UNIVERSITI PUTRA MALAYSIA

MITOGENIC ACTIVITY OF MESENCHYMAL STEM CELLS ON HEMATOPOIETIC STEM CELLS VIA CELLULAR ANALYSIS AND GENE EXPRESSION

MOHADESEH HASHEM BOROOJERDI

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By

MOHADESEH HASHEM BOROOJERDI

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

August 2015

DEDICATION

This thesis is dedicated to

My dearest Parents, Brother and Sister

The understanding and encouragement they provided during all the these years

of the study

Abstract of the thesis presented to the Senate of Universiti Putra Malaysia in the fulfillment of the requirement for the Degree of Doctor of Philosophy

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Chairman: **Rajesh Ramasamy, PhD**
Faculty: **Medicine and Health Sciences**

Introduction: During the last three decades, hematopoietic stem cell (HSC) transplantation has become a well-established treatment for many hematologic malignancies and deficiencies. However harvesting peripheral blood mobilized HSC from donors or cord blood are often hampered by inadequacy of cell numbers. This conundrum drives an alternate way to obtain a required HSC numbers for the demanding clinical therapies. It has been recently revealed that the stromal precursor, mesenchymal stem cells (MSC) profoundly regulates the expansion and differentiation of HSC at bone marrow's niche via producing hematopoietic growth factors and adhesion molecules. Although the intimate interaction between HSC and MSC is not fully elucidated but it has been confirmed that such communication is mandatory for the uninterrupted hematopoiesis. **Objective:** Thus, this project is aimed to explore the potential role of MSC in supporting the self-renewal; expansion and differentiation of HSC via cellular and genetic analysis. **Materials and Methods:** The first phase of this project has focused on optimizing the isolation and characterization of HSC from human cord blood. HSC were isolated using $CD34^+$ magnetic beads and the optimal growth conditions were determined. The holistic effect of MSC on HSC's life cycle was deduced using various functional assays that measure proliferation, cell cycle, viability, and differentiation status of HSC. At second phase, the molecular interaction between HSC and MSC was further decoded by micro array analysis by measuring largely dysregulated genes in HSC upon co-cultured with MSC. **Results:** Approximately 80% of HSC were isolated from human cord blood. The optimal growth culture a condition was noticed when HSC were cultured in DMEM-F12 basal media with cytokine cocktails. Expansion index of HSC at *in vitro* culture was significantly increased in the presence of MSC. Further cell cycle analysis of HSC showed that MSC drove HSC into active cell cycle phase where the larger numbers of HSC were committed to S phase of cell cycle. Flow cytometer analysis of viability and apoptosis status of HSC showed that MSC reduce the apoptosis rate of HSC. In addition, the total number of colonies that formed was generally increased in MSC co-culture. The specific gene expression that induced by MSC during HSC expansion was captured using micro array. The result showed that in the presence of MSC, 712 genes were differentially expressed in HSC. Important genes that involve in controlling the number of HSC such as self-renewal related signaling pathway regulator genes cell

cycle and apoptosis regulator genes were categorized by online DAVID software. The detailed analysis revealed that MSC dysregulated some genes that profoundly regulate HSC proliferation. **Conclusion:** The present study support the notion that the human umbilical cord derived MSC as potential feeder cells that could preserve and amplify the number of human cord blood derived-HSC. The cellular mechanisms that govern this expansion of HSC could be resulted from the protective activity exerted by MSC via reducing apoptosis whilst activating cell cycle. This phenomenon also was well reflected at gene expression study where up-regulation of HSC associated proliferation genes evidenced. Our results contributes a great deal to understand the signaling pathways that sustains HSC homeostasis, i.e. self-renewal, differentiation and apoptosis, and the modification of such signals has revealed the first possibilities to *in vitro* HSC expansion and delineated avenues for its future uses in clinical transplantation.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

AKTIVITI MITOGENIK SEL INDUK MESENKIMA TERHADAP SEL INDUK HEMATOPOISIS MELALUI ANALISA SEL DAN EXPRESI GEN

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Pengenalan: Dalam tempoh tiga dekad yang lalu transplantasi sel induk hematopoietik (HSC) telah menjadi satu rawatan yang mantap bagi panyakit barah dan defisiensi hematologik. Walau bagaimanpun, usaha mendapatkan darah periferi yang digerakkan HSC daripada penderma atau darah tali pusat sering terbantut disebabkan oleh kekurangan bilangan sel. Dilema ini mendorong satu cara alternatif untuk mendapatkan bilangan HSC yang diperlukan untuk terapi klinikal yang mencabar. Baru-baru ini telah didedahkan bahawa prekursur stromal, sel-sel induk mesenkima (MSC) mengawal perkembangan dan pembezaan HSC di nic sum-sum tulang secara jelas melalui penghasilan faktor pertumbuhan hematopoietik dan molekul-molekul lekatan. Walaupun interaksi rapat di antara HSC dan MSC tidak difahami sepenuhnya tetapi disahkan bahawa komunikasi tersebut adalah penting untuk proses hematopoiesis yang tanpa gangguan. **Objektif:** Oleh itu, projek ini bertujuan untuk menyiasat komunikasi di peringkat molekul antara kedua-dua sel ini untuk memahami isyarat biologi yang berpotensi yang diekploitasi bagi mengembangkan HSC pada skala yang lebih besar. **Bahan dan Kaedah:** Fasa pertama projek ini telah memberi tumpuan kepada optimasi pengasingan dan pencirian HSC dari darah tali pusat manusia. HSC telah diasingkan menggunakan manik-manik magnetik $CD34^+$ dan keadaan pertumbuhan optimum telah ditentukan. Kesan holistik MSC terhadap kitaran hidup HSCs telah didedahkan dengan menggunakan pelbagai asai berfungsi yang mengukur percambahan, kitaran sel, viabiliti dan status pembezaan HSC. Pada fasa kedua, interaksi molekul di antara HSC dan MSC telah dikemukakan lanjut menggunakan analisis tatasusunan mikro, sebahagian besarnya dengan mengukur gen-gen disregulasi dalam HSC apabila ia dikulturkan bersama dengan MSC. **Keputusan:** Kira-kira 80% tulen HSC telah diasingkan daripada darah tali pusat manusia. Keadaan optimum kultur pertumbuhan diperhatikan apabila HSC dikulturkan di dalam media basal DMEM-F12 dengan kombinasi sitokin. Indeks pengembangan HSC pada kultur *in vitro* telah meningkat secara ketara dengan kehadiran MSC. Analisis lanjut kitaran sel HSC menunjukkan bahawa MSC mendorong HSC ke dalam fasa kitaran sel aktif di mana jumlah HSC yang lebih besar berada dalam

fasa S kitaran sel. Analisis sitometer aliran terhadap viabiliti dan status apoptosis HSC menunjukkan bahawa MSC mengurangkan kadar apoptosis HSC. Namun jumlah koloni yang terbentuk secara umumnya telah meningkat di dalam kultur bersama MSC. Penzahiran gen spesifik yang diaruhkan oleh MSC semasa pengembangan HSC telah diperolehi menggunakan tatasusunan mikro. Hasil menunjukkan bahawa dengan kehadiran MSC, 712 gen telah dizahirkan secara berbeza dalam HSC. Gen penting yang terlibat dalam mengawal bilangan HSC seperti gen pengatur isyarat laluan yang berkaitan pembaharuan kendiri, kitaran sel dan gen pengatur apoptosis dikategorikan oleh perisian atas talian DAVID. Analisis terperinci mendedahkan bahawa MSC telah mendisregulasi beberapa gen yang jelas mengawal percambahan HSC. **Kesimpulan:** Kajian ini menyokong tanggapan bahawa MSC yang diambil daripada tali pusat manusia berpotensi sebagai sel pembekal yang boleh memelihara dan meningkatkan bilangan HSC daripada darah tali pusat manusia. Mekanisme sel yang mengawal perkembangan HSC ini boleh berpunca daripada aktiviti perlindungan yang diaruhkan oleh MSC melalui pengurangan apoptosis semasa mengaktifkan kitaran sel. Keputusan kami memberi sumbangan besar untuk memahami laluan isyarat yang mengekalkan HSC homeostasis, iaitu pembaharuan diri, pembezaan dan apoptosis, dan pengubahsuaian isyarat itu telah mendedahkan kemungkinan pertama dalam vitro pengembangan HSC dan saluran ditandakan untuk masa depannya menggunakan dalam klinikal pemindahan.

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This thesis was submitted to the Senate of University Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS/ NOTATIONS/ GLOSSARY OF TERMS

Abbreviation	Meaning
>	More than
≤	Equal and less than
=	Equal to
%	Percentage
Ang-1	Angiopoietin
BD	**BECTON DICKINSON**
BDNF	Brain-derived neurotrophic factor
BM	Bone Marrow
BOK	BCL2-related ovarian killer
BMPR1A	Bone morphogenetic protein receptor, type IA; similar to ALK-3
BMP4	Bone morphogenetic protein 4
CASP1	Caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)
CB	Cord blood
CCR10	Chemokine (C-C motif) receptor 10
CCR2	Chemokine (C-C motif) receptor 2
CCND1	Cyclin D1
CD	Cluster of differentiation
CDKs	Cyclin-dependent kinases
CDKN2A	Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)
CFU	Colony-forming units
CDH2	Cadherin 2, type 1, N-cadherin
CDH11	Cadherin 11, type 2, OB-cadherin
CDH13	Cadherin 13, H-cadherin
CLP	Common lymphoid progenitor
CMP	Common myeloid progenitor
CPDA-1	Citrate phosphate dextrose adenine
CRLF2	Cytokine receptor-like factor 2
CSF2RB	Colony stimulating factor 2 receptor, beta, low-affinity
CTF1	Cardiotrophin 1
CXCR4	C-X-C chemokine receptor type 4
CXCL12	C-X-C motif chemokine 12
CXCL16	C-X-C motif chemokine 12
CX3CR1	Chemokine (C-X3-C motif) receptor 1
DAAM2	Dishevelled associated activator of morphogenesis 2
DCN	Decorin

DEGs	Differentially expressed genes
DKK1	Dickkopf homolog 1
DMEM-F12	Dulbecco's modified eagle's medium with nutrient mixture F-12
DSP	Desmoplakin
DSG2	Desmoglein 2
ECM	Extra cellular matrix
FGF	Fibroblast growth factor
FGF2	Fibroblast growth factor 2
FGFR1	Fibroblast growth factor receptor 1
EI	Expansion index
FL	Flt3-ligand
FLNC	Filamin C, gamma (actin binding protein 280)
FOXD1	Forkhead box D1
FZD4	Frizzled homolog 4
FZD7	Frizzled homolog 7
FZD8	Frizzled homolog 8
GAP	Glyceraldehyde-3- phosphate
GDF5	Growth differentiation factor 5
GLI3	GLI family zinc finger 3
GM-CSF	Granulocyte-macrophage colony–stimulating factor
GNG12	Guanine nucleotide binding protein (G protein), gamma 12
GO	Gene ontology
GX	GeneSpring
HCB	Human cord blood
Hh	Hedgehog
HLA	Human leukocyte antigen
HOXC4	Homeobox C4
HOXC6	Homeobox C6
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplantation
HSPB1	Heat shock 27kDa protein-like 2 pseudogene; heat shock 27kDa protein 1
IGFBP3	Insulin-like growth factor binding protein 3
IL3	Interleukin 3
IL4	Interleukin 4
IL6	Interleukin 6
IL11	Interleukin 11
IL11RA	Interleukin 11 receptor, alpha
IL1R2	Interleukin 1 receptor, type II
IL9R	Interleukin 9 receptor
IL17RA	Interleukin 17 receptor A

IMDM	Iscove's Modified Dulbecco's Medium
INHBA	Inhibin, beta A
JAK-STAT	Janus kinase/ Signal Transducer and Activator of Transcription
KREMEN1	kringle containing transmembrane protein 1
LIF	Leukemia inhibitory factor
MAPK	Mitogen-activated protein kinases
M-CSF	Macrophage colony stimulating factor
MSC	Mesenchymal stem cells
NINL	Ninein-like
NTRK1	Neurotrophic tyrosine kinase, receptor, type 1
NTF3	Neurotrophin 3
P	*p* value
PBS	Phosphate buffered saline
PB	Peripheral blood
PCDHGA8	Protocadherin gamma subfamily A, 8
PDGFRA	Platelet-derived growth factor receptor, alpha polypeptide
PERP	PERP, TP53 apoptosis effector
PI	Propidium iodide
PITX2	Paired-like homeodomain 2
PLCB1	Phospholipase C, beta 1 (phosphoinositide-specific)
PXN	Paxillin
QRT-PCR	Quantitative real time RT-PCR
SCF	Stem cell factor
SCRL	Stem cell research laboratory
SDF-1	Stromal derived factor-1
SERPINE1	Serpin peptidase inhibitor, clade E (Nexin, plasminogen activator inhibitor type 1)
SMAD3	SMAD family member 3
SMARCA1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 1
SMO	Smoothened homolog
SOCS1	Suppressor of cytokine signaling 1
SPRY1	Sprouty homolog 1, antagonist of FGF signaling
TEPA	Tetraethylenepentamine
TGF- β	Transforming growth factor beta
THBS2	Thrombospondin 2
THBS3	Thrombospondin 3
TNF	Tumor necrosis factor (TNF superfamily, member 2)
TNFRSF10D	Tumor necrosis factor receptor superfamily, member 10D
TNFRSF11B	Tumor necrosis factor receptor superfamily, member 11b
TNFRSF12A	Tumor necrosis factor receptor superfamily, member 12A
TNFRSF4	Tumor necrosis factor receptor superfamily, member 4

TNFSF4	Tumor necrosis factor (ligand) superfamily, member 4
TNFSF14	Tumor necrosis factor (ligand) superfamily, member 14
TNFRSF12	Tumor necrosis factor (ligand) superfamily, member 12
TPO	Thrombopoietin
TUBB6	Tubulin, beta 6
UCB	Umbilical cord blood
VEGF	Vascular endothelial growth factor
WNT	Wingless-type MMTV integration site family
WNT5A	Wingless-type MMTV integration site family, member 5A
ZFYVE9	Zinc finger, FYVE domain containing 9

CHAPTER 1

INTRODUCTION

1.1 Introduction

Haematopoietic stem cell transplantation (HSCT) has become an inevitable therapy for many blood related disorders. Among all stem cell-based therapies, HSCT is the only one with a well-established clinical regimen and remains an effective approach for patients with certain hematological diseases (Gluckman *et al.,* 2011; Resnick *et al.,* 2010; Thomas *et al.,* 2011). Basically, HSCT involves the intravenous infusion of autologous or allogeneic stem cells that collected from bone marrow (BM), peripheral blood (PB) or umbilical cord blood (UCB) to the patients. However, the successfulness of HSCT is critically relying on the initial number of Haematopoietic stem cell (HSC) that has been infused. Inadequate or low number of HSC for therapeutical use is often resulted in delayed engraftment or graft failure. Thus, *in vitro* expansion of HSC using current advancement and technologies would provide a perspective to overcome this limitation (Thomas *et al.,* 2011).

The amplification and maintenance of HSC in BM is dependent on cytokine and niche factors that delivered by mesenchymal stem cells (MSC). Several lines of evidence suggest that MSC produce an array of essential hematopoietic growth factors and adhesion molecules to support the self-renewal and differentiation of HSC. The reciprocal interaction between MSC and HSC in close proximity allow well-balanced HSC self-renewal and commitment into progenitors by secretion of regulatory molecules such as cytokines and growth factors and the specialized microenvironment that allow highly orchestrated process of hematopoiesis (Mishima *et al.,* 2010; Mohanty *et al.,* 2010; Kelly *et al.,* 2009; Li *et al.,* 2007).

It has been shown that MSC execute the regulation of hematopoiesis particularly HSC both at *in vitro* culture and *in vivo* through cell-to-cell contact and secreted soluble growth factors that are responsible for homing, proliferation and differentiation of hematopoietic cells. The *in vitro* co-culture of MSC and HSC proved a significant increase in HSC number (Mishima *et al.,* 2010; Mohanty *et al.,* 2010; Da Silva *et al.,* 2010). Although much substantial evidences have indicated the capability of MSC in supporting HSC's expansion and enhancement of hematopoietic engraftment, yet the exact mechanisms for above said biological functions are still unclear. MSC may affect HSC by producing growth factors and chemokines that take parts in signaling pathways of HSC. Consecutively, the downstream signals received from the receptors and adhesion molecules on HSC surface further transduced to cytoplasmic and DNA levels which leads to transcription of an appropriate set of genes (Shangqin *et al.,* 2009). Hence, a better understanding of the interaction between MSC and HSC is needed to possibly escalate the expansion of HSC to equate the request of HSC transplantation (Mishima *et al.,* 2010; Tian *et al.,* 2012; Jing et *al.,* 2010).

1.2 Problem statement

During the last three decades HSCT has become a well-established treatment for many hematologic malignancies and deficiencies (Appelbaum, 2007; Gluckman *et al.*, 2011). However, harvesting peripheral mobilized HSC from donors or UCB is often hampered by inadequacy of cell numbers. In fact, the most important limitation for HSC transplantation is the low number of HSC that can lead to delayed engraftment or graft failure (Gluckman *et al.*, 2011). This conundrum drives an alternate way to obtain a required HSC numbers for the demanding clinical therapies.

Although BM serves as an ideal source for HSC yet several factors such as very painful invasive procedure, post infections risk, limitation of donor availability and the age of patients are often circumvent its wide applications. Nevertheless, the successful transplantation of UCB in 1988 has open the gateway to UCB for being considered as an attractive alternative source of HSC in the treatment of hematological malignancies (leukemia & lymphoma), and non-malignant blood diseases (thalassaemia & sickle cell disease).

Although HSCT has become a big breakthrough in the field of cellular therapy, yet the number of HSC harvested for cryopreservation or therapy is still remains an issue. A substantial number of UCB that been collected by the national and private UCB banks are discarded due to low number of mononuclear cells which subsequently leads to smaller stem cells fraction. Insufficient numbers of transplantable/storable stem cells barricade the success of clinical and experimental HSC transplantation.

Alternatively, numerous attempts have been made to expand HSC derived from UCB in *in vitro* via various means such as supplementation with a range of growth factors and basal media; variety of extracellular matrixes; dynamic 3D culture system (Andrade-Zaldívar *et al.*, 2008), and also utilizing stromal cells as feeder layer (Mishima *et al.*, 2010; Mohanty *et al.*, 2010; Jing *et al.*, 2010). Among all, MSC as feeder cell for expanding HSC had shown a significant improvement in term of cell yield and its qualities as culturing HSC on the surface of MSC resemble the BM specific niche (Mishima *et al.*, 2010; Mohanty *et al.*, 2010).

Thus the current study explored the inherent potential of human umbilical cord derived MSC in supporting the expansion of human umbilical cord blood derived-HSC via deciphering the cellular and genetic modulations. This study revealed the influence of MSC in affecting the gene expression of HSC that critically controls the expansion of HSC. Further profiling of responsible gene expression or suppression that mediated MSC will pave a platform to manipulate HSC expansion by discovering and introducing growth factors to increase the number of HSC in culture.

1.3 Objectives

1.3.1 General objective

To explore the potential role of MSC in supporting the self-renewal, expansion and differentiation of HSC via cellular and genetic analysis

1.3.2 Specific objectives

The specific objectives of this research are as follows:

a. To optimize the isolation and characterization of HSC from human cord blood
b. To investigate the effect of MSC on HSC proliferation and apoptosis status
c. To study the impact of MSC on HSC differentiation
d. To elucidate the role of MSC on HSC expansion by deciphering the gene expression pattern via micro array

1.4 Hypothesis

Umbilical cord derived MSC may act as a biological mitogen and could positively control the HSC number by regulating HSC's cellular activities and gene expressions as tool to regulate cell cycle and apoptosis.

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