology. VEGF is known to promote tumour invasion and metastasis in a number of different cancers[21,22] and ADMSC has been shown to promote migration and invasion of breast cancer cells *in vitro* and *in vivo*.[23]

Are mesenchymal stem cells capable of engrafting and transdifferentiating?

Substantial evidence exists that mesenchymal stem cells are capable of engraftment in different tissues in response to organ injury. Following engraftment it has been suggested that bone marrow derived mesenchymal stem cells in particular, can transdifferentiate (acquire a new phenotype) into several different tissue types (e.g. skeletal muscle, endothelial cells, myofibroblasts) to facilitate repair and/or regeneration.

Such a situation may exist in patients who experience long term remission from inflammatory bowel disease (IBD) following allogenic or autologous haemopoetic stem cell transplantation, either for a concomitant haematological malignancy or primarily for IBD.[24] Transdifferentiation of haemopoetic stem cells into components of the gut mucosa may provide the cellular explanation for this clinical improvement, as may the pro-angiogenic effect of the stem cell.[25] In animal models of IBD transplanted bone marrow derived mesechymal stem cells have been shown to transdifferentiate into endothelial cells and myofibroblasts contributing to mucosal restitution.[26,27]

Animal models have also provided evidence of stem cells playing a similar role in the cancer setting. Direkze et al.[28] demonstrated engraftment of transplanted mesenchymal stem cells (MSC) in a mouse model of pancreatic insulinoma. Female mice transfected with an insulin promoter gene (causing the development pancreatic β cell tumours) were irradiated, then transplanted with bone marrow from male mice. Immunohistochemistry and *in situ* hybridisation on the pancreata of the sacrificed, recipient female mice demonstrated 25% of myofibroblasts within the tumour stroma were donor derived (detected by the presence of a Y chromosome). Donor derived fibroblasts and insulin like cells were also detected. In other words, the transplanted transdifferentiated MSC significantly contributed to cancer associated stroma.

Direkze et al.,[29] subsequently demonstrated the expression of α smooth muscle actin and mRNA of pro(α1) collagen in the Y chromosome positive myofibroblast population, by immunohistochemistry and *in situ* hybridisation respectively. This demonstrated that engrafted bone marrow cells can transdifferentiate and assume a functional role within their new niche.[29]

Can transplanted mesenchymal cells form an epithelium at risk of malignant change?

If transplanted mesenchymal stem cells (such as ADMSC) are capable of engraftment and transdifferentiation, a key question is whether they can transdifferentiate into epithelial cells at risk of malignant change. The experimental evidence here is conflicting.

Krause et al.[30] observed both multiple organ epithelial engraftment when looking at the long term repopulation of irradiated female mice with male bone marrow from a single haemopoetic stem cell line (CD34/SCA 1 + ve). After 11 months, both blood and solid organ epithelial cells examined for Y chromosome showed positive cells. Results

demonstrated the majority of bone marrow and peripheral blood cells were male derived, along with small numbers of epithelial cells in the lung, gastrointestinal and biliary tracts.

Houghton et al.[31] used a mouse model to demonstrate that chronic infection with Helicobacter, a known carcinogen, induced repopulation of the stomach with bone marrow derived cells which then progressed through metaplasia and dysplasia to intraepithelial cancer. Infected female mice were irradiated and then received bone marrow from donor mice positive for a number of reporter genes (beta galactosidase or green fluorescent protein (GFP)). Engraftment of bone marrow derived cells could thus be tracked by staining for X-galactosidase (X-gal). These 'X-gal' positive cells were first detected at 20 weeks of Helicobacter infection (just after the peak of gastric mucosa apoptosis in this model). By 52 weeks all observed intraepithelial neoplasia in the 52-week infected mice were beta-galactosidase positive, indicating that these cells arose from donor marrow and strongly suggesting an inherent vulnerability of this population to malignant progression. Houghton's work demonstrated that, in response to chronic *Helicobacter* infection, bone marrow derived cells can home to, and repopulate, the gastric mucosa. Furthermore, over the time these engrafted cells may contribute to metaplasia, dysplasia, and cancer.

Hutchinson et al.[32] backed up animal work by studying tissue from a male patient with adenocarcinoma of the oesophagus who had previously received a bone marrow transplant from a female donor. Fluorescent *in situ* hybridisation demonstrated the bone marrow cells contributed to both epithelial cells and stromal elements of the cancer.

However, such *in vivo* studies should be interpreted with caution before assuming engrafted mesenchymal stem cells can give rise to epithelial cancers. The very nature of the pathological burden in these animal models, which involve destruction of bone marrow through irradiation and considerable target organ inflammation, may exert a selection pressure in favour of the engrafted cells which does not occur naturally. Furthermore, as Alison et al.[33] point out "*it is one thing for a circulating cell to engraft in another organ and assume some or all of the phenotypic traits of that organ..... it is quite another to claim that the engrafted cell has become a local stem cell in its new niche*". In other words, mesenchymal stem cells may engraft and transdifferentiate but this does not mean they undergo clonal expansion, which would be a pre-requisite for cancer formation. Some authors have also shown the apparent transdifferentiation seen experimentally is actually the result of cell fusion, i.e. transplanted mesenchymal stem cells are fusing with mature epithelial cells rather than exhibiting true cell lineage switch.[34,35]

In the largest human study to date, Peters et al.[36] looked at six patients who had received bone marrow transplantation from donors of the opposite sex and subsequently developed epithelial cancers. Using fluoresence *in situ* hybridisation and immunohistochemistry they found that only a small number of bone marrow derived stem cells contributed to vascular endothelium (4.9% engraftment rates) and none to tumour epithelial cells.

The overall conclusion here must be that *epithelial* engraftment is unlikely to significantly contribute to cancer risk in autologous fat transfer, though the evidence for *stromal*

engraftment and carcinogenic influence, which is discussed below, is perhaps more compelling.

Does the tissue stroma contribute to carcinogenesis?

Mesenchymal-epithelial cell communication is increasingly recognized as vital in maintenance of epithelial stem cell homeostasis. Multiple cell signalling pathways from the stroma to the epithelium regulate epithelial cell proliferation and differentiation. Consequently, abnormal stromal components may initiate and/or promote epithelial tumour growth.[37] Alterations in fibroblasts in the stroma adjacent to transformed epithelial cells have been documented in several tumour systems.[38,39]

In the breast, tumour initiating mutations can arise in the stroma before those seen in the breast epithelial cells, and may induce the latter's malignant transformation. Moinfar et al.[40] looked for genetic alterations (loss of heterozygosity - LOH) in mammary stroma in samples from 11 women with ductal carcinoma *in situ* (DCIS), including five with invasive ductal carcinoma (IDC), compared with normal breast tissue excised during reduction mammoplasty. Both macroscopically 'normal' stroma distant from areas of DCIS or IDC and that surrounding the tumours were microdissected, along with epithelial cells. Tumour suppressor gene LOH was found in the majority of stromal and epithelial cells from DCIS/IDC samples, and was seen at multiple loci in stromal cells. Significantly LOH was also seen in the macroscopically normal looking stroma 'distant' from the sites of DCIS/IDC. No LOH was detected in samples from reduction mammoplasty.

The importance of cancer associated stroma in epithelial cell control has been further demonstrated in prostate carcinoma by Olumi et al.[41] 'Carcinoma associated' fibroblasts were obtained from prostatic tissue adjacent to malignant cells in patients undergoing radical prostatectomy, which were morpholologically and immunocyto-chemically identical to the fibroblasts obtained from normal prostates. The two groups of fibroblasts were grown independently both with normal prostatic epithelial cells, and with prostatic epithelial cells immortalized with Sv40 large T antigen (an initiated cell line, which bears some markers of transformation but are non-tumorigenic when grown alone). Tissue recombinants of 'carcinoma associated' fibroblasts and initiated prostatic epithelial cells demonstrated significantly increased growth and altered histological appearance (resembling poorly differentiated adenocarcinomas), whilst recombinants of the initiated epithelial cells and normal fibroblasts exhibited normal growth. Growth of uninitiated (i.e. normal) epithelial cells was minimal with both normal and 'carcinoma associated' fibroblasts. In this experimental model 'carcinoma associated', though morphologically normal, fibroblasts/stroma were capable of stimulating the progression of initiated epithelial cells.[41] More recent work has demonstrated a significant proportion of cancer associated fibroblasts that promote tumour growth, were derived from mesenchymal stem cells and recruited to the stomach in a murine model of gastric cancer.[42]

In vivo, Barcellos-Hoff and Ravani[43] transplanted a breast cell line (COMMA-D - non tumorogenic, but capable of ductal outgrowths) into previously irradiated or nonirradiated mammary stroma of female BALB/c mice (mammary glands were surgically cleared of

epithelia at 3 weeks of age leaving a gland free mammary fat pad, capable of accepting the cell line graft). All cell lines grafted into irradiated stroma (fat pads) resulted in tumours compared to only a small number of ductal outgrowths in the same cell line grafted in to non-irradiated stroma. The authors concluded that changes in the stromal microenvironmental, induced by ionising radiation prior to cell line engraftment, resulted in the large, rapidly proliferating tumours seen.[43] Further studies support the notion that the stromal cell microenvironment contributes centrally to the acquisition of a neoplastic phenotype of breast epithelial cells.[44,45] The evidence of the stroma's influence on epithelial carcinogenesis is compelling and rapidly accumulating.

Could engrafted adipose derived mesenchymal stem cells provide a carcinogenic stromal influence?

Manabe et al.[46] demonstrated that adipocytes increased proliferation of breast carcinoma cells *in vitro*. The authors co-cultured rat adipocytes and preadipocytes with Estrogen Receptor (ER) positive and negative breast cancer cell lines in 3D collagen matrices. Mature adipocytes increased proliferation of ER positive cancer cell lines as measured by bromodeoxyuridine (BrdU) uptake. This suggests adipocytes in the supporting stroma may have a growth promoting role in breast cancer. Iyengar et al.[47] found that adipocytes increased cell proliferation and the invasive potential of malignant breast epithelial cells *in vitro*, as well as promoting tumour angiogenesis through secretion of adipokines.

Further evidence was provided by Yu et al.[48] who found that human adipose derived mesenchymal stem cells when injected cocurrently with tumour cells into nude mice enhanced tumour growth and reduced apoptosis.

Perrot et al.[49] looked at nude mice injected with human osteosarcoma cell line with or without human fat injection. Tumour growth was significantly more pronounced in mice receiving concurrent fat injections. In the same murine model a separate osteosarcoma cell line was injected with, or without, murine mesechymal stem cells. Earlier onset and increased rate of tumour growth were also seen in animals receiving mesenchymal stem cells in addition to the osteosarcoma cell line. Osteosarcoma cell line growth *in vitro* was likewise enhanced in the presence of mesecnchymal stem cells.[49]

Such experimental findings have been brought in to sharp focus following a recent case report from the same authors,[49] which provided some anecdotal evidence of a potential human tumour recurrence as a consequence of fat grafting. The authors reported the case of a late, local recurrence of osteosarcoma following autologous fat transfer. The female patient had the original surgical resection and neoadjuvant chemotherapy aged 17 for an osteosarcoma of the proximal humerus in 1994. Thirteen years after the initial treatment, and 18 months following three treatments of autologous fat transfer to reconstruct the post surgical defect, she presented with a tumour recurrence at the site of reconstruction. Such late, local recurrence is extremely rare following complete remission of osteosarcoma.[49]

It has long since been demonstrated that wide local excision (WLE) plus adjuvant radiotherapy, as opposed to mastectomy, is oncologically safe for certain breast cancers.[50]

I.e. Leaving some breast tissue behind does not have a deleterious effect on recurrence. The significance (and potential concern) of autologous fat transfer in this clinical context is that it has been proposed that engrafted cells may not be as stable or as responsive to local tissue cues as intrinsic cells.[31] Direkze et al's[29] work demonstrated that mesenchymal stem cells can engraft within, and contribute functionally to, cancer associated stroma. Experimental data suggests that cancer associated stroma may be capable of progression (and possible initiation) of epithelial tumours. Thus, in patients who have undergone breast conserving surgery, providing an additional, potentially less stable, population of mesenchymal stem cells which can engraft, and functionally contribute to any residual breast stroma may represent an unacceptable or undetermined risk for an aesthetic result.

Conclusion

In the absence of long term retrospective data, or prospective data from case controlled trials, it remains unknown whether autologous fat grafting affects breast cancer recurrence. There have been no studies demonstrating an increased risk of breast malignancy associated with fat grafting, although the aforementioned case of a late osteosarcoma recurrence following fat transfer is potentially a 'shot across the bows' for those using this technique for post cancer reconstruction. The ASPS Fat Graft Task Force has recommended that clinicians "exercise caution when considering high risk patients" for autologous fat grafting to the breast (i.e. those with past history or family history of breast cancer, BRCA-1, BRCA-2).[11]

We would reiterate this, particularly in patients who have had breast conserving surgery for breast cancer (the hypothetical risk should, in theory, be lower in post mastectomy patients as all the breast tissue (and thus "cancer associated" stroma) has been removed), until large prospective trials can demonstrate there is no elevated risk of disease recurrence. We would also like to suggest national registries for breast cancer patients undergoing fat grafting should be instituted, so any potential trends in cancer recurrence in this cohort of patients might be identified at an early stage.

A different situation exists in flap based breast reconstruction where tissue is transferred en bloc with its blood supply. This therefore maintains the normal tissue architecture and cell-extracellular matrix connections. Any ADMSCs contained, for example, within a deep inferior epigastric artery perforator (DIEP) flap remain in their niche and within their normal homeostatic constraints. Cells within a flap do not engraft as they are nourished by their own blood supply.

The evidence presented in this review predominantly relates to experiments that are "proof of principle" for the questions raised in Table 1. Of course, results from *in vivo* and *in vitro* work do not neccessarily reflect the true clinical picture in patients. However, the emerging scientific evidence on the role of the stroma on the carcinogenesis of epithelial cell tumours is enough to warrant the oncoplastic breast surgeon pause for thought before embarking on fat transfer in the breast, particularly in patients treated with WLE or quadrantectomy. In these patients, transference of adipose tissue and adipose derived stem cells to an environment that has been in the locale of previous malignant change may constitute an unacceptable risk for doctor and patient.

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Table 1

Key questions concerning safety of fat transfer in cancer reconstruction: summary of current experimental evidence.

Are there stem cells in adipose tissue?	**Yes** (ADMSC)[19,20]
Are mesenchymal stem cells capable of engrafting and transdifferentiating?	**Yes**-MSC can transdifferentiate into multiple supporting tissues (such as stroma).[26-29]
Can mesenchymal cells form an epithelium at risk of malignant change?	**Uncertain**-Evidence of MSC transdifferentiation into epithelial cells is less conclusive.[31,32,33,36]
Does the tissue stroma contribute to carcinogenesis?	**Probably**-Mesenchymal–epithelial interaction in carcinogeneis is an area of intense research interest in a number of different organ systems. *In vitro* cancer associated stroma can initiate transformed but non-tumorigenic epithelial cells[41,43]
Could engrafted ADMSC provide a carcinogenic stromal influence?	**Potentially**-Engrafted MSC thought to be less able to regulate growth patterns. Animal models following BM transplant are convincing[29,31]