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

(Experimental Study)

Thesis

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By

Ahmed Atef Mohamed Ahmed

M.B.B.Ch., M.Sc.

Under supervision of

Prof Ayman Abu El Makarem Shaker

Professor of Plastic and Reconstructive Surgery
Faculty of Medicine - Ain Shams University

Prof Suzi Sobhy Atalla

Professor of Histology
Faculty of Medicine - Ain Shams University

Dr Eman Mohammed Yahya Sadek

Associate Professor of Plastic and Reconstructive Surgery
Faculty of Medicine - Ain Shams University

Dr Nahed Samir Boughdadi

Associate Professor of Plastic and Reconstructive Surgery
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain shams university
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بسم الله الرحمن الرحيم

(قَالُواْ سُبحَانَكَ لا عِلمَ لَنَا إلا مَا عَلَّمتَنَا إنَّكَ

أنتَ العَلِيمُ الحَكِيمُ)

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List of Abbreviations

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

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