UNIVERSITI PUTRA MALAYSIA

CHARACTERISATION OF ERYTHROPOIETIN GENE-MODIFIED HUMAN MESENCHYMAL STEM CELLS AND ANTI-APOPTOTIC EFFECT OF GLUTAMATE EXCITOTOXICITY IN A RETINAL NEURON CELL LINE

SHIRLEY DING SUET LEE

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By

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June 2017

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Retinal degeneration is a prominent feature in ocular disorders. In exploring possible treatments, Mesenchymal Stem Cells (MSCs) have been recognised to yield therapeutic role for retinal degenerative diseases. Studies have also shown that erythropoietin (EPO) administration into degenerative retina models confers significant neuroprotective actions in limiting pathological cell death. For this reason, introducing anti-apoptotic proteins, such as erythropoietin (EPO), may exhibit a superior effect in enhancing beneficial activity of MSCs and hence, the treatment in retinal degenerative disorders. The objective of this study was to characterise *EPO* gene-modified human MSCs and evaluate its anti-apoptotic effect of glutamate excitotoxicity in a retinal neuron cell line. MSCs derived from the human Wharton's jelly of umbilical cord were cultured, expanded, and characterised for immunophenotypical expression of MSC surface markers and multipotency differentiation potentials. Following that, MSCs were genetically modified to carry EPO through lentiviral transduction. The cells were transduced with lentivirus particles encoding *EPO* and green fluorescent protein (*GFP*), as a reporter gene. The cultured MSCs displayed plastic adherence properties and formed spindle-shaped cells that resembled a fibroblast. MSC immunophenotyping revealed high expression of CD90, CD73 (SH3), CD105 (SH2), CD29, and HLA-ABC but lack of expression for CD34, CD14, CD45, CD80, and CD86. Furthermore, MSCs were capable to undergo bilineage mesenchymal differentiation into adipocytes and osteocytes. EPO-expressing MSCs (MSC-EPO) also demonstrated a greater capacity to promote cell differentiation into nestin-expressing neurospheres when compared to non-transduced cells. The supernatants of the transduced and non-transduced cells were collected and used as a pre-conditioning medium for Y79 retinoblastoma cells (retinal neuron cell line), following exposure to glutamate treatment to induce apoptosis. Cellular recovery of human retinoblastoma (Y79) subjected to glutamate at a toxic dose was assessed following incubation with supernatants harvested from *EPO*-

transduced MSCs. Retinal cells exposed to glutamate showed enhanced improvement in cell viability and reduced mitochondrial depolarization when incubated with the pre-conditioned medium collected from *EPO*-transduced cells. The outcome of this study established a proof-of-concept that MSCs could be used as a candidate for the delivery of *EPO* therapeutic gene in the treatment of retinal degenerations and that generated MSC-EPO can further differentiate into neural lineage that may serve as an alternative for cell replacement therapy for degenerating retinal neurons.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KARAKTERISASI GEN ERITROPOIETIN SEL STEM MESENKIMA MANUSIA DAN KESAN ANTI-APOPTOSIS EXCITOTOXICITY GLUTAMATE DALAM SEL NEURON RETINA

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Degenerasi retina adalah unsur yang utama dalam gangguan okular. Dalam usaha mencari penawarnya, sel-sel stem mesenkima (MSCs) telah pun diiktiraf peranan terapeutiknya dalam merawati penyakit-penyakit degeneratif retina. Kajian juga telah menunjukkan bahawa pemasukan Eritropoietin (EPO) ke dalam retina telah memberikan sifat-sifat pelindungan saraf yang signifikan dengan menghadkan kematian sel secara patologi. Bagi tujuan ini, penggunaan protien anti apoptotik seperti EPO boleh memberi kesan yang unggul dalam mempertingkatkan aktiviti bermanfaat MSCs dan digunakan sebagai rawatan bagi penyakit-penyakit degeneratif retina. Objektif kajian ini adalah untuk mencirikan ubahsuaian gen EPO MSCs manusia dan menilai kesan anti apoptotik eksitotoksisiti glutamat dalam titisan sel neuron retina. Dalam kajian ini, gen MSCs telah diubahsuai untuk merembeskan protein EPO dengan menggunakan transduksi lentivirus dan media pra-penyesuaian yang diterbitkan daripada MSCs mengekspresi EPO yang mana ia telah dikulturkan dengan retinoblastoma manusia (Y79) yang diaruhi glutamat, model in vitro. Secara ringkasnya, MSCs yang diperolehi daripada lendir Wharton pada tali pusat manusia, telah dikulturkan, dikembangkan dan dicirikan untuk ekspresi immunofenotipikal pada penanda permukaan MSCs dan juga untuk multipotensi keupayaan pembezaan MSCs. Berikutan itu, MSCs telah digunakan untuk pemasukan EPO melalui transduksi lentivirus. Sel ditranduksi dengan partikel lentivirus yang dikodkan dengan EPO dan protein fluoresen hijau (GFP), iaitu gen pelapor. Supernatan bagi sel-sel yang ditransduksi dan yang tidak ditransduksi dikumpulkan dan digunakan sebagai medium pra-penyesuaian untuk sel Y79 retinoblastoma (titisan sel neuron retina) dan diikuti dengan rawatan glutamat. Pemulihan sel Y79 retinoblastoma manusia tertakluk kepada glutamat pada dos toksik dinilai berikutan inkubasi (eraman) dengan supernatan yang diperolehi daripada MSCs yang ditransduksi EPO. Oleh itu, kajian ini bersasarkan untuk mengukur keupayaan sel-sel mengekspresi EPO membeza kepada nasabah

neural dengan mengkulturkan sel-sel tersebut dalam koktel pembezaan neural. Sel-sel retina yang dirawati glutamat menunjukkan peningkatan kebolehhidupan sel dan mengurangkan depolarisasi mitokondria apabila diinkubasi dengan medium pra-penyesuaian yang dikumpul daripada sel-sel ditransduksi EPO. Di samping itu, MSCs mengekspresi EPO (MSC-EPO) menunjukkan kapasiti yang lebih besar dalam menggalakkan pembezaan sel kepada neurosfera mengekspresi nestin berbanding dengan sel-sel tidak ditransduksi. Hasil kajian ini menubuhkan suatu konsep kebuktian yang MSCs boleh digunakan untuk penghantaran gen terapeutik EPO dalam rawatan degenerasi retina dan MSC-EPO yang dijanakan, selanjutnya dapat membeza kepada nasabah neural, dan juga menjadi alternatif untuk terapi penggantian sel bagi neuron retina yang merosot.

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LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
MSCs	Mesenchymal stem cells
EPO	Erythropoietin
Y79	Human retinoblastoma
ELISA	Enzyme-linked immunosorbent assay
ONL	Outer nuclear layer
RPE	Retinal pigment epithelium
OPL	Outer plexiform layer
INL	Inner nuclear layer
IPL	Inner plexiform layer
RGC	Retinal ganglion cell
FDA	Food and drug administration
VEGF	Vascular endothelial growth factor
APTC	Anti-platelet trialists' collaboration
ESCs	Embryonic Stem Cells
NCT	National clinical trial
iPSC	Induced pluripotent stem cell
Oct3/4	Octamer-binding protein 3/4
SOX2	SRY-box
Klf4	Krüppel-like factor 4
NK	Natural killer
CD	Cluster of differentiation
NA	Not available
HLA-II	Human leukocyte antigen class II
ISCT	International society for cellular therapies
NeuroD-1	Neurogenic differentiation 1
TUBβ4	Tubulin-beta 4
MAP2	Microtubule-associated protein 2
GAP-43	Growth-associated protein 43
Wnt	Wingless-type MMTV (mouse mammary tumour virus) integration site
Dkk-1	Dickkopf Wnt signalling pathway inhibitor 1
NOG	Noggin
IGF1	Insulin-like growth factor 1
bFGF	Basic fibroblast growth factor
miRNA-203	microRNA-203
OPN1MW	Opsin 1 medium wave
NR2E3	Nuclear receptor subfamily 2, group E, member 3
Nrl	Neural retina leucine zipper
miRNA-410	microRNA-410
MITF	Microphthalmia-associated transcription factor
LRAT	Lecithin retinol acyltransferase
RPE65	Retinal pigment epithelium 65
EMMPRIN	Extracellular matrix metalloprotease inducer
MUSE	Multilineage-differentiating stress-enduring

SSEA-3	Stage-specific embryonic antigen-3
TRA-1-60	Tumour resistance antigen 1-60
Nanog	Nanog homeobox
α-MEM	Alpha minimal essential medium
FBS	Foetal bovine serum
EGF	Epidermal growth factor
N_2	Nitrogen
DMEM/F12	Dulbecco's modified eagle medium/nutrient mixture
Shh	Sonic hedgehog
RA	Retinoic acid
β-ME	Beta-mercaptoethanol
HPL	Human platelet lysate
HIF–1α	Hypoxia-inducible factor-1 alpha
CNTF	Ciliary neurotrophic factor
BDNF	Brain-derived neurotrophic factor
TNF–α	Tumour necrosis factor-alpha
IL–1β	Interleukin-1 beta
PGE2R	Prostaglandin E2 receptor
NGF	Nerve growth factor
GDNF	Glial cell line-derived neurotrophic factor
MCP-1	Monocyte chemotactic protein-1
α-SMA	Alpha-smooth muscle actin
ICAM-1	Intercellular adhesion molecule-1
PDL	Programmed death-ligand
CTLA	Cytotoxic T-lymphocyte antigen
BRB	Blood-retina barrier
MMPs	Matrix metalloproteinases
IRBP	Interphotoreceptor retinoid–binding protein
IFN-γ	Interferon gamma
T_h1	T helper type 1
TGF-β	Transforming growth factor-beta
EAU	Experimental autoimmune uveitis
FOXP3	Forkhead box P3
IL-1RA	IL-1 receptor antagonist
TLRs	Toll-like receptors
TSP-1	Thrombospondin type-1
SDF-1	Stromal cell-derived factor 1
PAI-1	Plasminogen activator inhibitor 1
LTβP-1	Latent transforming growth factor β binding protein type 1
SHP-1	Sarcoma homology region 2 domain-containing phosphatase-1
iNOS	Inducible nitric oxide synthase
NT-4	Neurotrophin-4
Bcl-2	B cell lymphoma-2
BIRC	Baculovirus inhibitor-of-apoptosis repeat containing
MAPK	Mitogen-activated protein kinase
TrkB	Tropomyosin receptor kinase B
IL-1RA	IL-1 receptor antagonist
IOP	Intraocular pressure

MOG	Myelin oligodendrocyte glycoprotein
rds	Retinal degeneration slow
MIDGE	Minimalistic, immunologically defined gene expression
Pax6	Paired box protein 6
Atoh	Atonal bHLH transcription factor 7
Brn3b	Brain-specific transcription factor 3b
LPD	Liposome-protamine-DNA complex
BFU-E	Erythroid progenitor cells
CFU-E	Proerythroblasts
RBC	Red blood cell
EPOR	EPO receptor
STAT	Signal transducer activator-of-transcription
Bax	Bcl-2-associated X
Jak2	Janus kinase-2
NF-kB	Nuclear factor-kappa light chain enhancer-of-activated B cells
PI3-K	Phosphatidylinositol-3-kinase
IKK	I-kB kinase
GP130	Glycoprotein 130
SOD	Superoxide dismutase
IAP	Inhibitors of apoptosis
βcR	Interleukin beta-common receptor
GSK	Glycogen synthase kinase
Lef1	Lymphoid enhancer-binding factor 1
Tcf	T-cell factor
EPC	Endothelial progenitor cell
PHD	Prolyl hydroxylase domain
VEGFR	VEGF receptor
NO	Nitric oxide
eNOS	Endothelial nitric oxide synthase
MSC-EPO	EPO-expressing MSCs
E. coli	Escherichia coli
$MgCl_2$	Magnesium chloride
$CaCl_2$	Calcium chloride
GFP	Green fluorescent protein
HIV	Human immunodeficiency virus
CMV	Cytomegalovirus
LTR	Long terminal repeat
RSV	Rous sarcoma virus
PCR	Polymerase chain reaction
MTS	3-(4,5-dimethythiazol-2yl)-5-(3-carboxymethoxyphenyl)-2-(4-sufophenyl)-2H-tetrazolium
IC_{50}	Inhibitory concentration
JC-1	5,5′,6,6-tetrachloro-1,1,3,3-tetraethylbenzimidazolylcarbocyanine iodide
GMEM	Glasgow Minimum Essential medium
NEAA	Non-essential amino acids
ANOVA	One-way analysis of variance
FSC	Forward scatter

SSC	Side scatter
CM	Conditioned medium
S.E.M	Standard error of the mean
Crx	Cone-rod homeobox
Rxrγ	Retinoid X receptor-gamma
Thβ2R	Thyroid hormone β2 receptor isoform
EAAT	Excitatory amino acid transporter
GM-CSF	Granulocyte macrophage colony-stimulating factor
EtBr	Ethidium bromide
BSA	Bovine serum albumin
PBS	Phosphate-buffered saline
mM	Millimolar

CHAPTER 1

INTRODUCTION

1.1 Background

Ocular disorder is a universal health condition affecting either the anterior or posterior lining of the eye [1]. Over the years, expanding efforts have been carried out globally by the World Health Organization (WHO) to minimize visual impairment or blindness [1]. Treatment to reduce pathological condition affecting the posterior eye (majority in the retina) deserves greater attention due to the limited accessibility to treatment [1,2].

Retinal degeneration is a structural defect acquired in both inherited and sporadic ocular disorders, such as Age-related Macular Degeneration (AMD) and retinitis pigmentosa [3–7]. Loss of retinal neurons could lead to either fractional or massive loss of visual acuity. To date, there is no clinically translatable antidote for blindness. Existing conventional treatments such as surgical intervention or drug treatments [8–10], are only indicated for patients with early diagnoses to prevent aggravation of the disorder [11].

The idea of using stem or precursor cells has emerged in the last decade as a leading approach for a regenerative strategy to address ocular disease [11,12]. In this context, mesenchymal stem cells (MSCs) are lead candidates for cellular therapy not only for ocular disease [13], but multiple diseases characterized by fibrosis [14,15]. MSC is a type of adult stem cell which is capable of differentiating into multiple functional cell phenotypes, such as bone, cartilage, fat cells, and others [16,17]. Umbilical cord Wharton's jelly-, amniotic fluid-, and adipose- derived MSCs are easily isolated [18–22], expanded, and immunologically tolerated, allowing for allogeneic, off-the-shelf transplantation.

The use of multipotent MSCs have been reported as promising for the treatment of numerous degenerative disorders in the brain, spinal cord, and kidney [23–27]. In retinal degenerative diseases, MSCs exhibit the potential to regenerate into retinal neurons and retinal pigment epithelium in both *in vitro* and *in vivo* studies [28–37]. Delivery of stem cells was found to improve retinal morphology and function, and delay retinal degeneration [20,29,32,34,38,39]. It is possible that MSCs may secrete restorative extracellular trophic factors that encourage endogenous cellular recovery and replenishment [40–42]. Accumulating evidence shows that treatment to reverse degeneration using MSCs are feasible.

Furthermore, the ability to use pre-prepared allogeneic cells for cell-based therapy allows for a level of quality control and scalability that far exceeds autologous strategies. Study by Sun et al [43] reported that MSCs grafted in rd1 mice could intervene photoreceptor cell apoptosis under the influenced of MSC secretion of pigment epithelium-derived factor (PEDF), otherwise, MSCs was reported to relieve intraocular pressure and enhance progenitor cell proliferation when transplanted on rat model of ocular hypertension [44]. Likewise, culturing of MSCs with conditioning medium derived from RPE cultures successfully generated photoreceptor-like cells after 7 days, with 28.87% positive shift [45]. In accordance, existing clinical treatments with MSCs had successfully warranted its therapeutic use in age-related macular degeneration (ID: NCT02016508; https://www.clinicaltrials.gov), glaucoma (ID: NCT01920867), and retinitis pigmentosa (ID: NCT01560715).

1.2 Problem Statement

Notwithstanding the therapeutic potentials of MSCs, several issues have been raised in current conventional approach, whereby cells administered in aqueous medium generally resulted in poor transplanted cell survivability in the pathological microenvironment [46,47]. Direct MSC transplantation also yield unspecific dispersion of cells at the site of injection that could be attributed to indirect hampering of MSC therapeutic outcome [24]. Moreover, several conditions such as oxidative stress, inflammation or ischemia have been shown to be associated with poor transplanted MSC survival rate [48,49].

Substantial advances in our understanding of MSCs regulatory machinery and their beneficial secretory proteins have paved the way for further development that intersects with genome engineering to maximize MSCs therapeutic insight for stem cell replacement therapy [4,20,39,50–57]. For clinical translation of stem cell therapy in ocular degenerative disorders, integration of tissue engineering approaches may overcome limitations associated with low transplanted cell survivability and cell dispersion, and further encourage a targeted delivery system in transplanted MSCs [24,46,47].

Hence, introducing anti-apoptotic proteins, such as erythropoietin (EPO), may thus aid in enhancing both MSCs survivability and engraftment [58–60], leading to improvement in the treatment outcomes of retinal degenerative disorders. Erythropoietin (EPO) is an essential glycoprotein hormone mainly responsible for the development of red blood cells or erythropoiesis, in the human body [61]. Recently, studies have shown that EPO proteins and its receptors are present in various extra-hematopoietic tissues including retina tissue [62,63]. Earlier literature has reviewed on the clinical significance of EPO in the management of ocular disorders through its anti-apoptotic, anti-inflammatory, anti-oxidative, and neuroregenerative properties [32,60,64–68].

1.3 Research Objectives

1.3.1 General Objective

To determine the anti-apoptotic effect of EPO-expressing MSC in a glutamate-induced excitotoxicity retinal cell line.

1.3.2 Specific objectives

i. To establish and characterise MSCs from human Wharton's jelly.
ii. To construct viral particles carrying *EPO* and *GFP* genes.
iii. To establish and characterise EPO-expressing MSC.
iv. To determine the effect of MSC-EPO conditioned media on survival of excitotoxicity-induced Y79 retinal cell line.
v. To examine *in vitro* differentiation potential of MSC-EPO into neurospheres.

1.4 Hypothesis

The hypotheses of this study are the following:

1. MSC-EPO conditioned media will enhance survival of excitotoxicity-induced Y79 retinal cell line.
2. EPO-expressing MSC will promote *in vitro* differentiation potential of MSCs into neurospheres.

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