UNIVERSITI PUTRA MALAYSIA

POTENTIAL OF STEM CELL THERAPY DURING DENGUE INFECTION IN MICE

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Thesis Submitted to School of Graduate Studies, Universiti Putra Malaysia in Fulfillment of the Requirements for the Degree of Master of Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirements of the Degree of Master of Science

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May 2017

Chairman : Suresh Kumar Subbiah, PhD
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Dengue is one of the most common arthropod-borne infections in the world which has been the major concern to the governments and World Health Organization (WHO). The virus causes over 390 million infections annually. Individual infected with dengue virus are suffering from several clinical symptoms including leukopenia, thrombocytopenia and hemorrhagic manifestations. Stem cell based therapy has been widely used for many disorders. The advance in regenerative therapy promises the alternative therapy for infectious diseases. Researchers reported about the stem cells treatment for infections in relation to HIV, malaria and tuberculosis. The success of these reports had laid a positive path to work in current objective, to investigate the potential of stem cells and progenitor cells with the growth factor infusion in protecting and repairing the injuries in dengue infected mice. Eight week old male BALB/c mice were divided into three groups; Control group: mice injected with eagle minimum essential media (EMEM) and phosphate buffer saline (PBS); Group 1: mice infected with DV-2 (G1); Group 2: mice infected with DV-2 and treated with hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs) and growth factor (GF) (G2). Mice in G1 and G2 were inoculated with DV-2. At day 2 of post infection, mice in G2 were infused stem cells (HSCs, EPCs and GF) intraveneously. Blood was collected from all groups at 5^{th}, 10^{th}, 15^{th}, and 21^{st} d.p.i for hematological assay, biochemical assay, and sacrificed for histopathological analysis and viral clearance analysis. Dengue infection in G1 results in thrombocytopenia, leucopenia and lymphocytopenia by 21^{st} d.p.i, with low hemoglobin level and red blood cells count. Additionally, the biochemical assays (AST & ALT) increased showing significant correlation with the histopathological damages in liver. Moreover, blood vessel histopathology revealed injury correlating to the blood profile and all the damages was persistent till 21^{st} d.p.i. The DV-2 infection with stem cell treatment group (G2) exhibits protective effect in blood profile, liver, blood vessel histopathology and viral clearance with the recovery initiated from 10^{th} d.p.i. In conclusion, stem cell could be a new potential therapy not only to recover the altered

blood profile, severe organ structural injury with its protective effect, but also completely clear the viral particle in order to help in normal body functioning.

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

TERAPI SEL STEM YANG BERPOTENSI SEMASA JANGKITAN DENGGI DI TIKUS

Oleh

SAKINAH BT MAIDEENSA SYED GULAM

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Pengerusi : Suresh Kumar Subbiah, PhD
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Denggi adalah satu jangkitan bawaan artropod yang paling biasa di dunia yang menjadi kebimbangan utama kepada kerajaan dan Pertubuhan Kesihatan Sedunia (WHO). Virus ini menyebabkan lebih 390 juta jangkitan setiap tahun. Individu yang dijangkiti virus denggi mengalami beberapa gejala klinikal termasuk leukopenia, thrombocytopenia dan manifestasi berdarah. Terapi berasaskan sel stem telah digunakan secara meluas dalam pelbagai jenis penyakit. Kemajuan dalam terapi regeneratif ini menjanjikan terapi alternatif untuk penyakit berjangkit. Para penyelidik melaporkan mengenai rawatan sel stem untuk jangkitan berhubung dengan HIV, malaria dan tuberkulosis. Laporan-laporan ini telah meletakkan jalan positif untuk bekerja dalam objektif semasa untuk menyelidik potensi infusi sel stem dan sel-sel leluhur dengan faktor pertumbuhan dalam melindungi dan membaiki kecederaan dalam tikus dijangkiti denggi. Tikus jantan BALB/c berusia lapan minggu telah dibahagikan kepada tiga kumpulan; Kumpulan kawalan: tikus disuntik dengan eagle minimum essential media (EMEM) dan phosphate buffer saline (PBS); Kumpulan 1: tikus dijangkiti DV-2 (G1) dan Kumpulan 2: tikus yang dijangkiti DV-2 dirawat dengan sel stem hematopoietic (HSCs), sel leluhur endothelial (EPCs) dan faktor pertumbuhan (G2). Tikus di G1 dan G2 telah disuntik dengan DV-2. Pada hari selepas jangkitan (d.p.i) ke-2, tikus dalam G2 telah dirawat dengan sel stem hematopoietic (HSCs), sel leluhur endothelial (EPCs) dan GF melalui intravena. Darah diambil dari tikus di semua kumpulan pada hari ke- 5, 10, 15, dan 21 selepas jangkitan (d.p.i) untuk assay hematologi, assay biokimia, dan dikorbankan untuk histopatologi untuk dianalisis. Jangkitan denggi dalam G1 menyebabkan thrombocytopenia, leukopenic dan lymphocytopenia pada 21 d.p.i, dengan kadar hemoglobin dan sel-sel darah merah rendah. Selain itu, assay biokimia (AST & ALT) juga meningkat dalam G1 menunjukkan hubungan yang signifikan dengan kerosakan hati dalam analisa histopatologi dan penhapusan zarah virus. Selain itu, histopatologi saluran darah mendedahkan kecederaan yang berkait dengan profil darah dan kerosakan tersebut berterusan sehingga d.p.i ke-21. Rawatan sel stem dalam jangkitan DV-2 mempunyai kesan perlindungan dalam profil darah, assay biokimia,

histopahologi hati, saluran darah penghapusan virus dengan pemulihan yang dimulakan seawal d.p.i ke-10. Kesimpulannya, sel stem boleh menjadi terapi baru yang berpotensi bukan sahaja untuk membaikpulih semula profil darah dan kecederaan struktur organ yang teruk dengan kesan perlindungannya, tetapi juga menghapuskan sepenuhnya zarah virus untuk membantu dalam fungsi badan yang normal.

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

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LIST OF ABBREVIATIONS

%	Percentage
µg	Microgram
µL	Microliter
°	Degree
˚C	Degree celcius
$\cdot O^{-2}$	Superoxide
<	Less than
>	More than
×	Dilution/ Times
×g	Times gravity
≥	More than and equal to
µm	Micrometer
A.D.	After decades
ALT	Alanine aminotransferase
APC	Allophycocyanin
APTT	Activated partial prothrombin time
AST	Aspartate transaminase
b 1 integrin	Beta-1 Integrin
BFU	Burst forming unit
BM	Bone marrow
C	Capsid
C	Constant
CCL	C-C motif chemokine ligand
CD	Cluster of differentiation

CEC	Circulating endothelial cells
CFU	Colony forming unit
c-kit	Cellular kit
CLP	Common lymphoid progenitor
cm^2	Centimeter square
CMC	Carboxymethylcellulose
CMP	Common myeloid progenitor
c-Mpl	Megakaryocye proliferating ligand for platelet production
CO_2	Carbon dioxide
CPE	Cytopathic effect
CXCL	CXC chemokine ligand
D	Day
D	Magnitude of the difference
d.p.i	Day of post infection
DAB	3,3'-Diaminobenzidine
DC-SIGN	Dendritic cell-specific Intercellular adhesion molecule-3-grabbing non-integrin
DF	Dengue fever
DHF	Dengue hemorrhagic fever
DMEM	Dulbecco's modified eagle's medium
DMSO	Dimethyl sulfoxide
DSS	Dengue shock syndrome
DV or DENV	Dengue virus
E	Erythroid
ECGS	Endothelial cell growth supplement
ECs	Endothelial cells

EDTA	Ethylenediaminetetraacetic acid
Eg	Example
EGF	Epidermal growth factors
EMEM	Eagle minimum essential media
EPCs	Endothelial progenitor cells
EPO	Erythropoietin
ESCs	Embryonic stem cells
Evp	Envelope
FACS	Fluorescence-activated cell sorting
FBS	Fetal bovine serum
FcγII	Fc gamma 2
FcγRII	Fc gamma receptor 2
FFU	Foci forming assay
FGF	Fibroblast growth factors
FITC	Fluorescein
FLT	fms-like tyrosine kinase
G	Gram
G	Gauze
g/L	Gram per liter
G1	Group 1
G2	Group 2
GATA	Globin transcription factor
GDF	Growth differentiation factors
GP	Glycoprotein
h	Hour

HB	Hemoglobin
HCT	Hematocrit
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HSCs	Hematopoietic stem cells
HSPC	Hematopoetic stem progenitor cells
IACUC	Institutional animal care and use committees
ICAM	Intercellular adhesion molecule
IFA	Immunofluorescence assay
IFN	Interferon
IGF	Insulin-like growth factor
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interlukin
IMR	Institute for medical research
IP	Intraperitoneal
iPSCs	Induced pluripotent stem cells
IV	Intravenous
Kb	Kilobase
KC	Kupffer cells
kDa	Kilodalton
KDR	Kinase insert domain receptor
kg	Kilo gram
L	Liter
LDL	Low density lipopolysacharide L

LFA	ymphocyte function-associated antigen
LIF	Leukemia Inhibitory Factor
Lin	Lineage
LTR	Long terminal repeat
LYM	ymphocytes
mAb	Monoclonal antibodies
Mac-1	Macrophage-1 antigen
MCP	Monocyte chemoattractant protein
MEP	Megakaryocyte–erythroid progenitor
min	Minute
MK	Megakaryocyte
mL	Milliliter
mm	Millimeter
mm^3	Millimeter cube
MMP	Matrix metallopeptidase
MOH	Ministry of health
MPP	Multipotent progenitors
MSCs	Mesenchymal stem cells
n	Mumber
NA	Neutralizing antibodies
NF	No foci
NF-E2	Nuclear factor, erythroid-2
NO	Nitric oxide
NP-40	Nonyl phenoxypolyethoxylethanol 40
NS	Nonstructural proteins

PAI-1	Plasminogen activator inhibitor 1
PAIgM/ PAIgG	Platelet associated immunoglobulins
PBS	Phosphate buffer saline
PDGF	Platelet-derived growth factor
PE	Phycoerythrin
PLT	Platelets
PMID	PubMed-Indexed
PMN	Polymorphonuclear
prM	Premembrane
PSGL	P-selectin glycoprotein ligand
PT	Prothrombin time
RANTES	Regulated on activation, normal T cell expressed and secreted
RBC	Red blood cells
RM	Ringgit Malaysia
RNA	Ribonucleic acid
RO	Reverse osmosis
rpm	Revolutions per minute
s	Standard deviation of the variable
SC	Subcutaneous
Sca	Stem cells antigen
SCF	Stem cell factor
SDF	Stromal cell-derived factor
sICAM	Soluble intercellular adhesion molecule
sVCAM	Soluble vascular cell adhesion molecule

TGF	Transforming growth factor
Thy	Thymus
TNF	Tumor necrosis factor
TNTC	Too numerous to count
TPO	Thrombopoietin
U/L	Units Per Litre
UPM	Universiti Putra Malaysia
VE	Vascular endothelial
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
vWF	Von Willebrand factor
WBC	White blood cells
WHO	World Health Organization
α	Alpha
β	Beta
γ	Gamma

CHAPTER 1

INTRODUCTION

1.1 Background

Among the mosquito-borne viral disease, dengue is one of the most widely spread viruses by the female *Aedes aegypti*. The earliest appearance of dengue was in the 17th century but with low frequency. However, the world experiences major changes due to the recurrent presence of dengue virus (DV) in the past few years. Dengue illness commonly occurs in more than 128 nations with an approximation of 3.9 billion people are at great threat (Brady et al., 2012;) IMR, 2013). The smaller region, Malaysia, has faced increasing dengue cases every year. Dengue infection rose steadily from 7,103 cases in 2000 to 46,171 including 134 death cases in 2010. The number of cases and death reported in 2015 paint a frightening picture when the cases increased as much as 120,836 with 336 deaths due to dengue infection.

Dengue virus (DV) consists of four serotypes namely DV-1, DV-2, DV-3, and DV-4. However recent findings showed that there is an existence of another serotype, DV-5 (Brady et al., 2012). Among all these serotypes, DV-2 exhibits higher prevalence and cause more severe illness in the infected person. The first infections with any serotypes usually are asymptomatic, and sometimes may lead to mild dengue disease manifestations. Apart from the mild dengue fever (DF), dengue infection also leads to dengue hemorrhagic fever which usually appears during secondary infection. World Health Organization classifies dengue hemorrhagic fever (DHF) to present in a patient that undergoes thrombocytopenia with platelet count less than 100 000/mm^3, plasma leakage, hemorrhagic manifestation, and increasing capillary permeability. Dengue hemorrhagic fever may also develop into dengue shock syndrome (DSS) when an individual acquires severe hemorrhage and plasma bleeding (WHO, 2009).

Dengue virus (DV) infection causes thrombocytopenia by reducing the platelet production, increasing platelet consumption, or immune-complex formation. Platelets can engulf blood-borne bacteria and viruses, bind to macrophages and monocytes. Platelets not only involved in blood coagulation during bleeding but also involved in the immunity function across the innate and adaptive immune system (Elzey et al., 2003). Lack of platelets in the body can lead to the severe condition such as hemorrhage, plasma leakage, inability in removing the infectious agent and the worst case is death.

In accordance with thrombocytopenia, DV also causes plasma bleeding by infecting the endothelial cells (ECs) of blood vessels. Dengue virus (DV) changes the permeability of endothelium, enables virus replication and stimulates the immune reactions to act on the endothelial layer. The endothelial lining is the first-line fluid barricade of the blood vessel. This endothelial lining permeability is provoked by the responses influenced by DV, resulting in edema and hemorrhagic disease. In

addition, DV also causes multiple organ injuries during infection such as lung, heart, spleen and severe injury to the liver. These injuries are caused by direct DV infection, through metabolic alterations and also due to inflammatory reactions.

The people infected with DV, sometimes are unable to recover. They undergo deprived condition such as thrombocytopenia, leucopenia, hemorrhage, plasma leakage, vital organ injuries and dysfunction. This is due to the viral consumption of body machinery, and body inability to sustain the recovery which eventually leads to a fatal condition. Currently, the only available control measures for dengue infection are supportive fluid resuscitation to resolve plasma leakage and platelet transfusion to resolve thrombocytopenia. However, these supportive measures are sometimes not applicable for a patient with DHF or DSS, because it may worsen the patient condition. Various investigations are proceeding to discover the potential anti-dengue drug, however, there is still no promising candidate. In addition to that, the anti-dengue drug would help in virus clearance but its consumption does not revert the organ injuries caused by DV. The medicinal cure with antibiotics, antiviral, anti-parasitic and immunomodulatory drugs are challenged with side effects, resistance, and many other untoward results. The advance in the regenerative therapy of the stem cells promises the alternative therapy for infectious diseases since it can restore the injuries.

Stem cells therapy has been an emerging, new concept for the regeneration of cells, tissues, and organs. They are unspecialized cells with remarkable ability to self-renew and multiple cell type's differentiation to aid in homeostasis and tissue repair. There are various types of stem cells that are being explored such as induced embryonic stem cells (ESCs), pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs), for the conditions such as heart failure, Parkinson's disease, diabetes, arthritis, hematological disease, and vascular disease (Ahmed, Alexiades, & Lesniak, 2010; Alaiti, Ishikawa, & Costa, 2010; Devine et al., 2011; Siqueira, 2012). Stem cells treatment also been applied for HIV (Allers et al., 2011; Hutter, Schneider, & Thiel, 2009; Rabson, 2013), malaria (W. Wang, Qian, & Cao, 2015) and tuberculosis (MacMicking, 2014; Parida et al., 2015; Skrahin et al., 2014). The promising therapeutic success with stem cells for repair and regeneration mechanism in several communicable and non-communicable diseases laid a positive path to investigate the HSCs and EPCs for the treatment and organ damage prevention in dengue infection.

Hematopoietic stem cells (HSCs) therapies are now commonly used to treat cancer patients and disorders related to blood and immune systems. Hematopoietic stem cells (HSCs) are multipotent stem cells that can generate all hemato-lymphoid cells including red blood cells (RBCs), white blood cells (WBCs) and platelets (PLTs) (Banerjee, Crawford, Samuelson, & Feuer, 2010). The unceasing production of platelet into the blood circulation is maintained by the megakaryocytes (MKs) in the bone marrow with the support of specific growth factors such as thrombopoietin, which is crucial for preventing bleeding and thrombocytopenia. Endothelial progenitor cells (EPCs) are circulating in the blood with the potential of differentiating into ECs. It also plays an important role in retaining vascular integrity which is critical in diseases with the vascular insult in addition to its wide ability to

regenerate tissues, remodel tissues and preventing cancer. The endothelial integrity is also important for platelet preservation. However, EPCs role in infectious diseases still in need to be explored.

Since haematological alteration especially thrombocytopenia occurs during dengue infection, the use of HSCs can be suggested to restore the platelets in the circulation including other blood cells. Moreover, HSCs also involved in liver regeneration during liver injury. Apart from that, EPCs are also important to repair the endothelium injury caused by dengue infection in addition to its additional ability to involve in hematopoiesis. Thus, the present study was conducted to investigate the therapeutic effect of stem cells especially the HSCs and EPCs on the damages and alteration caused by the dengue infection.

1.2 Problem statement

Dengue, the most common arthropod-borne infectious disease in the world, has been the major concern to the governments and World Health Organization (WHO). The virus causes over 390 million infections annually. Several previous studies demonstrated that people infected with DV are suffering from several clinical symptoms including thrombocytopenia, leukopenia, hemorrhagic manifestations and internal organ injuries. Platelet transfusion and supportive fluid resuscitation have been the crucial maintenance for dengue patient with severe bleeding. However, the guideline by WHO in 2009, do not recommend the procedure to the thrombocytic patient which are hemodynamically stable. Platelet transfusion method is usually performed on patients with acute dengue and thrombocytopenia to stop severe bleeding (Lye, Lee, Sun, & Leo, 2009). However studies proved that this platelet transfusion did not minimize the clinical bleeding or accelerate platelet recovery, instead, results in fluid overload and prolong the duration of hospitalization (Lum, Abdel-Latif Mel, Goh, Chan, & Lam, 2003). At present, effective treatment is still unclear for dengue infection while current control measures such as larviciding, legally enforced breeding site reduction, fogging, and public education has not stopped the disease from spread nor cure the patient. Meanwhile, the discovery of anti-dengue drug is still not a promising candidate. There are some drugs have been tested such as chloroquine, intravenous immunoglobulin, balapiravir, and celgosivir, but were found to be less effective in protecting and recovering patients from dengue infection (Gan et al., 2014). Furthermore, the antiviral and immunomodulatory drugs can cause side effects to the consumer such as diarrhea, stomach cramps, vomiting, liver toxicity, and nephrotoxicity, drug resistance by the virus and many other untoward results. A new alternative therapy needs to be introduced as soon as possible to overcome these problems. The advance in regenerative stem cells therapy promises the alternative therapy for infectious diseases. The successful results reported from previous infectious studies had laid a positive path to work in the objectives of this current study.

1.3 Objectives

1.3.1 General Objective

To investigate the potential of stem and progenitor cells with the growth factor infusion in protecting and repairing the injuries in dengue infected mice.

1.3.2 Specific Objectives

i To investigate the potential of stem cell cocktail (HSCs, EPCs, and GF) infusion in order to normalize the hematological disorder (Platelets, white blood cells, lymphocytes, red blood cells, and hemoglobin) in dengue virus infected mice
ii To investigate the effect of stem cell cocktail (HSCs, EPCs, and GF) infusion in restoring the liver function after dengue infection
iii To investigate the effect of stem cell cocktail (HSCs, EPCs, and GF) infusion in structurally damaged blood vessel after dengue infection
iv To observe the ability of stem cell cocktail (HSCs, EPCs, and GF) infusion and clearance of dengue virus from dengue infected mice

1.4 Hypothesis

1.4.1 Null hypothesis

i There is no significant in increase of platelets and recovery of blood profile (white blood cells, lymphocytes, red blood cells, and hemoglobin) during dengue infection.
ii There is no significant recovery in the liver function during dengue infection
iii There is no significant recovery in the blood vessel during dengue infection
iv There is no significant clearance of DV-2 virus during dengue infections

1.4.2 Alternative hypothesis

i There is significant increase of platelet count and recovery in blood profile (white blood cells, lymphocytes, red blood cells, and hemoglobin) in the presence of stem cells infusion
ii There is significant recovery expected in the liver function after stem cells transfusion
iii There is significant recovery in the blood vessel after stem cells transfusion
iv There is possible in clearance of DV-2 virus after stem cells transfusion

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