

# **Role of Adipose Derived Stem Cells in Skin Flap Survival in a Rat Model**

(Experimental Study)

*Thesis*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

(قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ

أَنْتَ الْعَلِيمُ الْحَكِيمُ)

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## *List of Abbreviations*

<b>Abbreviation</b>	<b>Description</b>
<b>Ang-1</b>	Angiopoietin-1
<b>ANOVA</b>	Analysis of Variance
<b>ASCs</b>	Adipose Derived Stem Cells
<b>AVAs</b>	Arteriovenous Anastomoses
<b>BC</b>	Before Christ
<b>bFGF</b>	basic Fibroblast Growth Factor
<b>BMP-2</b>	Bone Morphogenetic Protein 2
<b>CAL</b>	Cell Assisted Lipotransfer
<b>CD</b>	Cluster of Differentiation
<b>DMEM</b>	Dulbecco's Modified Eagle Medium
<b>ECM</b>	Extracellular Matrix
<b>ELISA</b>	Enzyme-Linked Immunosorbent Assay
<b>EPCs</b>	Endothelial Progenitor Cells
<b>ESCs</b>	Embryonic Stem Cells
<b>FBS</b>	Fetal Bovine Serum
<b>FITC</b>	Fluorescein Isothiocyanate
<b>H&amp;E</b>	Hematoxylin and Eosin
<b>HGF</b>	Hepatocyte Growth Factor
<b>HIF-1</b>	Hypoxia-Inducible Factor-1
<b>HLA-DR</b>	Human Leukocyte Antigen-antigen D related
<b>HS</b>	Highly Significant
<b>IFATS</b>	International Federation for Adipose Therapeutics and Science
<b>IGF</b>	Insulin Growth Factor
<b>INF-<math>\gamma</math></b>	Interferon- $\gamma$

<b>iPS</b>	induced Pluripotent Stem cells
<b>ISCT</b>	International Society for Cellular Therapy
<b>KGF</b>	Keratinocyte Growth Factor
<b>LSD</b>	Least Significant Difference
<b>MHC-II</b>	Major Histocompatibility Complex-Class II
<b>MSCs</b>	Mesenchymal Stem Cells
<b>NGF</b>	Nerve Growth Factor
<b>NS</b>	Non Significant
<b>O.D</b>	Optical Density
<b>PBS</b>	Phosphate Buffered Saline
<b>PE</b>	Phycoerythrin
<b>PGE2</b>	Prostaglandin E2
<b>PLA</b>	Processed Lipoaspirate
<b>PDGF</b>	Platelet-Derived Growth Factor
<b>RPM</b>	Revolution per minute
<b>S</b>	Significant
<b>SD</b>	Standard Deviation
<b>SDF 1</b>	Stromal Derived Factor 1
<b>SPSS</b>	Statistical Program For Social Science
<b>SVF</b>	Stromal Vascular Fraction
<b>TGF <math>\beta</math></b>	Transforming Growth Factor Beta
<b>TNF- <math>\alpha</math></b>	Tumor Necrosis Factor- $\alpha$
<b>TRAM</b>	Transverse Rectus Abdominis Myocutaneous
<b>VEGF</b>	Vascular Endothelial Growth Factor
<b>VEGFR</b>	Vascular Endothelial Growth Factor Receptor

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## ***Introduction***

Skin flaps are commonly used in plastic and reconstructive surgery to repair defects resulting from trauma, congenital anomalies, or after tumor resection. Partial necrosis of the flap can be encountered postoperatively as a result of inadequate blood supply **(Lu et al., 2008)**. Subsequent management of flap necrosis usually includes time-consuming and repetitive dressing changes aimed at promoting secondary intention healing or even secondary reconstructive procedures **(Lubiatowski et al., 2002)**.

To overcome this potential problem, numerous studies have investigated methods for improving skin flap survival. Many have focused on enhancing flap viability with pharmacological agents as glucocorticoids and vasodilators to preserve the existing microcirculation. Although they are beneficial to some extent, the major drawback is the need for systemic application at relatively high doses to achieve significant improvement in flap survival, with increased possibilities of systemic side effects **(Kuru et al., 2003; Engel et al., 2007)**.

The administration of growth factors such as the basic Fibroblast Growth Factor (bFGF) and Vascular Endothelium Growth Factor (VEGF) to stimulate angiogenesis in skin flaps seems promising **(Haws et al., 2001; Pang et al., 2003; Qi et al., 2007)**. However, these growth factors have short half-life and so they need high initial doses and daily application **(Meirer et al., 2005)**.

The angiogenesis potential of adult stem cells has been reported, especially with stem cells derived from bone marrow and adipose tissue **(Planat-Benard et al., 2004; Tang et al., 2006; Uysal et al., 2010)**.

Stem cells are defined by their capacity to self-renew and differentiate into multiple cell lines; they are divided into two main groups: Embryonic stem cells and Adult stem cells (**Behr et al., 2010**).

Embryonic stem cells are pluripotent cells that can differentiate into any of the three primary germ layers. However, there are ethical concerns regarding the isolation of cells from live embryos. As a result, researchers have redirected attention to the adult stem cell populations as an alternative source (**Ko et al., 2011**).

Adult mesenchymal stem cells are multipotent cells that are capable of differentiating into mesenchymal lineages such as bone, cartilage, muscle, and fat. Mesenchymal stem cells can be isolated from various sites, including bone marrow and adipose tissue (**Ko et al., 2011**).

A set of standards were proposed by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy to define human mesenchymal stem cells. First, cells must be plastic adherent when maintained in standard culture conditions. Second, they express specific surface antigens. Third, the cells are capable of differentiation into osteoblasts, adipocytes and chondroblasts in vitro (**Dominici et al., 2006**).

Adipose tissue represents an attractive source of mesenchymal stem cells, the interest in using Adipose-derived stem cells (ASCs) has rapidly grown especially among plastic surgeons. The isolation of adipose tissue is much easier than bone marrow, with less donor site morbidity and available in greater quantities (**Zhu et al., 2008**).

ASCs can promote angiogenesis by secreting angiogenic growth factors as VEGF and bFGF (**Rehman et al., 2004**), and differentiating into endothelial cells (**Keerl et al., 2010**), thus improving skin flap survival (**Lu et al., 2008; Yang et al., 2010**).

Few studies have investigated the role of ASCs in skin flap survival, there was no previous clinical application. Furthermore, no previous studies investigated the optimal time for ASCs administration in the skin flap.