Influence of Stem Cells on Leukemogenesis Induced by 7, 12 Dimethyl Benz [a] Anthracene or Gamma Irradiation in Rats

A Thesis Submitted to the Ph.D. Degree

(Biochemistry)

By

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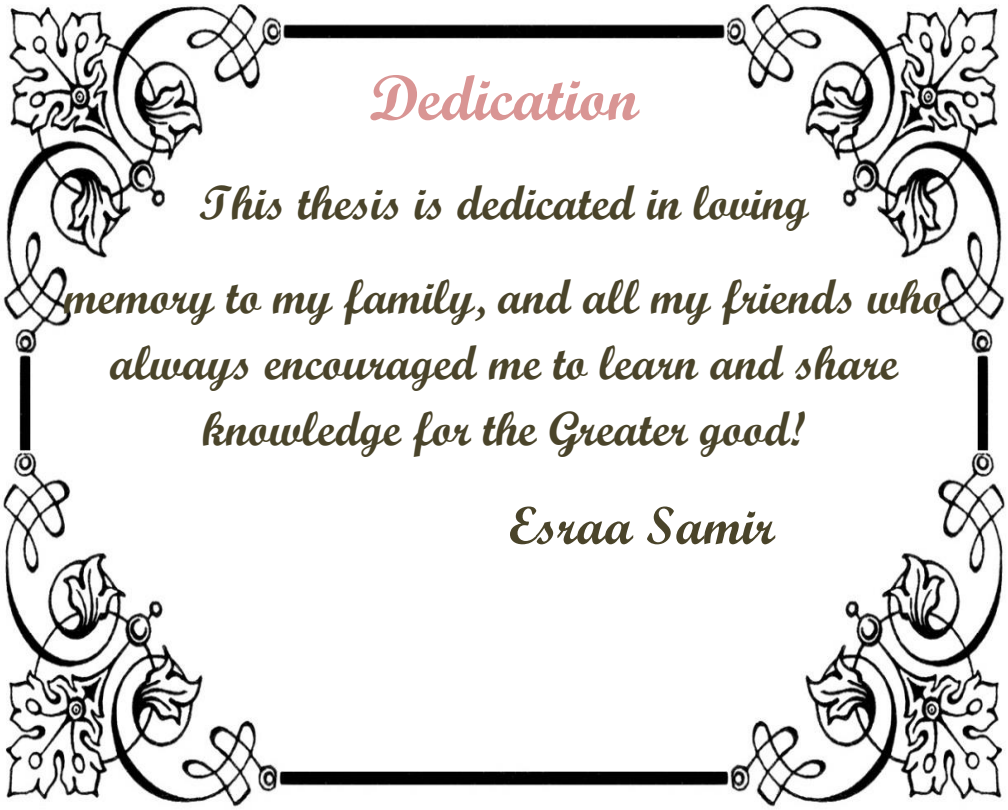
Declaration

I declare that this thesis is the product of my own work and effort and it has not been submitted before for any degree or examination in any other university.

Esraa Samir


Dedication
This thesis is dedicated in loving
memory to my family, and all my friends who
always encouraged me to learn and share
knowledge for the Greater good!
Esraa Samir

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Contents

Abstract

Mesenchymal stem cells (MSCs) are a promising source for cell therapy in regenerative medicine. Accordingly, the aim of the present study is to evaluate the potential effect of MSCs transplantation against leukemogenesis in rats. This aim was achieved by measuring inflammatory indices, chemokine, apoptotic markers and signaling growth factors.

The obtained results showed that MSCs transplantation enhance hematological parameters, alleviat bone marrow oxidative markers and inflammatory indices (TGF-β and IL-6). Additionally, MSCs transplantation increased the homing efficacy of hematopoietic stem cells to bone marrow throughout upregulation of CXCR-4 expression. Moreover, treatment with MSCs, modulate apoptosis/proliferation of bone marrow cells, the growth factors and signaling pathway that encounters bone marrow damage.

In conclusion, the obtained results provide evidence for the beneficial of BM-MSCs transplantation as effective candidate for treatment of leukemia throughout repair bone marrow damage, alleviate inflammation and modulate apoptosis and PI3K /AKT signaling pathway contributed to leukemogenesis.

List of Abbreviations

Abbreviation	Description
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AO/ PI	Acridine orange/ propidium iodide
AST	Aspartate aminotransferase
A-T	Adenine- thiamine
BAX	Bcl-2 associated x- protein
Bcl-2	B cell lymphoma-2 protein
CBC	Complete blood count
CCl_4	Carbon tetra cholorid
CD	Cluster of differentiation
cDNA	Complementary Deoxyribonucleic acid
CLL	Chronic lymphoblastic leukemia
CML	Chronic myeloid leukemia
Conc.	Concentration
Ct	Cycle threshold
CXCR-4	C-X-C motif chemokine receptor-4
DEPC	Di ethyl pyrocarbonate
DMBA	7,12-Dimethyl Benz[a] Anthracene
DMBA-DE	DMBA-3,4 di-hydro diol 1,2 epoxide

DMEM	Dulbecco's Modified Eagle's Medium
DMSO	diemthylsulfoxide
DNA	Deoxyribonucleic acid
dNTP	Deoxyuncleuotide triphosphate
DSBs	Double strand breaks
EDTA	Ethylene diamine tetraacetic acid
EGF	Epithelial growth factor
EGFR	Epidermal growth factor receptor
ERK/MAPK	Extracellular signal-regulated kinases
FAP	Familial adenomatous polyposis
FITC	Fluorescein isothiocyanate
G-C	Guanine –cytosine
GSH	Glutathione
GVHD	Graft versus host disease
Gy	Gray
H_2O_2	Hydrogen peroxide
HIF-1α	Hypoxia-inducible factor-1α
7.HMBA	7-sulfo-oxymethyl-12-methylbenz[a]anthracene
HRP	Horse radish peroxidase
HSCs	Hematopoietic stem cells
HT-29	A human colon cancer cell line
IL-6	Interleukine-6
KRAS	Kirsten rat sarcoma viral oncogene homolog

LIF	Leukemia inhibitory factor
LSC	Leukemic stem cell
LT-HSCs	Long term hematopoietic stem cells
MAPK	Mitogen-activated protein kinase
MDA	Malonodialdehyde
MDS	Myelodysplasia
mEH	Microsomal epoxide hydrolase
mM	Milli molar
MML-vRT	Moloney murine leukemia virus reverse transcriptase
MMPs	Matrix metalloproteinases (MMPs)
MPPs	Multi potent progenitors
MSCs	Mesenchymal stem cells
mSv	Milli sievert
mTOR	Mammalian target of rapamycin
NaCl	Sodium chloride
NFκB	Nuclear factor kappa B
NK	Natural killer cells
$O2^{\bullet-}$	Superoxide
$^1O_2$	Singlet oxygen
$^{\bullet}OH$	Hydroxyl radical
p53	Tumor suppressor gene
PAGE	Polyacrylamide gel electrophoresis

PAHs	Polycyclic aromatic hydrocarbons
PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
PDGF	Platelet derived growth factor
PE	phycoerythrin
PI3K	Phosphoinositide 3-kinase (PI 3-kinase), phosphatidylinositol 3-kinase
PKC	Protein kinase C
PTEN	Phosphatase and tensin homologue deleted on chromosome ten
PVDF	Polyvinylidene difluoride membrane
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rpm	Revolutions per minute
SDF-1	Stromal derived factor-1
SDS	Sodium dodecyle sulfate
SOD	Superoxide dismutase
Sv	sievert
SV	Spin or vacum
TBARS	Thiobarbituric acid reactive substance
TGF-β	Transforming growth factor- β
TMB	Tetra methyl benzidine
VEGF	Vascular endothelial growth factor

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