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Regenerative Therapy After Cancer: What Are the Risks?

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There is often a pressing need for reconstruction after cancer surgery. Regenerative therapy holds the promise of more natural and esthetic functional tissue. In the case of breast reconstruction postmastectomy, volume retention problems associated with autologous fat transfer could be ameliorated by augmentation with cells capable mediating rapid vascularization of the graft. Intentional placement of regenerating tissue at the site of tumor resection raises questions concerning the possibility of promoting cancer recurrence. Here we review coculture and animal models of tumor/mesenchymal stem cell interactions under regenerating conditions. Available evidence from case reports, cell lines, and clinical isolates favors the interpretation that regenerating tissue promotes the growth of active, high-grade tumor. In contrast, dormant cancer cells do not appear to be activated by the complex signals accompanying wound healing and tissue regeneration, suggesting that engineered tissue reconstruction should be deferred until cancer remission has been firmly established.

Introduction

Cancer surgery can be disfiguring

Restoring acceptable human appearance after cancer extirpation is an important part of the treatment process. In particular surgical excision of head and neck cancer or breast cancer, can lead to disfiguring aesthetic deformities and reconstruction is highly desirable. The field of regenerative medicine promises new alternatives to surgical reconstruction. Through the use of scaffolds and multipotent adult tissue stem cells, the restoration of stable, functional, and natural appearing tissue is envisioned. A major concern in the application of regenerative therapies after cancer, especially cell based therapies, is whether these new treatments will increase the risk of tumor recurrence. Unfortunately, the factors that accompany tissue regeneration and revascularization are also critical to cancer growth and metastasis. This article reviews what is known concerning interactions between multipotent mesenchymal stem cells (MSC) and cancer, with a view to assess the potential risks of regenerative therapy after cancer surgery.

Autologous fat transfer

Autologous fat transfer (AFT) for soft tissue reconstruction was initially described more than a century ago in a German-language article entitled *Fettransplantation* (Fat Transplantation). The initial indication for fat transplantation was for correction of facial defects[1] and was soon after introduced for breast reconstruction postmastectomy.[2] However, fat injection into the breast became controversial among plastic surgeons because of potential complications such as local calcifications and interference with mammographic breast cancer surveillance.[3] AFT remains an attractive reconstructive technique with low complication rates.[4] The first successful application of soft tissue regenerative therapy after cancer was performed more than a century ago by Czerny,[2] who restored breast symmetry postmastectomy by transplanting a benign autologous lipoma. Although transplantation of autologous fat yields satisfactory short-term cosmetic results, volume retention has been a recurring problem.[5,6] Recent fat transfer and lipoinjection protocols have focused on the addition of autologous adipose-derived stem/stromal cells (ASC) or freshly isolated adipose stromal vascular cells to promote graft volume retention.[7–9] Enthusiasm for the use of stem cell-augmented adipose transplantation for breast reconstruction has been tempered by the fear that the transplantation of self-vascularizing, self-renewing adipose tissue may promote tumor recurrence by supporting reactivation of occult breast cancer cells.

Potential advantages of cellular therapy

The variability in long-term graft survival[6,10] has been attributed to differences in local angiogenesis.[11,12] Recently, the

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addition of ASC to whole fat grafts was proposed to support the formation of a new vasculature[8,13] and promote graft retention.[14] Fat tissue is a rich source of both endothelial progenitors[15,16] which can mediate angiogenesis and multipotent MSC.[17] Both populations are present in the freshly isolated adipose stromal vascular fraction (SVF).[18] The SVF, when expanded in short term culture,[17,19,20] has been termed ASC[21] and resembles MSC in many important respects, which will be discussed below. The rationale for combining whole fat or lipoaspirate with SVF cells or ASC is that the organized fat tissue may serve as a scaffold upon which more concentrated stem/progenitor cells can organize and differentiate. Another attractive approach for guiding the three-dimensional organization of engineered tissue reconstruction is through the use of scaffolding,[22–24] which may be mineral, synthetic polymers, or biological and may incorporate growth factors naturally[25] or by design.[26–28]

Models of tumor cell/MSC interactions

Therapy for epithelial cancers is rarely curative and late recurrence after apparently successful therapy provides *prima facia* evidence for the persistence of dormant cancer cells. Precisely how regenerating engineered tissues may interact with active and dormant cancer cells *in vivo* is currently unknown. However, interactions of proliferating ASC and MSC with tumor cells have been addressed in coculture and human/murine xenotransplantation models. The major contribution of these studies is that they have provided insight into mechanisms of tumor invasion, demonstrating that secretion of the chemokine CCL5 by bone marrow-derived MSC (BM-MSC)[29] or ASC increase the motility of breast cancer cell lines in *in vitro* models of tumor invasion. These findings were reproduced by the addition of exogenous CCL5 to breast cancer cell line cultures.[30] Further, BM-MSC have been shown to promote *in vitro* epithelial to mesenchymal transition of breast cancer cells and reduce expression of proliferation-associated genes.[31]

Because these studies utilized immortalized cancer cell lines that grow rapidly in culture and give rise to large tumors in a very short time, they fail to model the crucial aspects of tumor heterogeneity, tumor dormancy, and reactivation of occult tumor cells. For example, coculture of MDA-MB-231, a hormone-independent breast cancer cell line, with MSC resulted in greater cell expansion after 4 days in culture (1.7-fold more cells), but tumor cells alone had a doubling time of $\sim$24 h.[32] This extreme lack of clinical realism is also apparent in tumor transplantation models. For example, Yu *et al.* coinjected 1×10^6 each of H460 cells (a human lung cancer cell line) and human ASC and reported measurable tumors in 5 days that grew to 20 mm^3 in 10 days.[33] Muehlberg *et al.* injected 5000 4T1 cells (a murine breast cancer cell line) and observed 125 mm^3 tumors in 21 days. Addition of murine ASC increased the size of 21 day tumors to 400 cubic mm.[34] In the model reported by Karnoub *et al*., tumors ranging in size from 50 to 500 mm^3 were detectable by day 30.[29] Clearly if these models bear any relevance to human disease, it would be in the context of rapidly growing high-grade therapy unresponsive tumors, where reconstructive surgery would not be a consideration. Our own approach has relied on a model system utilizing unpassaged sort-purified clinical isolates injected in limiting numbers (100 cells).[35,36] This model requires 3–6 months for the generation of vascularized epithelial tumors in the size range of 5–10 mm^3.

Apart from the ability to promote the growth of existing tumors, there is also a report in which implantation of ceramic scaffold charged with syngeneic murine MSC gave rise to sarcomas in a proportion of treated mice.[37]

There is also a degree of contradiction in the literature, in which ASC or MSC have been shown to inhibit the growth of tumor cells. For example, ASC have been reported to inhibit tumor growth of MDA-MB-231 cells,[38] and induce cell death of pancreatic adenocarcinoma cells lines, hepatocarcinoma, colon cancer, and prostate cancer.[39] MSC reportedly inhibit tumorigenesis from Kaposi's sarcoma cells[40] and hepatoma cells,[41] bone metastasis of prostate cancer,[42] and *in vitro* growth of hepatoma, lymphoma, and insulinoma cell lines.[43] Similarly, MSC derived from human umbilical cord blood are cytotoxic for human malignant glioma cells.[44] Multiple mechanisms have been invoked to relate these findings to the cytokines, chemokines, and prostaglandins secreted by MSC,[39] but little experimental evidence has been provided to define the mechanisms of tumor inhibition. Khakoo *et al.*[40] proposed contact-dependant inhibition of Akt protein kinase, whereas Qiao *et al.* cited down regulation of Wnt signaling, c-Myc, and Bcl-2.[41]

Phenotypic and functional characteristics of ASC and MSC

ASC phenotypically resemble BM-MSC[19] and share their multipotentiality and many surface markers[17,45] (Table 1), but are orders of magnitude more prevalent in fat than BM-MSC are in BM aspirates. In disaggregated freshly isolated adipose tissue, phenotypically defined pericytes comprise 1.7%, whereas CD34+ supra-adventitial stromal cells represent 27% of nucleated cells.[18] In contrast MSC represent only 0.001%–0.004% of BM aspirate cells.[20,46] Although ASC and BM-MSC are both promising candidates for reconstructive cellular therapy after tumor resection, the potential risk of promoting tumor reactivation is controversial. This is especially germane in breast cancer considering that up to 20% of patients will suffer from cancer recurrence during the first decade after adjuvant therapy.[47]

These data indicate strong phenotypic and functional similarities between ASC and BM-MSC. Like BM-MSC, ASC are able to give rise to differentiated progeny with characteristics of bone, cartilage, fat, and vessels and, like MSC, were predominantly CD105+/CD73+/CD90+/CD44+ (Table 1). However, low passage ASC also contain minor populations expressing the adipose pericyte-associated marker CD146[18] and CD34, a marker not associated with BM-MSC. The *in vitro* secretomes of ASC and MSC are also similar (Table 2). However, ASC secrete significantly higher quantities of leptin (140-fold) and adipsin (20-fold), and lower quantities of the angiogenic factors vascular endothelial growth factor and soluble vascular cell adhesion molecule (sVCAM). Production of leptin and adipsin is characteristic of mature adipocytes, but has also been described in ASC cultures.[35] The hormone leptin has been reported to increase angiogenic and proliferative signaling in ER+ and ER− breast cancer cell lines.[48] Adipsin, a trypsin-

Table 1. Functional and Phenotypic Characteristics of Mesenchymal and Adipose-Derived Stem Cells

	MSC	*ASC*
Developmental origin	Mesoderm, neural crest	Mesoderm, neural crest
Tissue of origin	BM	White adipose tissue
Selection	Plastic adherence	Plastic adherence
Principal antigenic markers (*in vitro*)	CD10, CD13, CD29, CD44, CD49a-f, CD63, CD73, CD90, CD105, CD106, CD140b, CD146, CD166, CD271, STRO-1[45,75–86]	CD10, CD13, CD29, CD34, CD44, CD49a, CD63, CD73, CD90, CD105, CD106, CD140b, CD146, CD166, CD271, STRO-1[19,83–90]
Differentiation potential	Adipose tissue[91,a]	Adipose tissue[87,a]
	Bone[91,a]	Bone[87,a]
	Cartilage[91,a]	Cartilage[87,a]
	Smooth muscle[92,a]	Smooth muscle[93,94]
	Skeletal muscle[95]	Skeletal muscle[87,a]
	Cardiac muscle[96]	Cardiac muscle[97]
	Endothelium[98]	Endothelium[15,16]
	Neurons[99]	Neurons[100]
	Hepatocytes[101]	Hepatocytes[102]
	Epithelium[103]	Epithelium[104]
Telomerase	Absent[105–107]	Absent or low[108,109]
Expansion *in vitro*	20–50 population doublings[110]	44–80 population doublings[17,111]
Precursors *in vivo*	Pericytes (subendothelial reticular cells, CD146+)[76,112]	CD34+ Supra-adventitial, pericytes[18]
Frequency estimate *in vivo* (percent of nucleated cells)	0.001%–0.004%[20,46]	2%–27%[18]

[a]Multipotentiality demonstrated at the clonal level.
ASC, adipose-derived stem cell; BM, bone marrow; MSC, mesenchymal stem cell.

like serine protease increases the concentration of acylation-stimulating protein, another adipose-derived hormone that regulates triglyceride synthesis.[49] It has no known role in cancer.

In vitro *model of ASC interaction using clinical isolates*

In vitro model systems can detect effects of secreted growth factors and cell adhesion-mediated effects, but lack the complexity of xenograft models. Through an *in vitro* coculture model utilizing heterogeneous cells isolated from clinical isolates (malignant pleural effusions), we confirmed the enhancing effect of ASC on the proliferation of breast cancer cells[35] which appeared as nest of epithelioid cells among a monolayer of carboxyfluorescein succinimidyl ester (CFSE)-labeled stromal cells. Our results are in agreement with those studies showing that the presence of mesenchymal cells promotes the growth of highly proliferative tumor cells.[32,50]

Tumor cell heterogeneity

The epithelial component of breast cancer clinical isolates is heterogeneous. Initially, a tumor cell subset identified as CD44+/CD24-/CD326 (ESA, EpCAM)+ was shown to be enriched for tumorigenic cells as detected in a xenotransplantation model.[51] In an accompanying editorial it was hypothesized that these cells represent breast cancer stem cells.[52] Gradually, evidence has accrued substantiating the fact that clonogenic tumor cells share, constitutively or conditionally, many characteristics with adult tissue stem cells. Most prominently these include self-renewal[53,54] and therapy resistance.[36,55] As a cause or consequence of these functional similarities, adult tissue stem cells and clonogenic epithelial tumor subsets share expression of several markers. We previously demonstrated the tumorigenicity of CD90+ breast

Table 2. Cytokines, Chemokines, and Growth Factors Produced by Mesenchymal Stem Cell and Adipose-Derived Stem Cell

Cytokines/chemokines/ growth factors	*BM-MSC mean (ng/mL)*	*ASC mean (ng/mL)*
Adiponectin	<0.34	<0.34
Adipsin (CFD)	**3.8**	**74.0**
CCL2 (MCP1)	2.3	1.6
CCL5 (RANTES)	<0.02	<0.02
CRP	<0.03	<0.03
IL-1b	<0.0001	<0.0001
IL-2	<0.0001	<0.0001
IL-4	<0.0001	<0.0001
IL-5	<0.0001	<0.0001
IL-6	2.2	1.1
IL-10	<0.0001	<0.0001
IL-12	<0.0001	<0.0001
IL-13	<0.0001	<0.0001
Leptin	**0.05**	**7.0**
PAI-1 (serpine2)	>50	>50
Resistin	<0.04	<0.04
TGF-β1	1.2	1.2
TNF-α	<0.0001	<0.0001
sVCAM (CD106)	**30**	**0.5**
VEGF	**3.4**	**0.2**

BM-MSC data are unpublished internal control data of the authors using a single MSC isolate at passage 3. Analytes were measured by Luminex assay of supernatants harvested 3 days after plating when cultures were ~80% confluent. All supernatants (MSC and ASC) were processed simultaneously. The methods, media, standards, and blanks were identical to those published for ASC[35]. Bolded rows show major differences.

CRP, C-reactive protein; IL, interleukin; PAI, plasminogen activator inhibitor; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

cancer cells separated on the basis of light scatter into resting (low light scatter) and active (high light scatter) populations. Small resting CD90+ cells gave rise to tumors with high efficiency (50–100 cells/injection),[36,56] whereas large, active CD90+ cells were tumorigenic at high (600–13,000 cells),[36] but not low[56] dose. We further explored the phenotypic differences between resting and active CD90+ tumor cells, where low light scatter resting CD90+ nonheme cells were mostly quiescent in contrast to their high light scatter counterpart, which had a higher proportion of cycling/aneuploid cells.[56] We have demonstrated that ASC failed to augment the tumorigenicity of small resting CD90+ tumor cells, whereas they markedly enhanced tumorigenesis mediated by active CD90+ tumor cells.[35] Dormant and proliferating breast cancer cells display distinct genome-wide expression signatures, including differences for a high number of angiogenesis-related genes.[57] This is consistent with the hypothesis that ASC may support survival and proliferation of tumor cells *in vivo* by promoting angiogenesis, to which active cells are preferentially receptive.

Discussion

Escape from tumor dormancy: A working hypothesis

Throughout this article we have drawn a distinction between two potentially tumorigenic populations, resting (dormant) and active (proliferating) tumor cells. This distinction has parallels with adult tissue stem cells versus transit amplifying populations. The notion of cancer dormancy is prevalent in the cancer literature, but ill defined. Dormant cancer is subclinical cancer, and is known because of tumor recurrence after a symptom-free interval. It is not known whether dormant tumor cells are out of cell cycle (i.e., G0), or persisting in a dynamic state of balanced proliferation and death. The same can be said for normal tissue stem cells.[58] Regardless of the mechanism by which subclinical tumor persists, it is useful to hypothesize that dormancy is an intrinsic characteristic of the resting tumor cell, perhaps imposed by epigenetic programming.[59] As such, transition between dormant and active states requires genetic reprogramming and not merely the presence of signals such as those provided by hormones and hormone receptors, or even the presence of mutations that bypass the need for such signaling. Whatever the stimuli that drive dormant stem-like cancer cells into an active tumorigenic state, we hypothesize that they are distinct from those that favor the survival and proliferation of active progenitor-like tumor cells (Fig. 1). Therefore, the introduction of pro-angiogenic autologous mesenchymal stem cells to the site of a tumor bed would be non-contributory to local recurrence. Indeed, if increased local vascularization at the site of a tumor bed was an independent risk factor for recurrence, this fact would have become clear after observing patients reconstructed with local tissue flaps. In this commonly accepted method of reconstruction, a well vascularized tissue flap is in direct contact with the tumor bed and extensive local vascular remodeling occurs. Immediate autologous tissue flap reconstruction has not been correlated with increased recurrence rates.[113]

Risks assessment

In the absence of substantial clinical experience with tissue-engineered reconstructive surgery after cancer, one can also look to biological parallels to estimate the risks imposed by

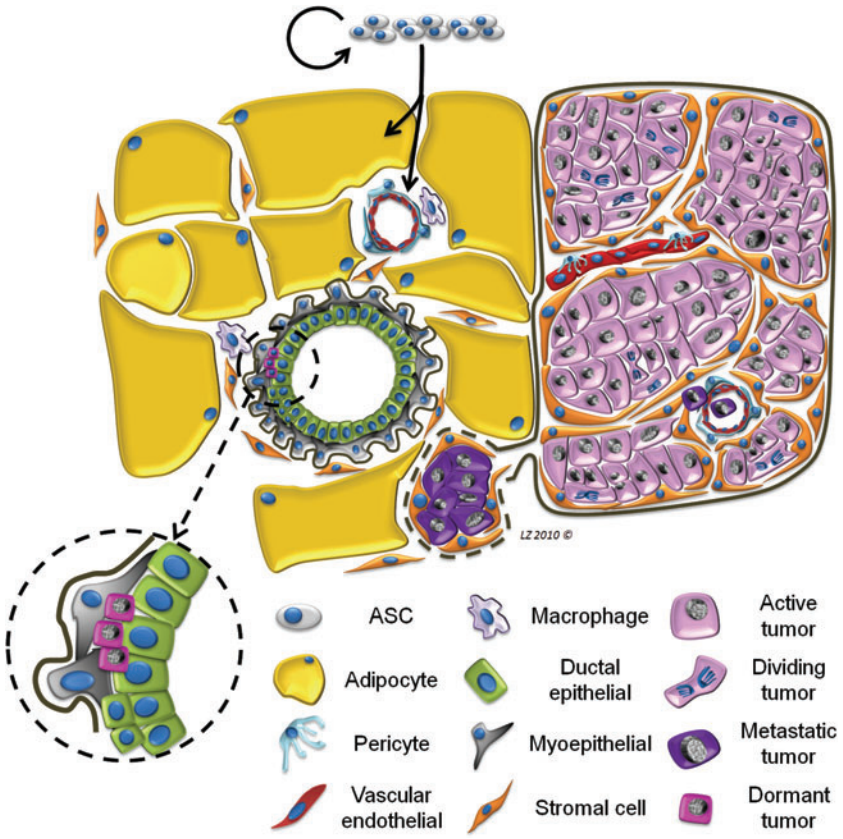

FIG. 1. Working hypothesis of the interaction between regenerating tissue and an epithelial cancer. The effect of adipose-derived stem cell administration on active breast cancer is depicted here. Introduction of ASC, which self-replicate and give rise to adipose, vessels, and stroma, promotes the growth of active tumor (purple) and induces motility and upregulation of adhesion molecules, promoting invasion and metastasis (deep purple). Dormant cancer cells, shown here nested in a normal breast duct (hot pink, inset), are unaffected by the wound healing signals resulting from regenerative therapy. ASC, adipose-derived stem cells. Color images available online at www.liebertonline.com/ten.

intentionally placing regenerating tissue at the site of tumor resection. The first and most obvious parallel is the wound healing that normally accompanies cancer therapy of any kind, whether surgical, chemotherapeutic, or radio-ablative. Even before antineoplastic therapy has been initiated, the tumor microenvironment has much in common with a wound.[60] The similarities have been well described[61] and include the presence of inflammation, growth factors, cross-linked fibrin, fibroblast activation, angiogenesis, and the deposition of a network of extracellular matrix. Thus, it is difficult in most cases to determine the extent to which wound healing associated with treatment contributes to relapse at the primary tumor site. Cancer recurrence in mastectomy scars has been reported, but is rare.[62] In colon cancer, recurrence at scar sites is also infrequent and associated with aggressive systemic disease.[63] There are even case reports of high-grade tumors recurring along the tracks of laparoscopy.[64–66] In stage I/II invasive breast cancer patients treated with radiation, in whom the incidence of early local recurrence is very low, high mitotic activity and high tumor grade were the major predictors of local recurrence.[67] Thus, the common feature shared by cancers that are recruited into treatment-associated wounds appears to be the presence of aggressive active disease.

A second, less obvious parallel comes from experience with allogeneic and autologous hematopoietic stem cell transplantation for hematologic malignancies, where there are decades of experience in regenerative therapy for cancer.[68,69] When disease is active at the time of transplantation (i.e., the patient has had multiple remissions or has active disease at the time of myeloablative therapy), relapse often occurs early in the peritransplant period when BM regeneration (and associated reestablishment of the components of the BM microenvironment) is at its peak.[70] When this occurs, the recurrent disease is usually very aggressive. In contrast, patients transplanted in first remission often have extended disease-free survival. The proportion of patients who eventually relapse often do so years after transplant, indicating that (1) residual disease survived myeloablative therapy; (2) these cells were dormant; and (3) dormant residual malignant cells were not reactivated as a result of massive injury to the BM and explosive hematopoietic regeneration ediated by the graft. An analogous argument can be made for cytokine mobilization in the context of autologous hematopoietic stem cell transplantation, where patients in remission are treated with consolidation chemotherapy and the hematopoietic growth factor granulocyte colony stimulating factor (G-CSF).[71] The patients experience BM suppression followed by explosive regeneration without triggering early relapse.

In the 1990s autologous hematopoietic transplantation was widely used to rescue the BM of breast cancer patients undergoing dose-intensive chemotherapy. This practice was discontinued when randomized trials failed to show superiority over conventional therapy.[72] However, the massive damage to all proliferative tissues by high-dose cytotoxic therapy and the ensuing tissue regeneration (including marrow reconstitution, revascularization, and reepithelialization) did not promote breast cancer relapse.

Currently, there is relatively little clinical experience pertaining specifically to regenerative therapy in the context of epithelial cancers. Delay *et al.* published a series of 880 breast reconstructions with autologous fat alone performed by injection of lipoaspirate. Some of the participants included patients undergoing nipple-areola reconstruction after mastectomy. In this cohort, which had a maximal follow-up of 10 years, there was no detectable increase in the risk of local recurrence or new cancer development.[4] A similar series was reported by Illouz and Sterodimas, who performed AFT on 820 patients, 381 of whom were treated for asymmetry after mastectomy and breast reconstruction.[73] Although 230 patients were followed with yearly mammography and ultrasonography for an average of 11.3 years, the author made no mention of the incidence of locoregional recurrence or metastasis among the breast cancer patients. Yoshimura *et al.* reported on the use of SVF-augmented AFT for cosmetic breast augmentation in 40 women, none of whom experienced serious complications during a follow-up interval ranging from 6 to 42 months.[8] Among the adverse effects reported after SVF-augmented breast reconstruction were calcifications and cyst formation in 4 of 40 patients. An additional cohort of 15 patients had successful breast reconstruction after experiencing complications of breast implant surgery.[74] In a cohort study (mean 7.2 year follow-up) reported by Rigotti, 137 patients treated with AFT breast reconstruction did not show increased risk of local recurrence after this treatment. While this study lacked a formal control group (the recurrence rates after treatment were referenced to both historical data and pre-reconstruction recurrence rates for the cohort), the data suggest that the addition of autologous adipose cells to a tumor bed does not impact any nascent cancer cells.[114] Yoshimura *et al.* also performed cell-augmented AFT on eight patients undergoing breast reconstruction after mastectomy,[8] but the clinical status of these patients was not reported.

Taken together with our published results in a xenograft model,[35] which indicate that ASC augment the growth of active but not resting breast cancer cells, the available data suggest that the critical factor determining whether regeneration augments tumor growth is the state of residual tumor: active disease is promoted, whereas dormant tumor is insensitive. This suggests that reconstructive therapy utilizing ASC-augmented whole fat should be deferred until cancer remission has been firmly established.

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Authors Contributions

Vera S. Donnenberg and Albert D. Donnenberg and Ludovic Zimmerlin, graduate student in the Donnenberg laboratory, contributed equally to this article. J. Peter Rubin provided clinical perspective and expertise in AFT.

Disclosure Statement

None of the authors have competing interests that would have influenced the preparation of this article.

References

1. Neuber, G.A. Fettransplantation. Chir Kongr Verhandl Deutsche Gesellschaft für Chirurgie **22,** 66, 1893.
2. Czerny, V. Plastischer Ersatz der Brustdruse durch ein Lipom. Chir Kong Verhandl **2,** 216, 1895.
3. ASPRS. Report on autologous fat transplantation. ASPRS Ad-Hoc Committee on New Procedures, September 30, 1987. Plast Surg Nurs **7,** 140, 1987.
4. Delay, E., Garson, S., Tousson, G., and Sinna, R. Fat injection to the breast: technique, results, and indications based on 880 procedures over 10 years. Aesthet Surg J **29,** 360, 2009.
5. Niechajev, I., and Sevcuk, O. Long-term results of fat transplantation: clinical and histologic studies. Plast Reconstr Surg **94,** 496, 1994.
6. Peer, L.A. Loss of weight and volume in human fat grafts: with postulation of a "Cell Survival Theory." Plast Reconstr Surg **5,** 217, 1950.
7. Yoshimura, K., Sato, K., Aoi, N., Kurita, M., Inoue, K., Suga, H., *et al.* Cell-assisted lipotransfer for facial lipoatrophy: efficacy of clinical use of adipose-derived stem cells. Dermatol Surg **34,** 1178, 2008.
8. Yoshimura, K., Sato, K., Aoi, N., Kurita, M., Hirohi, T., and Harii, K. Cell-assisted lipotransfer for cosmetic breast augmentation: supportive use of adipose-derived stem/stromal cells. Aesthet Plast Surg **32,** 48; discussion 6–7, 2008.
9. Matsumoto, D., Sato, K., Gonda, K., Takaki, Y., Shigeura, T., Sato, T., *et al.* Cell- assisted lipotransfer: supportive use of human adipose-derived cells for soft tissue augmentation with lipoinjection. Tissue Eng **12,** 3375, 2006.
10. Calabria, R., and Hills, B. Fat grafting: fact or fiction? Aesthet Surg J **25,** 55, 2005.
11. Billings, E., Jr., and May, J.W., Jr. Historical review and present status of free fat graft autotransplantation in plastic and reconstructive surgery. Plast Reconstr Surg **83,** 368, 1989.
12. Nguyen, A., Pasyk, K.A., Bouvier, T.N., Hassett, C.A., and Argenta, L.C. Comparative study of survival of autologous adipose tissue taken and transplanted by different techniques. Plast Reconstr Surg **85,** 378; discussion 87–89, 1990.
13. Moseley, T.A., Zhu, M., and Hedrick, M.H. Adipose-derived stem and progenitor cells as fillers in plastic and reconstructive surgery. Plast Reconstr Surg **118,** 121S, 2006.
14. Zhu, M., Zhou, Z., Chen, Y., Schreiber, R., Ransom, J.T., Fraser, J.K., *et al.* Supplementation of fat grafts with adipose-derived regenerative cells improves long-term graft retention. Ann Plast Surg **64,** 222, 2010.
15. Miranville, A., Heeschen, C., Sengenes, C., Curat, C.A., Busse, R., and Bouloumie, A. Improvement of postnatal neovascularization by human adipose tissue-derived stem cells. Circulation **110,** 349, 2004.
16. Planat-Benard, V., Silvestre, J.S., Cousin, B., Andre, M., Nibbelink, M., Tamarat, R., *et al.* Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. Circulation **109,** 656, 2004.
17. Zuk, P.A., Zhu, M., Mizuno, H., Huang, J., Futrell, J.W., Katz, A.J., *et al.* Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng **7,** 211, 2001.
18. Zimmerlin, L., Donnenberg, V.S., Pfeifer, M.E., Meyer, E.M., Peault, B., Rubin, J.P., *et al.* Stromal vascular progenitors in adult human adipose tissue. Cytometry A **77A,** 22, 2010.
19. Gronthos, S., Franklin, D.M., Leddy, H.A., Robey, P.G., Storms, R.W., and Gimble, J.M. Surface protein characterization of human adipose tissue-derived stromal cells. J Cell Physiol **189,** 54, 2001.
20. Strem, B.M., Hicok, K.C., Zhu, M., Wulur, I., Alfonso, Z., Schreiber, R.E., *et al.* Multipotential differentiation of adipose tissue-derived stem cells. Keio J Med **54,** 132, 2005.
21. Daher, S.R., Johnstone, B.H., Phinney, D.G., and March, K.L. Adipose stromal/stem cells: basic and translational advances: the IFATS collection. Stem Cells **26,** 2664, 2008.
22. Rubin, J.P., Bennett, J.M., Doctor, J.S., Tebbets, B.M., and Marra, K.G. Collagenous microbeads as a scaffold for tissue engineering with adipose-derived stem cells. Plast Reconstr Surg **120,** 414, 2007.
23. Stacey, D.H., Hanson, S.E., Lahvis, G., Gutowski, K.A., and Masters, K.S. *In vitro* adipogenic differentiation of preadipocytes varies with differentiation stimulus, culture dimensionality, and scaffold composition. Tissue Eng Part A **15,** 3389, 2009.
24. Leong, D.T., Nah, W.K., Gupta, A., Hutmacher, D.W., and Woodruff, M.A. The osteogenic differentiation of adipose tissue-derived precursor cells in a 3D scaffold/matrix environment. Curr Drug Discov Technol **5,** 319, 2008.
25. Hodde, J.P., Record, R.D., Liang, H.A., and Badylak, S.F. Vascular endothelial growth factor in porcine-derived extracellular matrix. Endothelium **8,** 11, 2001.
26. Zhu, Y., Liu, T., Ye, H., Song, K., Ma, X., and Cui, Z. Enhancement of adipose-derived stem cell differentiation in scaffolds with IGF-I gene impregnation under dynamic microenvironment. Stem Cells Dev 2010 Sep 6 [Epub ahead of print].
27. Ahmed, T.A., Dare, E.V., and Hincke, M. Fibrin: a versatile scaffold for tissue engineering applications. Tissue Eng Part B Rev 2008 May 1 [Epub ahead of print].
28. Ota, T., Gilbert, T.W., Schwartzman, D., McTiernan, C.F., Kitajima, T., Ito, Y., *et al.* A fusion protein of hepatocyte growth factor enhances reconstruction of myocardium in a cardiac patch derived from porcine urinary bladder matrix. J Thorac Cardiovasc Surg **136,** 1309, 2008.
29. Karnoub, A.E., Dash, A.B., Vo, A.P., Sullivan, A., Brooks, M.W., Bell, G.W., *et al.* Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature **449,** 557, 2007.
30. Zhang, Y., Yao, F., Yao, X., Yi, C., Tan, C., Wei, L., *et al.* Role of CCL5 in invasion, proliferation and proportion of CD44+/CD24- phenotype of MCF-7 cells and correlation of CCL5 and CCR5 expression with breast cancer progression. Oncol Rep **21,** 1113, 2009.
31. Martin, F.T., Dwyer, R.M., Kelly, J., Khan, S., Murphy, J.M., Curran, C., *et al.* Potential role of mesenchymal stem cells (MSCs) in the breast tumour microenvironment: stimulation of epithelial to mesenchymal transition (EMT). Breast Cancer Res Treat 2010 Jan 20 [Epub ahead of print].
32. Pinilla, S., Alt, E., Abdul Khalek, F.J., Jotzu, C., Muehlberg, F., Beckmann, C., *et al.* Tissue resident stem cells produce CCL5 under the influence of cancer cells and thereby promote breast cancer cell invasion. Cancer Lett **284,** 80, 2009.
33. Yu, J.M., Jun, E.S., Bae, Y.C., and Jung, J.S. Mesenchymal stem cells derived from human adipose tissues favor tumor cell growth *in vivo*. Stem Cells Dev **17,** 463, 2008.
34. Muehlberg, F.L., Song, Y.H., Krohn, A., Pinilla, S.P., Droll, L.H., Leng, X., *et al.* Tissue-resident stem cells promote breast cancer growth and metastasis. Carcinogenesis **30,** 589, 2009.
35. Zimmerlin, L., Donnenberg, A.D., Rubin, J.P., Basse, P., Landreneau, R.J., and Donnenberg, V.S. Regenerative therapy and cancer: *in vitro* and *in vivo* studies of the interaction

between adipose-derived stem cells and breast cancer cells from clinical isolates. Tissue Eng 2010 Jul 30 [Epub ahead of print].
36. Donnenberg, V.S., Luketich, J.D., Landreneau, R.J., DeLoia, J.A., Basse, P., and Donnenberg, A.D. Tumorigenic epithelial stem cells and their normal counterparts. Ernst Schering Found Symp Proc **5,** 245, 2006.
37. Tasso, R., Augello, A., Carida, M., Postiglione, F., Tibiletti, M.G., Bernasconi, B., *et al.* Development of sarcomas in mice implanted with mesenchymal stem cells seeded onto bioscaffolds. Carcinogenesis **30,** 150, 2009.
38. Sun, B., Roh, K.H., Park, J.R., Lee, S.R., Park, S.B., Jung, J.W., *et al.* Therapeutic potential of mesenchymal stromal cells in a mouse breast cancer metastasis model. Cytotherapy **11,** 289, 1 p following 298, 2009.
39. Cousin, B., Ravet, E., Poglio, S., De Toni, F., Bertuzzi, M., Lulka, H., *et al.* Adult stromal cells derived from human adipose tissue provoke pancreatic cancer cell death both *in vitro* and *in vivo*. PLoS ONE **4,** e6278, 2009.
40. Khakoo, A.Y., Pati, S., Anderson, S.A., Reid, W., Elshal, M.F., Rovira, I.I., *et al.* Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma. J Exp Med **203,** 1235, 2006.
41. Qiao, L., Xu, Z., Zhao, T., Zhao, Z., Shi, M., Zhao, R.C., *et al.* Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. Cell Res **18,** 500, 2008.
42. Chanda, D., Isayeva, T., Kumar, S., Hensel, J.A., Sawant, A., Ramaswamy, G., *et al.* Therapeutic potential of adult bone marrow-derived mesenchymal stem cells in prostate cancer bone metastasis. Clin Cancer Res **15,** 7175, 2009.
43. Lu, Y.R., Yuan, Y., Wang, X.J., Wei, L.L., Chen, Y.N., Cong, C., *et al.* The growth inhibitory effect of mesenchymal stem cells on tumor cells *in vitro* and *in vivo*. Cancer Biol Ther **7,** 245, 2008.
44. Kang, S.G., Jeun, S.S., Lim, J.Y., Kim, S.M., Yang, Y.S., Oh, W.I., *et al.* Cytotoxicity of human umbilical cord blood-derived mesenchymal stem cells against human malignant glioma cells. Childs Nerv Syst **24,** 293, 2008.
45. Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., *et al.* Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy **8,** 315, 2006.
46. Wexler, S.A., Donaldson, C., Denning-Kendall, P., Rice, C., Bradley, B., and Hows, J.M. Adult bone marrow is a rich source of human mesenchymal "stem" cells but umbilical cord and mobilized adult blood are not. Br J Haematol **121,** 368, 2003.
47. Brewster, A.M., Hortobagyi, G.N., Broglio, K.R., Kau, S.W., Santa-Maria, C.A., Arun, B., *et al.* Residual risk of breast cancer recurrence 5 years after adjuvant therapy. J Natl Cancer Inst **100,** 1179, 2008.
48. Rene Gonzalez, R., Watters, A., Xu, Y., Singh, U., Mann, D., Rueda, B., *et al.* Leptin-signaling inhibition results in efficient anti-tumor activity in estrogen receptor positive or negative breast cancer. Breast Cancer Res **11,** R36, 2009.
49. Baldo, A., Sniderman, A.D., St. Luce, S., Avramoglu, R.K., Maslowska, M., Hoang, B., *et al.* The adipsin-acylation stimulating protein system and regulation of intracellular triglyceride synthesis. J Clin Invest **92,** 1543, 1993.
50. Kucerova, L., Matuskova, M., Hlubinova, K., Altanerova, V., and Altaner, C. Tumor cell behaviour modulation by mesenchymal stromal cells. Mol Cancer **9,** 129, 2010.
51. Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J., and Clarke, M.F. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci U S A **100,** 3983, 2003.
52. Dick, J.E. Breast cancer stem cells revealed. Proc Natl Acad Sci U S A **100,** 3547, 2003.
53. Abraham, B.K., Fritz, P., McClellan, M., Hauptvogel, P., Athelogou, M., and Brauch, H. Prevalence of CD44+/CD24-/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. Clin Cancer Res **11,** 1154, 2005.
54. Sheridan, C., Kishimoto, H., Fuchs, R.K., Mehrotra, S., Bhat-Nakshatri, P., Turner, C.H., *et al.* CD44+/CD24- breast cancer cells exhibit enhanced invasive properties: an early step necessary for metastasis. Breast Cancer Res **8,** R59, 2006.
55. Kakarala, M., and Wicha, M.S. Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy. J Clin Oncol **26,** 2813, 2008.
56. Donnenberg, V.S., Donnenberg, A.D., Zimmerlin, L., Landreneau, R.J., Bhargava, R., Wetzel, R.A., *et al.* Localization of CD44 and CD90 positive cells to the invasive front of breast tumors. Cytometry B Clin Cytom 2010 Apr 30 [Epub ahead of print].
57. Almog, N., Ma, L., Raychowdhury, R., Schwager, C., Erber, R., Short, S., *et al.* Transcriptional switch of dormant tumors to fast-growing angiogenic phenotype. Cancer Res **69,** 836, 2009.
58. Quesenberry, P.J., Dooner, M.S., and Aliotta, J.M. Stem cell plasticity revisited: the continuum marrow model and phenotypic changes mediated by microvesicles. Exp Hematol **38,** 581, 2010.
59. Jones, P.A., and Laird, P.W. Cancer-epigenetics comes of age. Nat Genet **21,** 163, 1999.
60. Dvorak, H.F. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med **315,** 1650, 1986.
61. Hofer, S.O., Molema, G., Hermens, R.A., Wanebo, H.J., Reichner, J.S., and Hoekstra, H.J. The effect of surgical wounding on tumour development. Eur J Surg Oncol **25,** 231, 1999.
62. Warner, R.M., Wallace, D.L., Ferran, N.A., Erel, E., Park, A.J., Prinsloo, D.J., *et al.* Mastectomy scars following breast reconstruction: should routine histologic analysis be performed? Plast Reconstr Surg **123,** 1141, 2009.
63. Hughes, E., McDermott, F., Polglase, A., and Johnson, W. Tumor recurrence in the abdominal wall scar tissue after large-bowel cancer surgery. Dis Colon Rectum **26,** 571, 1983.
64. Winston, C.B., Chen, J.W., Fong, Y., Schwartz, L.H., and Panicek, D.M. Recurrent gallbladder carcinoma along laparoscopic cholecystectomy port tracks: CT demonstration. Radiology **212,** 439, 1999.
65. Faught, W., and Fung Kee Fung, M. Port site recurrences following laparoscopically managed early stage endometrial cancer. Int J Gynecol Cancer **9,** 256, 1999.
66. Agostini, A., Cohen, D., Cravello, L., Bretelle, F., Roger, V., and Blanc, B. Port-site recurrence following laparoscopic para-aortic lymphadenectomy for squamous carcinoma of the cervix. Eur J Obstet Gynecol Reprod Biol **98,** 258, 2001.
67. Schnitt, S.J., Connolly, J.L., Harris, J.R., Hellman, S., and Cohen, R.B. Pathologic predictors of early local recurrence in stage I and II breast cancer treated by primary radiation therapy. Cancer **53,** 1049, 1984.

68. Thomas, E.D., Lochte, H.L., Jr., Cannon, J.H., Sahler, O.D., and Ferrebee, J.W. Supralethal whole body irradiation and isologous marrow transplantation in man. J Clin Invest **38,** 1709, 1959.
69. Santos, G.W., Sensenbrenner, L.L., Burke, P.J., Colvin, M., Owens, A.H., Jr., Bias, W.B., *et al.* Marrow transplantation in man following cyclophosphamide. Transplant Proc **3,** 400, 1971.
70. Pasquini, M.C., and Wang, Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2010. Available at: www.cibmtr.org.
71. Heimfeld, S., Fogarty, B., McGuire, K., Williams, S., and Berenson, R.J. Peripheral blood stem cell mobilization after stem cell factor or G-CSF treatment: rapid enrichment for stem and progenitor cells using the CEPRATE immunoaffinity separation system. Transplant Proc **24,** 2818, 1992.
72. Stadtmauer, E.A., O'Neill, A., Goldstein, L.J., Crilley, P.A., Mangan, K.F., Ingle, J.N., *et al.* Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. N Engl J Med **342,** 1069, 2000.
73. Illouz, Y.G., and Sterodimas, A. Autologous fat transplantation to the breast: a personal technique with 25 years of experience. Aesthet Plast Surg **33,** 706, 2009.
74. Yoshimura, K., Asano, Y., Aoi, N., Kurita, M., Oshima, Y., Sato, K., *et al.* Progenitor-enriched adipose tissue transplantation as rescue for breast implant complications. Breast J **16,** 169, 2010.
75. Simmons, P.J., and Torok-Storb, B. Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. Blood **78,** 55, 1991.
76. Sacchetti, B., Funari, A., Michienzi, S., Di Cesare, S., Piersanti, S., Saggio, I., *et al.* Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. Cell **131,** 324, 2007.
77. Benayahu, D., Akavia, U.D., and Shur, I. Differentiation of bone marrow stroma-derived mesenchymal cells. Curr Med Chem **14,** 173, 2007.
78. Park, P.C., Selvarajah, S., Bayani, J., Zielenska, M., and Squire, J.A. Stem cell enrichment approaches. Semin Cancer Biol **17,** 257, 2007.
79. Quirici, N., Soligo, D., Bossolasco, P., Servida, F., Lumini, C., and Deliliers, G.L. Isolation of bone marrow mesenchymal stem cells by anti-nerve growth factor receptor antibodies. Exp Hematol **30,** 783, 2002.
80. Delorme, B., Ringe, J., Gallay, N., Le Vern, Y., Kerboeuf, D., Jorgensen, C., *et al.* Specific plasma membrane protein phenotype of culture-amplified and native human bone marrow mesenchymal stem cells. Blood **111,** 2631, 2008.
81. Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., *et al.* Multilineage potential of adult human mesenchymal stem cells. Science **284,** 143, 1999.
82. Vogel, W., Grunebach, F., Messam, C.A., Kanz, L., Brugger, W., and Buhring, H.J. Heterogeneity among human bone marrow-derived mesenchymal stem cells and neural progenitor cells. Haematologica **88,** 126, 2003.
83. Wagner, W., Wein, F., Seckinger, A., Frankhauser, M., Wirkner, U., Krause, U., *et al.* Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. Exp Hematol **33,** 1402, 2005.
84. Lee, R.H., Kim, B., Choi, I., Kim, H., Choi, H., Suh, K., *et al.* Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue. Cell Physiol Biochem **14,** 311, 2004.
85. Roche, S., Delorme, B., Oostendorp, R.A., Barbet, R., Caton, D., Noel, D., *et al.* Comparative proteomic analysis of human mesenchymal and embryonic stem cells: towards the definition of a mesenchymal stem cell proteomic signature. Proteomics **9,** 223, 2009.
86. Noel, D., Caton, D., Roche, S., Bony, C., Lehmann, S., Casteilla, L., *et al.* Cell specific differences between human adipose-derived and mesenchymal-stromal cells despite similar differentiation potentials. Exp Cell Res **314,** 1575, 2008.
87. Zuk, P.A., Zhu, M., Ashjian, P., De Ugarte, D.A., Huang, J.I., Mizuno, H., *et al.* Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell **13,** 4279, 2002.
88. Mitchell, J.B., McIntosh, K., Zvonic, S., Garrett, S., Floyd, Z.E., Kloster, A., *et al.* Immunophenotype of human adipose-derived cells: temporal changes in stromal-associated and stem cell-associated markers. Stem Cells **24,** 376, 2006.
89. Traktuev, D.O., Merfeld-Clauss, S., Li, J., Kolonin, M., Arap, W., Pasqualini, R., *et al.* A population of multipotent CD34-positive adipose stromal cells share pericyte and mesenchymal surface markers, reside in a periendothelial location, and stabilize endothelial networks. Circ Res **102,** 77, 2008.
90. Ishimura, D., Yamamoto, N., Tajima, K., Ohno, A., Yamamoto, Y., Washimi, O., *et al.* Differentiation of adipose-derived stromal vascular fraction culture cells into chondrocytes using the method of cell sorting with a mesenchymal stem cell marker. Tohoku J Exp Med **216,** 149, 2008.
91. Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., *et al.* Multilineage potential of adult human mesenchymal stem cells. Science **284,** 143, 1999.
92. Delorme, B., Ringe, J., Pontikoglou, C., Gaillard, J., Langonne, A., Sensebe, L., *et al.* Specific lineage-priming of bone marrow mesenchymal stem cells provides the molecular framework for their plasticity. Stem Cells **27,** 1142, 2009.
93. Harris, L.J., Abdollahi, H., Zhang, P., McIlhenny, S., Tulenko, T.N., and Dimuzio, P.J. Differentiation of adult stem cells into smooth muscle for vascular tissue engineering. J Surg Res 2009 Sep 4 [Epub ahead of print].
94. Kim, Y.M., Jeon, E.S., Kim, M.R., Jho, S.K., Ryu, S.W., and Kim, J.H. Angiotensin II-induced differentiation of adipose tissue-derived mesenchymal stem cells to smooth muscle-like cells. Int J Biochem Cell Biol **40,** 2482, 2008.
95. Dezawa, M., Ishikawa, H., Itokazu, Y., Yoshihara, T., Hoshino, M., Takeda, S., *et al.* Bone marrow stromal cells generate muscle cells and repair muscle degeneration. Science **309,** 314, 2005.
96. Toma, C., Pittenger, M.F., Cahill, K.S., Byrne, B.J., and Kessler, P.D. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation **105,** 93, 2002.
97. Planat-Benard, V., Menard, C., Andre, M., Puceat, M., Perez, A., Garcia-Verdugo, J.M., *et al.* Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. Circ Res **94,** 223, 2004.
98. Oswald, J., Boxberger, S., Jorgensen, B., Feldmann, S., Ehninger, G., Bornhauser, M., *et al.* Mesenchymal stem cells can be differentiated into endothelial cells *in vitro.* Stem Cells **22,** 377, 2004.
99. Woodbury, D., Schwarz, E.J., Prockop, D.J., and Black, I.B. Adult rat and human bone marrow stromal cells differentiate into neurons. J Neurosci Res **61,** 364, 2000.

100. Safford, K.M., Hicok, K.C., Safford, S.D., Halvorsen, Y.D., Wilkison, W.O., Gimble, J.M., *et al.* Neurogenic differentiation of murine and human adipose-derived stromal cells. Biochem Biophys Res Commun **294,** 371, 2002.
101. Lee, K.D., Kuo, T.K., Whang-Peng, J., Chung, Y.F., Lin, C.T., Chou, S.H., *et al. In vitro* hepatic differentiation of human mesenchymal stem cells. Hepatology **40,** 1275, 2004.
102. Seo, M.J., Suh, S.Y., Bae, Y.C., and Jung, J.S. Differentiation of human adipose stromal cells into hepatic lineage *in vitro* and *in vivo*. Biochem Biophys Res Commun **328,** 258, 2005.
103. Spees, J.L., Olson, S.D., Ylostalo, J., Lynch, P.J., Smith, J., Perry, A., *et al.* Differentiation, cell fusion, and nuclear fusion during *ex vivo* repair of epithelium by human adult stem cells from bone marrow stroma. Proc Natl Acad Sci U S A **100,** 2397, 2003.
104. Brzoska, M., Geiger, H., Gauer, S., and Baer, P. Epithelial differentiation of human adipose tissue-derived adult stem cells. Biochem Biophys Res Commun **330,** 142, 2005.
105. Banfi, A., Bianchi, G., Notaro, R., Luzzatto, L., Cancedda, R., and Quarto, R. Replicative aging and gene expression in long-term cultures of human bone marrow stromal cells. Tissue Eng **8,** 901, 2002.
106. Simonsen, J.L., Rosada, C., Serakinci, N., Justesen, J., Stenderup, K., Rattan, S.I., *et al.* Telomerase expression extends the proliferative life-span and maintains the osteogenic potential of human bone marrow stromal cells. Nat Biotechnol **20,** 592, 2002.
107. Zimmermann, S., Voss, M., Kaiser, S., Kapp, U., Waller, C.F., and Martens, U.M. Lack of telomerase activity in human mesenchymal stem cells. Leukemia **17,** 1146, 2003.
108. Katz, A.J., Tholpady, A., Tholpady, S.S., Shang, H., and Ogle, R.C. Cell surface and transcriptional characterization of human adipose-derived adherent stromal (hADAS) cells. Stem Cells **23,** 412, 2005.
109. Lin, G., Garcia, M., Ning, H., Banie, L., Guo, Y.L., Lue, T.F., *et al.* Defining stem and progenitor cells within adipose tissue. Stem Cells Dev **17,** 1053, 2008.
110. Ksiazek, K. A comprehensive review on mesenchymal stem cell growth and senescence. Rejuvenation Res **12,** 105, 2009.
111. Noer, A., Boquest, A.C., and Collas, P. Dynamics of adipogenic promoter DNA methylation during clonal culture of human adipose stem cells to senescence. BMC Cell Biol **8,** 18, 2007.
112. Crisan, M., Yap, S., Casteilla, L., Chen, C.W., Corselli, M., Park, T.S., *et al.* A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell **3,** 301, 2008.
113. Min, S.Y., Kim, H.Y., Jung, S.Y., Kwon, Y., Shin, K.H., Lee, S., Kim, S.W., Kang, H.S., Yun, Y.H., and Lee, E.S. Oncological safety and quality of life associated with mastectomy and immediate breast reconstruction with a latissimus dorsi myocutaneous flap. Breast J **16,** 356, 2010.
114. Rigotti, G., Marchi, A., Stringhini, P., Baroni, G., Galiè, M., Molino, A.M., Mercanti, A., Micciolo, R., and Sbarbati, A. Determining the oncological risk of autologous lipoaspirate grafting for post-mastectomy breast reconstruction. Aesthetic Plast Surg **34,** 475, 2010.

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