

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

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By

Dalia Azmy Mahmoud Elberry

Assistant lecturer of Physiology

Faculty of Medicine – Cairo University

Under supervision of

Prof. Dr. Maha Mohamed Gamal El-Din

Professor of Physiology

Head of Physiology Department

Faculty of Medicine – Cairo University

Dr. Shaimaa Nasr Amin

Lecturer of Physiology

Faculty of Medicine – Cairo University

Prof. Dr. Laila Ahmad Rashed

Professor of Biochemistry

Faculty of Medicine – Cairo University

Dr. Reham Shehab Elnemr Ismael

Researcher of Pathology

National Research Center

Faculty of Medicine - Cairo University

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿ مَنْ عَمِلَ صَالِحًا مِنْ ذَكَرٍ أَوْ أَنْتَهَىٰ وَهُوَ مُؤْمِنٌ فَلَنُجْزِيَنَّهُ
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

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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*).