

# Skin regeneration effect of adipose stem cells

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## Abstract

Skin is at the forefront of the body for physical, chemical, biological stress or irritation. Damage to the skin can cause health risks and poor quality of life. Skin regeneration involves almost all cells in the skin, but complete healing of the wound may be impossible. Adipose tissue-derived stem cells (ASCs) may play a role in angiogenesis, modulation of inflammation, extracellular matrix remodeling, and refractory skin wound healing. In skin regeneration, ASCs are provided in the form of enzymatically isolated SVF (cellular SVF), mechanically isolated SVF (tissue SVF), or lipograft. This review will discuss the administration method, clinical implications, and effects of ASCs involved in dermal wound healing.

## Introduction

The skin is a structure for protection barrier and has the function of producing, processing, storing and metabolizing bioactive molecules [1]. Skin regeneration undergoes a dynamic and complex process which is characterized by homeostasis, inflammation, proliferation, re-epithelization, and fibrosis [1]. Platelets and immune cells in the skin secrete cytokines to activate cells in the skin that are involved in wound healing [2].

Normally, hair follicle stem cells reside in a quiescent niche, but hair follicle stem cells are packed around the damaged tissue in the harmful event of skin to repair damage [3]. Only stem cells play a substantial role in skin regeneration and committed progenitor cells have a limited role [3]. Besides hair follicle stem cells, keratinocyte is a major component of the epidermis with various differentiation potentials [1]. Blood vessels, nerves, and specialized extracellular matrix (ECM) in the dermis are associated with tissue repairing systems as well as adipocytes and SVF (fibroblasts, immune cells, endothelial cells, pericytes, and ASCs) in subcutaneous layer [4]. In addition to ASCs in SVF, cultured ASCs also stimulate angiogenesis and growth human dermal fibroblast by cell-to-cell direct contact and paracrine activation through secretory factors, resulting in dermal wound regeneration [5].

In this review, we will discuss about the forms of administration of ASCs (i.e., cultured ASCs, SVF, and lipografting) and clinical applications to augment dermal wound healing.

## ASCs as cellular therapy

Stromal cells such as ASCs modulate the recovery of damaged parenchymal cell lines when restoring skin damage. ASCs are mesenchymal stromal stem cells that are present in SVF of subcutaneous tissue, encircling capillaries and microvessels as precursor cells (i.e., pericytes and periadventitial cells) [6]. Therapeutic effects of ASCs for wound healing ASCs are derived from constructive manner (differentiation), instructive manner (secretion of growth factors and cytokines), and reconstructive manner (remodeling the extracellular matrix) [7].

Lee et al. [8] and Bura et al. [9] investigated effects of cultured ASCs injected intramuscularly on revascularization of critical limb ischemia.

In study of Lee et al. [8] the ulcer healing occurred in 66.7% out of twelve patients after six months. In addition, pain reduction, improved walking distance in claudication, temperature rise was detected after six months with mild complications (mild fever, flu like syndrome, pain and headache). In the trial of Bura et al. [9], seven subjects participated in the experiment, and four of them underwent amputation within five months after injection of ASCs. The remaining 3 uncut patients showed decreased pain and increased tissue oxygen pressure compared to before injection. However, these two studies are not controlled randomized type. These studies showed have the disadvantage of small sample size and low level of evidence due to lack of control and randomization.

At least one of the mechanisms of the improved ulcer healing is augmented angiogenesis by the administered ASCs. A large number of patients were unresponsive to treatment. It may be a problem that ASCs injected into the muscle migrate to the target tissue, and loss of differentiation or paracrine ability may have occurred as the ASCs were cultured [10].

## Cellular or tissue SVF

Obtaining the SVF used for skin regeneration can be classified into two types i.e. cellular SVF (cSVF), tissue SVF (tSVF). In cSVF, intercellular connections and ECM are eliminated by enzymatic isolation procedures.

In tSVF, only the adipocyte is removed, resulting in having a regenerative trophic factor and the integrity of the stromal cells is maintained [4]. The ECM can play many roles in relation to skin regeneration. The ECM could instruct ASCs to differentiate, secrete their trophic factors to induce angiogenesis, resulting in reduced

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ischemia and apoptosis, remodel the native extracellular matrix, and reduce inflammation [4].

Han et al. [11] reported that patients with diabetic foot ulcers treated with cSVF and fibrinogen and thrombin showed higher complete healing rate than those treated with fibrinogen and thrombin alone (100% vs. 62%). Fibrinogen is activated by thrombin and transformed into fibrin, forming a dense network, which seems to help stabilize stem cells in cSVF [11].

## Lipografting

Lipografting, the transplantation of lipoaspirates (fragmented adipose tissue) can be used for treating promote dermal wound healing. Cervelli et al. [12] demonstrated healing effect of chronic lower extremity ulcers by use of lipografting (fat grafting) combined with platelet-rich plasma. Platelet-rich plasma have a role of improving cellular growth and differentiation of cells [12]. After 9.7 weeks, 80% of the ulcers in experimental groups had re-epithelialized, compared with 20% in the control group (treated with medication based on hyaluronic acid and collagen [12]. The skin regeneration effect of lipograft is mainly due to ASCs, but angiogenesis and proliferation of skin cells induced by hypoxia in lipograft may play additional role in tissue repairing [13].

## Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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