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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بسم الله الرحمن الرحيم

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

صدق الله العظيم

(النحل: آية ٩٧)

اهداء

الى والدي الحبيب...بين يدي الله

الى والدتي الحبيبة...حفظها الله

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Contents

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-ɣ	:	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 lives disease
NAPBI	:	N-acetyl-p-benzoquinone imine
NF-κB	:	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
TASO2	:	thioacetamide -S-dioxide
TGF-β1	:	transforming growth factor-beta1
THBS	:	thrombospondin
TIMP	:	tissue inhibitor of matrix metalloproteinase
TNF-α	:	tumor necrosis factor-α
TSP-1	:	thrombospondin-1
TβR	:	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).***