How Does Fat Survive and Remodel After Grafting?

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KEYWORDS

• Fat grafting • Adipose-derived stem/stromal cell • Tissue regeneration • Macrophages • Vascular endothelial cells

KEY POINTS

- Under severe ischemia, adipocytes die within 24 hours; adipose-derived stem/stromal cells (ASCs) survive up to 3 days and are activated, contributing to the repairing process through adipogenesis, angiogenesis, and paracrine effects.
- Adipocyte fate after fat grafting is categorized into three zones depending on the distance from the surface: survival, regeneration, and necrosis.
- ASCs do not die and give rise to new adipocytes in the regenerating zone; they die in the necrotizing zone. The balance between regeneration and degeneration determines the final volume retention after fat grafting.
- Dead adipocytes under better conditions (regenerating zone) are phagocytized by macrophages and are successfully replaced by new adipocytes.
- Dead adipocytes under worse conditions (necrotizing zone) are replaced with cicatrization or oil cyst formation depending on the size of oil drops.

INTRODUCTION

Adipose tissue and adipose-derived stem/stromal cells (ASCs) obtained from liposuction were shown to have potential for regenerative therapeutic use. However, clinical outcomes of fat grafting remain unpredictable and, to improve the outcomes, it is crucial to elucidate the detailed mechanism of engraftment of fat tissue. The "cell survival theory," which maintains that transplanted adipocytes partly survive once they receive adequate nutrients and remain alive in the recipient site, had been accepted for a long time.[1–3] In contrast, our recent studies showed how ASCs work in response to microenvironmental changes, such as ischemia and applied mechanical force,[4,5] and revealed the "cell replacement theory," which holds that most adipocytes undergo ischemic death and subsequent replacement with next generation during the first 3 months after fat grafting.[6,7] Further details, such as the cellular origin of adipose regeneration and the mechanism of cicatrization and oil cyst formation, were also demonstrated.[7]

BASIC SCIENCE: FUNCTIONAL ROLES OF ADIPOSE-DERIVED STEM/STROMAL CELLS IN TISSUE REMODELING

Adipose Tissue Biology

Adipose tissue is not only an organ of energy storage, but also an endocrine organ (releasing multiple adipose-derived hormones, such as leptin and adiponectin) that regulates metabolic

Financial Disclosure: Authors report no commercial associations or financial disclosures with regard to this article.
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Clin Plastic Surg 42 (2015) 181–190
http://dx.doi.org/10.1016/j.cps.2014.12.008
0094-1298/15/$ – see front matter © 2015 Elsevier Inc. All rights reserved.

homeostasis. Adipose tissue consists predominantly of adipocytes, ASCs, vascular endothelial cells (VECs), pericytes, fibroblasts, and connective tissue as well as adipose tissue-resident macrophages and lymphocytes (**Fig. 1**).[8] Our rough estimation of cellular component numbers are as follows; 1 cm^3 intact adipose tissue contains several millions cells; 1 million adipocytes, 1 million ASCs, 1 million VECs, and 1 million other cells (adipose-resident macrophages and lymphocytes, pericytes, fibroblasts, etc).[8] Adipose tissue is rich in capillary and every single adipocyte is attached to the capillary network. The size of adipocyte is 50 to 150 μm in diameter (if it becomes larger, it dies from ischemia) and its life span is several to 10 years in humans. ASCs are located perivascularly along the capillaries between adipocytes like pericytes. ASCs have been shown to release angiogenic factors responding to ischemia[4] and to differentiate physiologically into adipocytes and VECs.[9] A small subpopulation of ASCs (1%–2%) may have greater multipotency, corresponding with stem cells called multilineage differentiating stress enduring (Muse) cells.[10] The enlarged adipocytes in obese individuals occasionally die from relative ischemia and are subsequently surrounded by infiltrated M1 inflammatory macrophages (crownlike structure). The crownlike structure is seen after any types of adipocyte death (**Fig. 2**).

Adipose-Derived Stem/Progenitor Cells in Adipose Tissue Remodeling

ASCs are the main cell population contributing to adipocyte (re)generation in any types of adipose tissue remodeling/expansion, such as developmental growth, hyperplasia in obesity, repair processes after injury/ischemia,[4] or tissue expansion induced by internal/external mechanical forces.[5] These remodeling processes are in balance between adipocyte apoptosis/necrosis and adipogenesis managed by ASCs. In ASC-deficient tissues, such as irradiated or chronically inflamed tissues, any type of adipose tissue remodeling or expansion is impaired and thus fat grafting to fertilize such stem cell–depleted condition would be theoretically the right solution.[11] Adipose-tissue atrophy over aging is likely owing to a decrease in number of ASCs and consequent impaired physiologic turnover, as is commonly seen in other tissues and organs.

Ischemia to Adipose Tissue

Subcutaneous adipose tissue has the highest tissue partial oxygen tension (ptO_2; 40–60 mm Hg) among organs. The high ptO_2 of adipose tissue probably reflects high density of capillaries and low oxygen consumption rate of the tissue. Diabetic adipose tissue is relatively ischemic with low-grade chronic inflammation, which causes

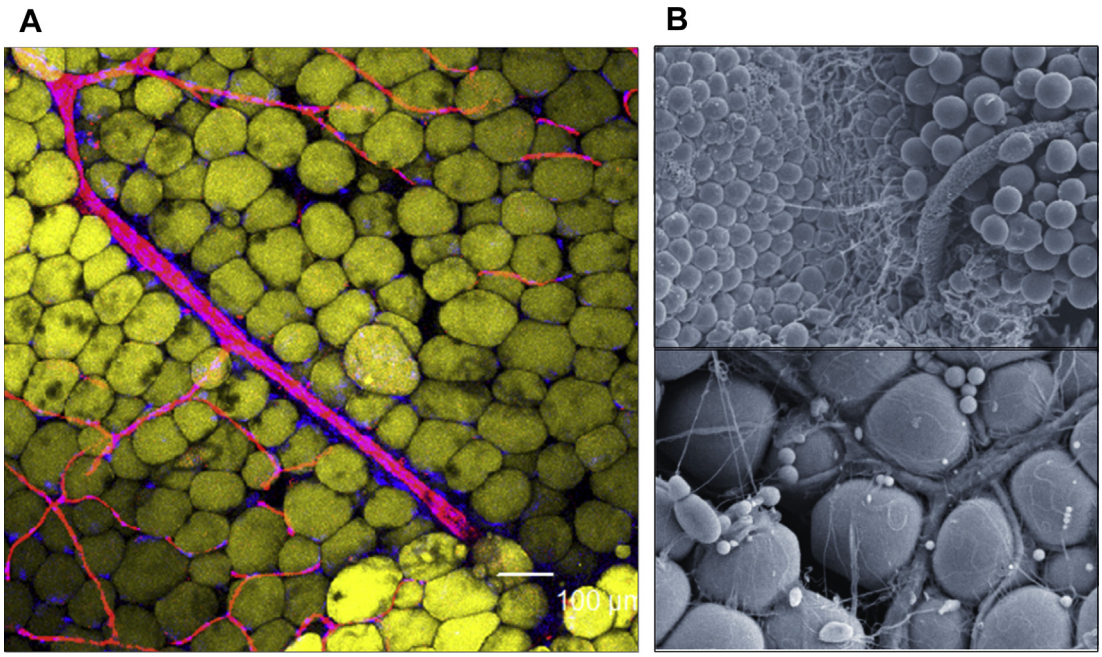

Fig. 1. Structure of human adipose tissue. (*A*) Adipose tissues are triple stained with BODIPY (adipocytes; *yellow*), lectin (endothelial cells; *red*), and Hoechst 33,342 (nuclei; *blue*). Adipose tissue is packed with adipocytes with scarce connective tissue and is rich in capillary network, though each adipocyte is exceptionally large in size. Scale bars = 100 μm. (*B*) Scanning electromicroscopic images.

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