

## Role of adipose-derived stromal cells in pedicle skin flap survival in experimental animal models

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### Abstract

The use of skin flaps in reconstructive surgery is the first-line surgical treatment for the reconstruction of skin defects and is essentially considered the starting point of plastic surgery. Despite their excellent usability, their application includes general surgical risks or possible complications, the primary and most common is necrosis of the flap. To improve flap survival, researchers have used different methods, including the use of adipose-derived stem cells, with significant positive results. In our research we will report the use of adipose-derived stem cells in pedicle skin flap survival based on current literature on various experimental models in animals.

**Key words:** Pedicle skin flap; Adipose stromal cells; Flap survival; Stem cell; Skin defect; Reconstructive surgery

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**Core tip:** The use of skin flaps in reconstructive surgery is the first-line surgical treatment for the reconstruction of skin defects and is essentially considered the starting point of plastic surgery. Our work, summarizing the current literature, presents the role of adipose-derived stromal cells in pedicle skin flap survival in experimental animal models.

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### INTRODUCTION

Flaps are used in plastic surgery for wound coverage

when insufficient blood supply impedes the viability of skin grafts. Examples of such applications include large wounds over a flexion crease or wounds with exposed bone, tendon, or other vital structures. Flaps are also preferred in plastic surgery over free grafts because they have a better aesthetic and functional result<sup>[1]</sup>. A first distinction of cutaneous flaps was established in the 1970s. Skin flaps were classified depending on the blood irrigation into the axial pattern flaps, which have an anatomically recognized arteriovenous system running along their long axis, and random pattern flaps, which lack any significant bias in their vascular patterns<sup>[2]</sup>.

Since then, there has been a rapid development of reconstructive surgery, which has kept pace with the goal of understanding, improving, and developing methods to avoid partial or total flap necrosis, the main complication of the use of skin flaps. Although the cause of skin flap necrosis has not been fully resolved yet, the lack of adequate nutrient blood supply certainly plays a significant role in the pathophysiology of necrosis. To reverse this phenomenon and strengthen vascular reserves, various therapeutic approaches have been pursued. For example, the administration of exogenous agents such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) has been shown to enhance revascularization and improve survival of ischemic flaps<sup>[3-5]</sup>. However, the beneficial effect of such exogenous factors is reduced due to their short half-life<sup>[6]</sup> and the limited number of existing endothelial cells. Hence, the abovementioned factors are not enough to control the complex cascade of wound healing.

In recent years the rapid development of cell biology and genetics has helped to highlight the ability of somatic stem cells, especially bone marrow-derived stem cells (BSCs) and adipose-derived stem cells (ADSCs), to promote neovascularization<sup>[7-12]</sup>. Various studies conducted to compare the forms of stem cells derived from bone marrow, umbilical cord, or adipose tissue showed no significant differences in terms of morphology, immunogenicity, and pluripotent differentiation<sup>[13]</sup>. The proangiogenic effect of ADSCs and BSCs has been well established, however the two groups seem to have different promoting angiogenesis mechanisms<sup>[14]</sup>. This fact, combined with the minimally invasive techniques in extraction, isolation, and culture from ADSCs<sup>[15-17]</sup>, places them in the first line of research for various therapeutic purposes in medical science<sup>[18]</sup>.

This review presents the therapeutic benefits of ADSCs in pedicle skin flap survival based on current literature on various experimental models in animals.

## EFFECT OF ADSCS ON VIABILITY OF RANDOM PEDICLE SKIN FLAPS

The first time adipose stem cells were used as an antinecrotic treatment in random pedicle flaps was by Lu *et al.*<sup>[19]</sup> in 2008. Intracutaneous injection of (DiI)-

labeled (*i.e.*, chemical used for labeling cell membranes and hydrophobic structures) adipose-derived stem cells in ICR mice (*i.e.*, mice originating from a Swiss mice strain from Institute for Cancer Research in Philadelphia) led to a statistically significant increase in survival of the flaps with considerable improvement in capillary density. Furthermore, the immunohistochemical test showed that on some occasions there was *in vivo* differentiation of ADSCs in endothelial cells. Uysal *et al.*<sup>[20]</sup> examined the behavior and properties of adipose-derived stem cells in an ischemia-reperfusion model in ICR mice. They established that ADSCs could prevent ischemia-reperfusion injury, mainly by regulating growth factors, especially VEGF, bFGF, and transforming growth factor-beta (TGF- $\beta$ ). Gao *et al.*<sup>[21]</sup> showed that topical use of ADSCs could improve viability of ischemic random pedicle skin flap in streptozotocin-induced diabetic mice *via* expression of hypoxia-inducible factor-1 $\alpha$ . Sheng *et al.*<sup>[22]</sup> implicated the beneficial effect of BSCs vs stromal vascular factor (SVF), which contains a group of heterogeneous cells in the adipose tissue, including ADSCs. No statistically significant difference in promoting vascularization and survival of pedicle skin flaps in Wistar rats could be observed.

In 2013, Karathanasis *et al.*<sup>[23]</sup> examined whether genetically modified autologous ADSCs increase graft survival. They conducted an experimental study in which autologous green fluorescent protein (GFP)-producing ADSCs were injected intracutaneously into random-pattern skin flaps in Wistar rats. The results indicated that transplantation of modified GFP-ADSCs improves the survival of the flaps. GFP-ADSCs were detected in the endothelium of blood vessels co-expressing the endothelial marker von Willebrand factor, suggesting that they promoted blood vessel regeneration *in vivo*<sup>[23]</sup>. The same year, Yue *et al.*<sup>[24]</sup>, using a hypoxic preconditioning experimental flap model, showed that preoperative transplantation of ADSCs, combined with hypoxic preconditioning, effectively improves the survival of ischemic skin flaps in Lewis rats by enhancing neovascularization associated with the production and activation of hypoxia-inducible factor 1 alpha (HIF-1 $\alpha$ ), together with an increase in VEGF. Comparing the effectiveness of different administration routes of ADSCs in improving the viability of random-pattern skin flaps, Lee *et al.*<sup>[25]</sup> indicated that the collagen sponge method delivers ADSCs most effectively within the flap, increasing flap vascularity. Nevertheless, the intravascular administration of ADSCs also positively affects the skin-flap survival, as shown in experiments established by Suartz *et al.*<sup>[26]</sup> in Wistar rats.

Recently, Park *et al.*<sup>[27]</sup> investigated the effects of low-level light therapy (LLLT) on transplanted human adipose-derived mesenchymal stromal cells in the skin flaps of mice. The results indicated that LLLT is an effective biostimulator of ADSCs in vascular regeneration, which enhances the survival of ADSCs and stimulates the secretion of growth factors in skin flaps. Therefore, although the use of ADSCs led to improved viability

**Table 1** The most relevant studies on the effect of adipose-derived stem cells on viability of pedicle skin flaps in experimental animal models

Ref.	Year	Contribution
Lu <i>et al</i> <sup>[19]</sup>	2008	Intracutaneous injection of (DiI)-labeled ADSCs improves capillary density
Uysal <i>et al</i> <sup>[20]</sup>	2009	ADSCs prevent ischemia-reperfusion injury by regulating growth factors, especially VEGF, bFGF, TGF- $\beta$
Gao <i>et al</i> <sup>[21]</sup>	2011	Human-ADSCs improve viability of ischemic random pedicle skin flap in mice <i>via</i> expression of hypoxia-inducible factor-1 $\alpha$
Sheng <i>et al</i> <sup>[22]</sup>	2011	BSCs vs SVF promotes vascularization
Karathanasis <i>et al</i> <sup>[23]</sup>	2013	Transplantation of modified GFP-ADSCs promotes blood vessel regeneration <i>in vivo</i>
Yue <i>et al</i> <sup>[24]</sup>	2013	Transplantation of ADSCs, combined with hypoxic preconditioning, enhances neovascularization associated with the production and activation of HIF-1 $\alpha$ , together with an increase in VEGF
Lee <i>et al</i> <sup>[25]</sup>	2014	ADSCs delivered <i>via</i> sponge method increase flap vascularity
Suartz <i>et al</i> <sup>[26]</sup>	2014	Administration of ADSCs affects positively in skin-flap survival
Derby <i>et al</i> <sup>[28]</sup>	2014	Genetic modified GFP-ADSC improves overlying skin composition and appearance after fat graft transplantation
Park <i>et al</i> <sup>[27]</sup>	2015	LLLT on transplanted human-ADSCs in the skin flaps of mice stimulates the secretion of growth factors in skin flaps
Reichenberger <i>et al</i> <sup>[29]</sup>	2012	Topical application of ADSCs embedded in a fibrin matrix, increases ischemic tissue survival, blood flow and expression of pro-angioactive genes in an animal epigastric skin flap model
Reichenberger <i>et al</i> <sup>[30]</sup>	2012	ADSCs in an extended inferior epigastric artery skin flap enhance blood supply and tissue regeneration
Feng <i>et al</i> <sup>[31]</sup>	2014	Heterologous transplantation of human ADSCs in axial pedicle skin flaps improves viability of axial skin flap in mice
Xu <i>et al</i> <sup>[32]</sup>	2015	Transplantation of ADSCs promotes capillary formation
Tomita <i>et al</i> <sup>[33]</sup>	2013	Utilization of ADSCs in Lewis rats improved the sensory capability of skin flaps <i>via</i> the production of neurotrophic factors and nerve growth factors
Uysal <i>et al</i> <sup>[36]</sup>	2010	ADSCs and BSCs increased the vascular density, and the VEGF
Li <i>et al</i> <sup>[37]</sup>	2010	ADSCs increase the vascular density and the survival percentage of the flaps producing high cytokine levels such as VEGF-A

ADSCs: Adipose-derived stem cells; HIF-1 $\alpha$ : Hypoxia-inducible factor 1 alpha; SVF: Stromal vascular factor; VEGF-A: Vascular endothelial growth factor A; VEGF: Vascular endothelial growth factor; bFGF: Basic fibroblast growth factor; TGF- $\beta$ : Transforming growth factor-beta; BSCs: Bone marrow-derived stem cells; GFP: Green fluorescent protein; LLLT: Low-level light therapy.

of skin flaps, their combination with LLLT significantly enhanced their action.

Derby *et al*<sup>[28]</sup> used the well-documented epithelial stem cell marker p63 to identify *in vivo* transdifferentiation of genetic modified GFP-ADSC in epithelial cells, and therefore show, their contribution to the improvement of overlying skin composition and appearance after fat graft transplantation.

## EFFECT OF ADSCS ON VIABILITY OF AXIAL PEDICLE FLAPS

To the best of our knowledge, the first attempt to examine the effect of ADSCs in axial pedicle skin flap survival took place in 2012<sup>[29]</sup>. Reichenberger *et al*<sup>[29]</sup> indicated that the topical application of ADSCs embedded in a fibrin matrix increases ischemic tissue survival, blood flow, and expression of pro-angioactive genes in an animal epigastric skin flap model. In the same year it was also shown that the administration of ADSCs in an extended inferior epigastric artery skin flap-which was used as a flap ischemia reperfusion injury (IRI) model-may protect axial skin flaps from IRI by enhancing blood supply and tissue regeneration<sup>[30]</sup>. The heterologous transplantation of ADSCs in axial pedicle skin flaps was examined by Feng *et al*<sup>[31]</sup>, in which an increase in the viability of human adipose-derived stem cells was observed after local intra-arterial injection in the superficial epigastric arteria of axial skin flaps in mice. A further study was conducted by Xu *et al*<sup>[32]</sup> in which stem cells were shown to contribute positively to the survival of axial flaps. Xu

and his team established a rabbit ear venous-congested skin flap model, where they transplanted ADSCs. After histological and immunofluorescence evaluation, it was indicated that ADSCs not only increase the survival of venous-congested skin flaps but also promote capillary formation.

Tomita *et al*<sup>[33]</sup> investigated the phenomenon of flap reinnervation through the utilization of ADSCs. They indicated that the use of the aforementioned cells improved the sensory capability of skin flaps in Lewis rats *via* the production of neurotrophic factors and nerve growth factors<sup>[33]</sup>.

## EFFECT OF ADSCS ON VIABILITY OF PREFABRICATED PEDICLE FLAPS

The concept of flap prefabrication is relatively new to the field of reconstructive surgery and was first introduced by Yao<sup>[34]</sup> in the 1980s. In the procedure of flap prefabrication, a vascular pedicle is introduced in a donor area that lacks any axial vascularization, improving the blood supply and enhancing the viability of the surrounding tissues. Although the above flaps can be used for wound coverage in almost any part of the body, their use in head and neck regions has prevailed, especially after extensive burns in which the available reconstructive options are scarce<sup>[35]</sup>.

Despite the undeniable utility of prefabricated flaps in plastic surgery, the risk of total or partial necrosis after flap transplantation remains a problem for further investigation. Among the concepts employed to resolve this potential complication is the application of ADSCs.

There are two studies in the literature in which ADSCs have been used in prefabricated flaps as an anti-necrosis therapy. Uysal *et al*<sup>[36]</sup> used the femoral artery, vein, and fascia of Wistar rats as a vascular crane for a prefabrication model in which they introduced ADSCs and BSC. Their experiments showed that both of the aforementioned cells increased the vascular density, and the VEGF indicated that mesenchymal stem cells could be useful in any prefabrication procedure in which neovascularization is necessary. Li *et al*<sup>[37]</sup> applied a prefabricated abdominal island flap model in rats, also using the right femoral artery, in which ADSCs were injected. The post-operative control demonstrated that ADSCs increased the vascular density and the survival percentage of the flaps producing high cytokine levels such as vascular endothelial growth factor A. Table 1 summarizes the most relevant studies on the effect of ADSCs on viability of pedicle skin flaps in experimental animal models.

## CONCLUSION

The current literature shows that in all cases where ADSCs were applied to investigate their effect on pedicle skin flap survival, they led to improved viability of the flaps. This was established through the increase of skin flap vascularity *via* the production of growth factors and/or ADSCs' direct transformation into epithelial cells with neoangiogenesis. Although the number of experimental studies on the application of stem cells as an anti-necrosis therapy is limited, an increasing number of researchers have been focusing on this field. This tendency, combined with the already successful clinical application of adipose stem cells in other fields of medical science, might show that their future use in the field of reconstructive surgery - where skin flaps are widely used-is no longer utopian.

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