UNIVERSITI PUTRA MALAYSIA

EXPLORING THE POTENTIAL OF HUMAN DENTAL PULP STEM CELLS FOR TREATMENT OF RETINAL DEGENERATION IN SPRAGUE DAWLEYRAT MODEL

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By

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EXPLORING THE POTENTIAL OF HUMAN DENTAL PULP STEM CELLS FOR TREATMENT OF RETINAL DEGENERATION IN SPRAGUE DAWLEY RAT MODEL

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Chairman : Suresh Kumar Subbiah, PhD
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Blindness and vision impairment are caused by irremediable retinal degeneration in affected individuals worldwide. Cell therapy for a retinal replacement has the potential to rescue their vision, specifically for those who lost most or all the light sensing photoreceptors in the eye. As such, well-characterized retinal cells are required for the replacement purposes. Stem cell-based therapy has been well received for retinal pigment epithelium and photoreceptor transplantation in the eye, however, the drawbacks of retinal transplantation is the limited clinical protocols development, insufficient number of transplanted cells for recovery, the selection of potential stem cell sources that can be differentiated into the target cells, and the ability of cells to migrate into the host tissue. Dental pulp stem cells (DPSC), a type of mesenchymal stem cells, are recently being studied due to its high capability of differentiating into cells of the neuronal lineage. Therefore, the main objective of the current study is to assess the potential of dental pulp stem cells therapy for ocular disorder in the Sprague-Dawley rat eye model. hDPSCs were cultured expanded and assessed for their mesenchymal stemness *in-vitro*. About 300.000 of DPSCs were transplanted intravitreal into the right eye of the rat retina n = 3. Moreover, the function of the retina was recorded by assessing the a- and b- wave amplitudes of ERG. Structural changes and protein expression were determined through IHC staining. The findings of the current study demonstrated that the transplanted hDPSCs slowed down the retinal degeneration progression and protected retinal functions for up to 4 weeks and according to the following results, (1) the visual functions level of the treated retina with hDPSCs were comparably better than the control, (2) the b-wave amplitude was higher compared to control at day-40, (3) no formation of tumor was observed in the retinal tissue, (4) the protein expression of the RHO and RPE65 was highly observed in the treated retina compared to the control. In conclusion, my results

suggested that hDPSCs are an effective source for retinal degeneration therapy, and intravitreal injection boosts the therapeutic effect of hDPSCs.

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

MENEROKAI POTENSI SEL STEM GIGI PULPA MANUSIA UNTUK DEGENERASI RETINA KE ATAS MODEL TIKUS SPRAGUE DAWLEY

Oleh

HIBA AMER FADHIL ALSAEEDI

November 2018

Pengerusi : Suresh Kumar Subbiah, PhD
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Kehilangan serta kemerosotan penglihatan adalah disebabkan oleh degenerasi retina yang tidak dapat dielakkan pada seseorang individu di seluruh dunia. Terapi sel untuk menggantikan retina berupaya menyelamatkan penglihatan khususnya bagi mereka yang telah kehilangan sama ada hampir keseluruhan penglihatan mereka ataupun kesemua fotoreseptor deria pengcahayaan dalam mata. Oleh yang demikian, sel-sel retina yang dicirikan dengan baik amat diperlukan untuk tujuan penggantian. Terapi berasaskan sel stem telah diterima baik untuk epitelium pigmen retina dan transplantasi fotoreseptor pada mata. Namun, limitasi protokol klinikal yang sedia ada, jumlah sel yang dipindahkan untuk pemulihan yang terhad, serta kekangan bagi pemilihan sumber sel stem berpotensi yang boleh dibezakan kepada sel sasaran, dan keupayaan sel untuk berpindah ke tisu hos. Sel-sel stem pulpa gigi (DPSC), merupakan sejenis sel stem *mesenchymal* yang sedang dikaji dengan mendalam sejak kebelakangan ini kerana dipercayai ianya berupaya untuk membezakan kepada sel-sel keturunan saraf. Oleh yang demikian, tujaun utama kajian ini adalah untuk mengenalpasti potensi terapi hDPSC untuk penyakit mata dalam model tikus *Sprague Dawley*. hDPSC telah dikulturkan, diperkembangkan serta dinilai untuk sifat keupayaan *mesenchymal* dalam vitro. Sekitar 300,000 DPSC ditransplantasikan secara intravitral ke dalam mata kanan model tikus, n=3. Selain itu, fungsi retina direkodkan melalui penilaian gelombang ERG amplitud *a* dan *b.* Perubahan terhadap struktur dan ekpresi protein ditentukan melalui pewarnaan IHC. Hasil penemuan dari kajian ini menunjukkan bahawa hDPSC yang ditransplantasikan memperlahankan perkembangan degenerasi retina dan melindungi fungsi retina sehingga 4 minggu dan berdasakna keputusan yang diperolehi, (1) fungsi penglihatan dalam mata yang dirawat dengan sel stem pulpa gigi jauh lebih baik berbanding dengan kawalan, (2) gelombang amplitud *b* lebih tinggi berbanding dengan kawalan pada hari ke-40, (3) tiada pertumbuhan tumor yang diperhatikan dalam tisu retina, (4) ekspresi protein untuk RHO dan RPE65 diperhatikan lebih tinggi di dalam retina

berbanding dengan kawalan; mencadangkan bahawa sel stem pulpa gigi merupakan sumber yang berkesan untuk terapi degenerasi retina dan suntikan intravitral berupaya meningkatkan kesan teraputik sel stem pulpa gigi.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

RD	Retinal degeneration
DR	Diabetic retinopathy
AMD	Age related macular degeneration
RPE	Retinal pigment epithelium
PR	Photoreceptors
RCS	Royal college of surgeons
hDPSC	Human dental pulp stem cell
BMSC	Bone marrow stem cell
NaIO3	Sodium iodate
ONL	Outer nuclear layer
INL	Inner nuclear layer
OS	Outer segment
ATP	Adenosine triphosphate
DNA	Deoxyribonucleic acid
MHC	Histocompatibility complex
FasI	Fas ligand
CNV	Choroidal neovascularization
BrM	Bruch's membrane
BlamD	Basal laminar deposit
BlinD	Basal linear deposit
VEGF	Vascular endothelial growth factor
LCA2	Leber's congenital amaurosis
CNG	Cyclic-neucleotidegate
FDA	Food and drug administration
hESC	Human embryonic stem cells
RGC	Retinal ganglion cells
STGD	Stardgart's disease
SC	Stem cell
HSCs	Hematopoietic stem cells
MSC	Mesenchymal stem cell

G-CSF	Granulocyte colony-stimulating factor
Lin-HSCs	Lineage-negative hematopoietic stem cells
ABMC	Autologous bone marrow stem cell
PKCalpha	Protein kinase C alpha
GFAP	Glial fibrillary acidic protein
CNTF	Ciliary neurotrophic factor
bFGF	Fibroblast growth factor
BDNF	Brain-derived neurotrophic factor
iPS	Induced pluripotent stem cell
SHED	Human exfoliated stem cell
PDLSC	Periodontal ligament stem cell
DFPC	Dental follicle progenitor stem cell
SCAP	A stem cell from apical papilla
NGF	Nerve growth factor
GDNF	Glial cell derived neurotrophic factor
BMP2	Bone morphogenetic protein 2
DMSO	Dimethyl sulfoxide
DMEM-F12	Dulbecco's modified eagle's medium
PBS	Phosphate buffer saline
FBS	Fetal bovine serum
BSA	Albumin bovine serum
HBSS	Hank's balanced salt solution
SSC	Saline sodium citrate
H&E	Hematoxylin and eosin
ERG	Electroretinography
CO2	Carbon dioxide
Tdt	Terminal deoxynucleotide transferase
DAPI	4′,6-diamidino-2-phenylindole, dihydrochloride
NTF-SCs	Stem cell-derived neurotrophic factor
IP	Intraperitoneal injection
IV	Intravenous injection
IVRL	Intravitreal injection
SI	Subretinal injection

PFA	Paraformaldehyde
RT	Room temperature
ECGS	Endothelial cell growth supplement
EDTA	Ethylenediaminetetraacetic acid
Eg	Example
EGF	Epidermal growth factors
FITC	Fluorescein
IGF	Insulin-like growth factor
mRNA	Messenger ribonucleic acid
UPM	University Putra Malaysia
IHC	Immunohistochemistry
RPE65	Retinal pigment epithelium-specific 65 kDa protein
RHO	Photorodopsin
PKCa	Protein kinase alpha
UCB	Umbilical cord blood
AAV	Adeno associated virus

CHAPTER 1

INTRODUCTION

1.1 Background

Retinal degeneration (RD) is a common symptom that is seen in a series of eye diseases that can cause permanent blindness due to the deterioration of retinal photoreceptor cells (Li *et al.*, 2016). Comparatively, the retinal degenerative disorder is a group of heterogeneous diseases which affect roughly 1:3000 to 1:4000 of people worldwide (Rivolta *et al.*, 2002). Among hundreds of retinal degenerative diseases, the most critical are retinitis pigmentosa (RP) (Hartong, Berson and Dryja, 2006a), diabetic retinopathy (DR) (Pu, 2015), and age-related macular degeneration (AMD) (Mardin, 2004). Those are the riskiest types among all eye diseases because they are neither curable nor preventable will eventually cause loss of vision (Chen *et al.*, 2014).

AMD is considered as one of the major reasons of vision impairment, including blindness, especially for those aged 60 years and above (Fine *et al.*, 2000; Klein *et al.*, 2004). AMD is pathologically classified into two major types: dry AMD or non-neurovascular; and wet AMD or neurovascular (Knickelbein *et al.*, 2015). Dry AMD is the most prevalent type of macular degeneration in both genders (ie. males & females) and affects 85% of cases (Johnson, Rabinovitch and Kaeberlein, 2013).Its pathology is described by the accumulation of drusen deposits that deposits beneath the retinal pigment epithelium (RPE) within the Bruch's membrane. Whereas wet AMD is characterized by the separation of both retinal layers (RPE and choroid) which lead to an abundant flow of choroidal blood vessel beneath the macula (Johnson, Rabinovitch and Kaeberlein, 2013). Treatments for AMD like laser, drug treatment, surgery is still in use by researchers worldwide. Yet, no satisfactory treatment has been found to reverse vision loss.

RP is a part of the genetical retinal degenerative disease that can cause irreversible blindness if not treated. Initially, RP progresses when rod photoreceptors are severely impaired followed by cone impairment (Zhang, 2016). RP affects all ages and is considered as one of the major inherited forms of retinopathies with an incidence rate of 1 in 4,000 worldwide (Hartong, Berson and Dryja, 2006a; Daiger, Bowne and Sullivan, 2007). Hundred genes and above have been recently identified associated with RP, most of them are found in rod photoreceptors and retinal pigment epithelium, thus, photoreceptors (PR) and retinal pigment epithelium (RPE) are the major pathways of RP (Vithana *et al.*, 2001). For example, the pre-mRNA processing factor *(PRPF*) genes pre-mRNA processing factor-8(*PRPF8*), pre-mRNA

processing factor-3(*PRPF3*), pre-mRNA processing factor-31(*PRPF31*), and poly A polymerase-1(*PAP-1*) (McKie *et al.*, 2001; Chakarova *et al.*, 2002).

Currently, efficient treatments like ionizing radiation, laser surgery and/or drug treatment have been aimed at protecting the neural retina and preventing vision loss (Jonas *et al.*, 2006). However, the efficiencies of these treatments did not give a complete effective reduction in the progression of vision impairment (Sivan *et al.*, 2016). Therefore, there is a need for new therapeutic methods like transplantation to replace retinal apoptotic cells and restore vision. While, stem cell-based therapy has been suggested as an effective therapy for most diseases. Yet, in recent studies are still in progress to treat neural cells of the retina with stem cells (Li *et al.*, 2013).

In 2006, MacLaren clarified the capability of post-mitotic photoreceptor cells to migrate into the retinal outer nuclear layer after being transplanted into the sub-retinal area. Furthermore, his research showed that the transplanted cells could differentiate into rod photoreceptors thus creating a connection of synapses with the interneurons (MacLaren *et al.*, 2006). Subsequently, the same team have shown that these transplanted cells are also able to create a line of visual circuitry to the visual cortex and repair the impaired photoreceptor cells in a mice model (Pearson *et al.*, 2012). The results of these studies proved that the transplantation method is an effective pathway for treating retinal diseases as well as other diseases. However, the main challenge facing the medical community is to find the proper cell sources for treating retinal diseases.

New delivery systems have recently been developed for transplantation of bone marrow cells to treat choroidal neovascularization of RCS rat's eye. Where a single Epiretinal injection of stem cells was given to RCS rats, which recorded no detachment or hemorrhage in the choroid layer. This suggested that cell transplantation has the possibility to salvage vision in a rat model over 5 months (Tzameret *et al.*, 2014). In contrast, when the intravitreal injection was administered, cell clumps were found accumulated in the vitreous space and the function of the retina was restored for over than 12 weeks (Tzameret *et al.*, 2014). These results clarified that the transplantation method has significantly affected the regeneration potential of stem cells to treat a damaged eye. Therefore, by using the best administration method, determining the exact location and accuracy might help to achieve the goal of rescuing blindness.

Dental pulp stem cells (DPSCs) are specialized cells that has a different potential of a variety of cells. A study that was done in 2015 provided evidence that DPSCs can secrete neurotrophins more effectively than BM-MSC and were able to replace retinal ganglion cells of the primary adult rat retina (Mead and Scheven, 2015). However, applying dental pulp stem cells as a source for

replacing photoreceptor cells has not been studied yet. Therefore, this current study was conducted to treat both retinal layers, RPE and photoreceptors by intravitreal transplantation of dental pulp-derived mesenchymal stem cells in a Sprague Dawley rat model.

1.2 Problem statement

Retinal degeneration is the primary cause of visual impairment. RPE and photoreceptor cells are the main cause of uncurable blindness worldwide. A genetical retinal disease such as retinitis pigmentosa affects approximately 1 in 3000 of all cases, whereas Age-Related Macular Degeneration (AMD) affects 1 in 10 of people aged over 60 years (Guyer *et al.*, 1986). Patients with visual impairment suffer blurred vision with or without black spot(s) in the central part of the macula. However, the main area of the eye that could be affected is the retina, which contains ten delicate layers but the most exposed layers to risk are RPE and photoreceptors due to their principle functions in creating images by converting the light signals into electrochemical impulses and sending it to the brain for further functional processing.

Many therapeutic approaches were used to treat this type of blindness. Yet, no effective treatment could give permanent recovery. Several studies were proposed indicating that the transplantation method of different stem cell sources might give rise to retinal cells and replace the apoptotic cells in an animal model. Furthermore, due to the similarities in the anatomical and physiological features between animal and human eyes, using animal models for understanding diseases including retinal degeneration are the main tool used to explore an effective therapy for eye diseases.

The transplantation of normal RPE and photoreceptors can slow down retinal degeneration. It is usually taken from allogeneic or xenogeneic sources (Peyman *et al.*, 1991). However, the drawbacks of this treatment are limited to the source of RPE donors and low harvesting efficiency in primary culture as well as immunological rejection which may cause failure in such therapy (Yamamoto, Hiroi and Honda, 1993; ALGVERS *et al.*, 1995). Therefore, there is a need to search for an alternative source to obtain these cells. Adult stem cells have been recently proven to differentiate into several cell lineages both *in-vitro* and *in-vivo*. In this study, we will be testing the ability of stem cells taken from dental pulp to differentiate into RPE, and photoreceptor cells to regenerate damaged retina.

1.3 Objectives

1.3.1 General objective

The main aim of this study is to determine and evaluate the efficacy of dental pulp-derived mesenchymal stem cells to protect and replace apoptotic retinal cells specifically for retinal pigment epithelium and photoreceptors.

1.3.2 Specific objective

1. To assess the stemness of human dental pulp-derived mesenchymal stem cells in vitro by flow cytometric analysis.
2. To induce damage to the Sprague Dawley rat retina with intravenous injection of sodium iodate ($NaIO_3$).
3. To observe the visual capacities of a rodent's retina before and after the fact treatment with hDPSCs utilizing Electroretinography test.
4. To identify the morphology and protein expression from the treated retinal tissue with stem cells derived from dental pulp tissue and untreated Sprague Dawley rat model via immunohistochemistry method.

1.4 Hypothesis

1.4.1 Null hypothesis

1. There is no significant damage in the Sprague Dawley rat retinal function after intravenous injection of sodium iodate (NAIO3).
2. Human dental pulp stem cells are not able to express mesenchymal markers.
3. There are no obvious changes in (a) and (b) waves of electroretinography before and after human dental pulp stem cells transplantation into Sprague Dawley rat retina.
4. There are no significant changes in the structure of the rat retinal layers after human dental pulp stem cells treatment in addition to no significant result in retinal gene expression.

1.4.2 Alternative hypothesis

1. There is significant damage in the Sprague Dawley rat retinal function after intravenous injection of sodium iodate (NAIO3).

2. Human dental pulp stem cells are able to express mesenchymal markers.
3. There are obvious changes in (a) and (b) waves of electroretinography before and after human dental pulp stem cells transplantation into Sprague Dawley rat retina.
4. There are significant changes in the structure of the rat retinal layers after human dental pulp stem cells treatment in addition to significant result in retinal gene expression.

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