

Effect of Naïve Versus Hepatogenic Partially Differentiated Mesenchymal Stem Cells on The Hepatic and Cognitive Functions in Thioacetamide Induced Liver Cirrhosis in Male Rats

Thesis

Submitted in partial fulfillment of MD Degree

in

Physiology

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2016

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿ مَنْ عَمِلَ صَالِحًا مِنْ ذَكَرٍ أَوْ أَنْتَهَىٰ وَهُوَ مُؤْمِنٌ فَلَنُحْيِيَنَّهٗ
حَيَاةً طَيِّبَةً وَلَنَجْزِيَنَّهُمْ أَجْرَهُمْ بِأَحْسَنِ مَا كَانُوا يَعْمَلُونَ ﴾

صدق الله العظيم

(النحل: آية ٩٧)

اهداء

الى والدي الحبيب... بين يدي الله

الى والدي الحبيبة... حفظها الله

Acknowledgement

*First of all, thanks to **ALLAH**, the most merciful, who gave me the power and patience throughout my work. May the peace and blessing be upon our prophet Muhammad, our guide and the greatest teacher.*

*I had the honor and I feel really blessed to accomplish my work under the supervision of **Prof. Dr. Maha Muhammad Gamal Eldeen**, Professor of Physiology and Head of Physiology Department, Faculty of Medicine, Cairo University. I'm really indebted to her for her unlimited support, kind encouragement, valuable enrichment of this work and meticulous supervision.*

*No words can express my deep appreciation to my sincere friend and dear colleague **Dr. Shaimaa Nasr Amin**, Lecturer of Medical Physiology, Faculty of Medicine, Cairo University, for her valuable help, tremendous support and faithful guidance throughout this study.*

*I would like to express my deep thanks to **Prof. Dr. Laila Ahmed Rashed**, Professor of Medical Biochemistry, Faculty of Medicine, Cairo University, for expert guidance, precious advice and appreciable help in the practical part of this work.*

*Special thanks for **Dr. Reham Shehab Elnemr**, Researcher at Pathology Department, National Research Center, for her continuous help and great effort in performing the histopathological work of this study.*

Finally, I wish to express my deep thanks and gratitude to my respectable professors, dear colleagues and all members of Physiology Department, Faculty of Medicine, Cairo University, for their kind support and insightful suggestions.

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List of Abbreviations

α –SMA	: α smooth muscle actin
Ach	: acetylcholine
AChE	: acetylcholinesterase
AFP	: alpha fetoprotein
ALT	: alanine aminotransferase
AMPA	: α -amino-3-hydroxy-5-methyl 4-isoxazolepropionic acid
AST	: aspartate aminotransferase
Bax	: Bcl-2-associated x protein
BBB	: blood–brain barrier
Bcl2	: B-cell lymphoma 2
Bcl-xl	: B-cell lymphoma-extra large
BDL	: bile duct-ligated
BG	: basal ganglia
BMSCs	: bone marrow derived stem cells
BSA	: bovine serum albumin
CA	: cornu ammonis
CA-MMP	: cysteine array matrix metalloproteinase
cAMP	: cyclic adenosine monophosphate
CCl ₄	: carbon tetra-chloride
CD	: cluster of differentiation
cDNA	: complementary deoxyribonucleic acid
CHE	: chronic hepatic encephalopathy
CK	: cyto-keratin
CNS	: central nervous system
Cpu	: caudate–putamen
CR	: competitive reaction
C _T	: cycle threshold
CYP450	: cytochrome P450
D1 receptors	: dopamine type 1 receptors

DA	: dopamin
DCs	: dendritic cells
DEPC	: diethyl pyrocarbonate
DG	: dentate gyrus
DMN	: dimethyl nitrosamine
DNA	: deoxyriboNucleic Acid
dNTPs	: deoxynucleotide triphosphate
DP	: direct pathway
EAAC-1	: excitatory amino acid carrier
EB	: embryoid bodies
EC	: entorhinal cortex
ECM	: extracellular matrix
EGF	: epithelial growth factor
ELISA	: enzyme-linked immunosorbent assay
EMT	: epithelial-to-mesenchymal transition
ESCs	: embryonic stem cells
FGF	: fibroblast growth factor
FITC	fluorescein isothiocyanate
FLIP	: FLICE-like inhibitory protein
GABA	: gamma amino butyric acid
GAPDH	: glyceraldehyde 3-phosphate dehydrogenase
GDH	: glutamate dehydrogenase
GFAP	: glial fibrillary acidic protein
GFP	: green fluorescent protein
Gln	: glutamine
GLT	: glutamate transporter
GLUT	: glucose transporter
GPI	: glycosyl phosphatidyl inositol
GS	: glutamine synthase
H&E	: hematoxylin and eosin
hBMMSCs	: human bone-marrow MSCs
HD cells	: head-direction cells

HE	: hepatic encephalopathy
HGF	: hepatocyte growth factor
HLA	: histocompatibility locus antigen
HMGB-1	: high mobility group box-1
HPRI	: Human Placental Ribonuclease Inhibitor
HPX	: hemopexin
HSCs	: hepatic stellate cells
HSCs	: hematopoietic stem cells
IDO	: indoleamine 2,3-dioxygenase
IFN- γ	: Interferon-gamma
IL	: interleukin
IP	: indirect pathway
iPSCs	: induced pluripotent stem cells
KCs	: Kupffer cells
KGA	: α -ketoglutaric acid
KO mice	: knockout mice
LAP	: latency-associated peptide
LDH	: lactate dehydrogenase
LGP	: lateral globus pallidus
LTBP	: latent TGF- β binding protein
LTP	: long term potentiation
MAO	: monoamine oxidase
MAPK	: mitogen-activated protein kinase
MFs	: myofibroblasts
mGluR1	: metabotropic glutamate receptor 1
MGP	: medial globus pallidus
MHC	: major histocompatibility complex
miRNAs	: micro ribonucleic acids
MMLV	: moloney murine leukemia virus
MMP	: matrix metalloproteinase
MPT	: mitochondrial permeability transition
MSCs	: mesenchymal stem cells

MT	: masson trichrome
MT-MMPs	: membrane type matrix metalloproteinases
MWM	: Morris water maze
Nac	: nucleus accumbans
NADPH	: nicotinamide adenosine dinucleotide phosphate
NAFLD	: nonalcoholic fatty liver disease
NAPBI	: N-acetyl-p-benzoquinone imine
NF- κ B	: nuclear factor kappa B
NGF	: nerve growth factor
NKCs	: natural killer cells
NMDA	: N-methyl D-aspartate
NOS	: nitric oxide synthase
NOX	: NADPH oxidase
NR	: NMDA receptor subunit
NS	: neurosteroids
NT	: neurotransmitter
OD	: optical density
ONS	: oxidative nitrosative stress
ONS	: oxygen nitrogen species
PAG	: phosphate-activated glutaminase
PBS	: phosphate buffer saline
P-C	: porto-central
PCA	: porto-caval anastomosis
PCR	: polymerase chain reaction
PCS	: porto-caval shunt
PD	: programmed death
PDGF	: platelet derived growth factor
PD-L	: programmed death ligand
PER	: perirhinal cortex
PFC	: prefrontal cortex
PMC	: pre-motor cortex
POR	: postrhinal cortex

P-P	: portal to portal
PSD	: post-synaptic density
PTBR	: peripheral-type benzodiazepines receptors
PTP	: permeability transition pore
qRT-PCR	: quantitative real time-polymerase chain reaction
RAM	: radial-arm maze
RNase	: ribonuclease
RNS	: reactive nitrogen species
RONs	: reactive oxygen and nitrogen species
ROS	: reactive oxygen species
RQ	: relative quantification
SAP	: synapse-associated protein
SCF	: stem cell factor
SCNT	: somatic cell nuclear transfer
SDF	: stromal cell-derived factor
SNr	: substantia nigra pars reticulata
TAA	: thioacetamide
TASO	: thioacetamide sulfoxide
TASO ₂	: thioacetamide -S-dioxide
TGF- β 1	: transforming growth factor-beta1
THBS	: thrombospondin
TIMP	: tissue inhibitor of matrix metalloproteinase
TNF- α	: tumor necrosis factor- α
TSP-1	: thrombospondin-1
T β R	: TGF- β receptor
VEGF	: vascular endothelial growth factor
VMt	: ventro-medial thalamus

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Introduction

Liver cirrhosis represents the final pathologic outcome for the majority of chronic liver diseases (*Salama et al., 2014*). It is a term which describes the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury caused by multiple factors like; hepatitis B, hepatitis C, alcoholic liver disease, hepatotoxic drugs and toxins (*Huang et al., 2013*).

Due to the functional overcapacity of liver, fibrosis and even cirrhosis are frequently asymptomatic until it is complicated by a life threatening event such as variceal hemorrhage, spontaneous bacterial peritonitis and hepatic encephalopathy (*Schuppan & Afdhal, 2008*).

Despite of the improvements in management of liver cirrhosis, the overall outcome of the disease remains poor (*Bai et al., 2014*). Current treatment for liver cirrhosis is to prevent further damage of the functional hepatocytes as well as liver transplantation. Although a great advance in liver transplantation has took place, still it has several limitations, including lack of donors, surgical complications, immunological suppression and high medical cost (*Singal et al., 2011*). Alternative therapeutic approaches through stem cells may become other options (*Chang et al., 2009*).

Stem cells are undifferentiated highly specialized cells having capacity to renew itself and are capable of dividing for long period of time to grow different cell types (*Ding et al., 2011*). Stem cells are either isolated from natural sources or bioengineered from adult somatic cells through “therapeutic cloning” or “nuclear reprogramming” (*Nelson et al., 2009*).

Among the different types of stem cells, mesenchymal stem cells (MSCs) in particular have been thought as a promising source of stem cells in regenerative medicine (*Shetty et al., 2015*) because of their high capability for self-renewal and differentiation without ethical or tumorigenic problems (*Jang et al., 2013*). MSCs are non-hematopoietic multipotent stem cells that are capable of differentiating into both mesenchymal and non-mesenchymal lineages (*Shetty et al., 2015*).