Published in final edited form as:

Wound Repair Regen. 2014 May ; 22(0 1): 11–13. doi:10.1111/wrr.12164.

Healing of Grafted Adipose Tissue: Current Clinical Applications of Adipose-Derived Stem Cells for Breast and Face Reconstruction

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Abstract

Since their isolation and characterization nearly a decade ago, adipose-derived stem cells (ASCs) have become one of the most popular adult stem cell populations for soft tissue engineering and regenerative medicine applications. Compared to other stem cell sources, ASCs offer several advantages including abundant autologous source, minor invasive harvesting (liposuction), significant proliferative capacity in culture, and multi-lineage potential. In this mini-review, we focus on some of the more salient published clinical and pre-clinical data to date regarding ASC treatment for breast and facial soft tissue reconstruction.

Keywords

Adipose derived stem cells; Autologous fat grafting; Cell-assisted lipotransfer; Stem cells; Adipogenesis

Background

Adipose tissue is the key component of soft tissues throughout the body that protect underlying structures and impart a normal appearance. According to the American Society of Plastic Surgeons (ASPS), nearly 300,000 surgical procedures related to breast (after mastectomy) and craniofacial reconstructions were performed in 2012 [www.plasticsurgery.org]. Tissue flap procedures are considered to produce a more natural reconstruction, but are highly invasive with significant donor site morbidity, while implants have associated long-term problems of migration, extrusion, and capsular contracture. Though the use of low-pressure aspiration (for harvesting) and cautious injection of smaller particles have had some impact on clinical outcomes, long-term outcomes of fat graft survival and durability still remain highly unpredictable. For long-term successful clinical outcomes after tissue reconstruction, the use of autologous fat tissue (rather than artificial implants), as well as complete regeneration of healthy vascularized adipose tissue, would be the ideal therapy. Based upon their stem cell properties, adipose-derived stem cells (ASCs) are the lead candidate for such clinical applications. Although ASC supplementation has

been studied in clinical trials for wound healing therapies [1], this mini-review is not meant to be comprehensive but is aimed at focusing on some of the more relevant published clinical and pre-clinical (i.e., animal) data to date using ASCs related to breast and maxillofacial soft tissue reconstruction.

Adipose-Derived Stem Cells (ASCs) and Fat Grafting

Human adipose-derived stem cells, first termed preadipocytes, were isolated nearly 40 years ago, though their multi-lineage potential was discovered only 10 years ago by Zuk and colleagues [2]. Since that time, many biological properties of ASCs have been characterized via in vitro and in vivo studies. For clarity, in this mini-review, 'ASCs' are defined as the plastic-adherent cell population isolated from collagenase digests of adipose tissue. Given their tremendous plasticity, human ASCs are known to differentiate into numerous cell lineages including adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, and neurogenic-like cell types (Table 1). Also, because ASCs are derived from the (vascular-rich) stromal vascular fraction (SVF) of processed adipose tissue, ASCs have been shown to possess angiogenic characteristics and to differentiate into vascular endothelial cells [3]. Furthermore, studies [4] have demonstrated that ASCs express/secrete multiple growth factors including insulin-like growth factor (IGF), hepatocyte growth factor (HGF), transforming growth factor beta 1 (TGF- β 1), and the pro-angiogenic growth factor, vascular endothelial growth factor (VEGF). Because of these biological characteristics, adipose tissue, a once previously discarded and unwanted tissue, has recently proven to be an invaluable stem cell source for clinical application.

In addition to lower donor site morbidity during harvesting, ASCs can be extracted at clinically-relevant yields, thus obviating the need for in vitro propagation. Compared to stem cells derived from bone marrow, adipose tissue has been reported to contain 1000X the number of stem cells (per gram tissue) [5]. As a result, the currently proposed clinical uses of ASCs for tissue repair/regeneration are both remarkable and numerous [4]. Although most of these studies are still in the preliminary stages, the most striking progress for clinical application of ASCs is in the area of fat grafting. Although the molecular signaling mechanisms are currently poorly-understood, angiogenic induction and minimal metabolic requirements by these progenitor cells are believed to contribute to improved long-lasting grafting results observed in the clinic [6].

One technique that has changed soft tissue reconstruction and is utilized world-wide by plastic surgeons is a fat processing technique termed the Coleman method [6]. This technique involves removal of a fat (lipoaspirate) sample from one region of the body (e.g., abdomen, thigh, buttocks), followed by centrifugation and subsequent grafting of the smaller, processed fat particles. Importantly, this procedure attempts to minimize trauma while placing grafted fat in small aliquots at many levels. Another revolutionary technique for fat grafting, termed cell-assisted lipotransfer (CAL), converts ASC-poor fat to ASC-rich fat via supplementation with SVF isolated from adipose tissue [7]. This procedure of harvesting fat from one part of body, processing it, and placing it into another body site is not FDA-approved in the United States, though numerous clinical trials have been

conducted overseas. Such clinical trials, along with their respective outcomes, are briefly discussed below.

Pre-clinical Studies: Fat Grafting + ASCs

A considerable amount of data has demonstrated that fat supplementation with ASCs can improve long-term graft survival and retention. In one of the earliest studies, Masuda et al. [8] transplanted omental tissue with or without preadipocytes isolated from epididymal adipose tissues under the dorsal skin of Wistar rats. After 12 weeks, high levels of triacylglycerol content, capillary density, and VEGF production were observed. More importantly, co-transplantation with preadipocytes significantly enhanced adipose tissue formation. In a related study, Matsumoto and others [3] found that cell-assisted lipotransfer (CAL) fat had a increased survival rate (35% greater masson average) than non-CAL fat, and that the microvasculature was more prominent in CAL fat, especially in the outer layers. Moreover, using nude mice, Moseley et al. [9] demonstrated that fat supplemented with ASCs (either freshly-isolated or cultured) maintained its adipocyte-rich appearance and weighed 2.5X greater compared to grafted fat not supplemented with ASCs. Similar findings have been documented elsewhere, including increased capillary density and neovascularization within fat grafts treated with ASCs [10,11]. Of particular note in all of these studies is the hypoxic tissue conditions in the acute phase following transplantation. Indeed, several studies have demonstrated that hypoxia induces cultured human ASCs to synthesize and release numerous angiogenic growth factors [12–14], perhaps contributing to increased fat graft microvasculature.

Clinical Studies

Autologous Fat Transfer

Although ASC therapy is not FDA-approved in the United States, autologous fat transfer is approved for use in the clinical arena. Several case studies of autologous fat grafting using the Coleman technique have been published. Clinical outcomes of facial structural fat grafting for the first three patients treated with this method were reported in 2006 [6]. Overall results indicated significant volume corrections and retentions following long-term follow-ups (nearly 12 years for one patient). In each of these cases, of particular significance was the integration of the transplanted fatty tissue within the surrounding tissue. Additionally, in a retrospective examination of 17 breast procedures performed from 1995 to 2000 using the Coleman method of fat grafting, all patients had a significant improvement in their breast size and/or shape postoperatively (up to 98 months) and all had breasts that exhibited soft and natural appearance and feel [15]. As the authors noted in this study, most patients underwent mammography approximately 1 year post-operation without any screening complications. Though additional prospective studies are required, the authors concluded this technique as safe as, and perhaps even more efficacious than, many other breast contouring procedures.

The CAL technique has been and is currently being utilized clinically around the world, predominantly in Japan by Dr. Kotaro Yoshimura. Preliminary results from these clinical studies are very promising, with natural tissue appearance/feel and a lack of rejection or

inflammation. In one of the earliest published studies, Yoshimura et al. [16] performed CAL on six patients with facial lipoatrophy. After follow-up periods of 9 to 13 months, the CAL group had a better clinical improvement score than did the non-CAL patients. Only one complication of necrosis was noted in a non-CAL patient, and was easily treated. Similarly, Yoshimura and colleagues [16,17] conducted two clinical trials in which CAL was utilized for breast augmentation or reconstruction. After treatment of 55 total patients with follow-up of 6–12 months, clinical results were very satisfactory with favorable graft retention. In addition, cyst formation or microcalcification occurred in only four patients and did not impair breast cancer screening. Similar augmentation and retention results were reported by Kitamura et al. [18] following CAL treatment in five female patients previously treated for breast cancer. To date, no human studies have reported an increased risk of cancer associated with either autologous fat grafting or CAL therapies. Additionally, the utilization of fat grafting in the breast has been described by Salgarello et al. for both pre-radiotherapy [19] and post-radiotherapy [20] scenarios with potential reduction of radiation-induced complications in implants. Doctor Yoshimura has successfully executed approximately 500 breast augmentation and breast reconstruction procedures since 2003 with very encouraging results, and more importantly, without any reported disease complications. Because noncomparative studies of retained volume after fat grafting, with or without ASC supplementation, have been reported in the literature, larger randomized studies are necessary to assess both the long-term safety and efficacy of these promising new options for world-wide use (including the United States) regarding soft tissue trauma and reconstructive surgery.

Conclusions

The use of autologous fat for correction of soft tissue defects has been utilized for more than a century. However, the principal issue facing plastic surgeons is the low survival rate and relatively rapid resorption of transplanted fat. Adipose-derived stem cells (ASCs) hold tremendous promise for direct clinical translation related to soft tissue defect repair and regeneration. Outside of the United States, several clinical and preclinical studies have demonstrated notable efficacy and safety of ASC therapy, and other clinical trials are still ongoing. Unfortunately, universally-accepted harvesting and processing methodologies, as well as proper in vitro and in vivo models of ASC growth/differentiation, are lacking. Such standardized protocols and models, as well as larger randomized controlled trials, are necessary before ASC therapy can be effectively and safely translated to the clinic. Furthermore, new strategies (e.g., cellular, pharmacological) for maintenance and long-term retention of soft tissue grafting should help progress the next generation of ASC therapies.

Acknowledgments

The authors gratefully acknowledge support for this research from NIH R01CA114246 (to J.P.R.). The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Table 1

Adipose-derived Stem Cell Differentiation Potential: Multi-Cell Lineages

Adipocytes
Cardiomyocytes
Chondrocytes
Endothelial Cells
Epidermal Cells
Glial-like cells
Hepatocytes
Myocytes
Neuron-like cells
Osteoblasts

Differential plasticity of adipose-derived stem cells (ASCs). Under proper conditions, multiple cell lineages can be derived from mesenchymal ASCs. Due to their stem cell properties, ASCs are currently being investigated as a potential cell-based therapy for numerous clinical applications. [21]

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