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GLOBAL GENE PROFILING AND ANTI-TUMOUR ACTIVITY OF HUMAN MESENCHYMAL STEM CELLS ON BV173 B LEUKAEMIA CELL LINE

VAHID HOSSEINPOUR SARMADI

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By

VAHID HOSSEINPOUR SARMADI

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

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DEDICATION

This thesis is dedicated:

To my beloved wife Salma for all her love, unwavering and tireless moral support, endless encouragement and unrelenting faith in my ability to accomplish this thesis. You are a gift from God and you mean the world to me.

and

To my parents, my endless love source, for their continuing support, encouragement and love during my absence abroad, who believed in me and are absolutely unique and perfect parents in the world.

Life is never boring when you're around!

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

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Chairman: Assoc. Prof. Rajesh Ramasamy, PhD
Faculty: Medicine and Health Sciences

In 2013, there were 8.2 million cancer deaths worldwide and cancers were the second leading cause of death after cardiovascular diseases. Thus, it represents one of the major health issues all over the world. Current therapies such as the conventional methods of targeting the tumour cells by non-specific chemotherapy and radiotherapy have not yielded satisfactory outcomes as seen in many cancer remission cases, and an efficient treatment for cancer cells has yet to be identified. The recent development in mesenchymal stem cell research promises an efficient anti-cancer therapy via a possible mode of cell cycle arrest, apoptosis and immunosuppressive activity.

Umbilical cord mesenchymal stem cells (UC-MSCs) are considered as post-natal stem cells present in the Wharton's jelly of the umbilical cord tissue and are considered as an appealing source of adult stem cells for the cell therapy and tissue engineering as they are easily obtained and expanded while maintaining their multi-lineage differentiation potential. The past research studies have shown that UC-MSCs profoundly inhibited the growth of various tumour cells, however, the molecular mechanisms that execute this inhibition have yet to be identified. Although MSCs contribute to the haematopoiesis and support the growth of blood cells but also able to inhibit highly proliferating cells. Therefore, this study aims to investigate the inhibitory effect of UC-MSCs on haematopoietic tumour cells proliferation at *in vitro* by elucidating the molecular mechanisms and the relevant gene expression profiles.

Wharton's jelly from human umbilical cord was subjected to the collagenase digestion and the single cells were cultured to generate UC-MSCs. The

adherent cells were characterized based on a universally accepted immunophenotyping and mesodermal differentiation. Haematopoietic origin tumour cell lines HL-60, K562, Jurkat and BV173 cell lines were purchased from ATCC and maintained in 10% foetal bovine serum supplemented RPMI media. Umbilical cord MSCs and tumour cells were co-cultured and the effect of UC-MSCs on tumour cell proliferation, apoptosis, cell cycle arrest, gene expression, biological process and signalling pathways were evaluated. Finally, the six selected genes were validated using SYBER GREEN qPCR.

The results demonstrated that in the presence of UC-MSCs, tumour cell proliferation were profoundly inhibited in dose dependent manner as measured by ^{3}H-thymidine uptake and MTS Assay. Transwell assays indicated that UC-MSCs mediated inhibition was mainly attributed to the cell-to-cell contact mode. Umbilical cord MSCs did not induce apoptosis as their mode of anti-proliferative activity. Further investigation on the tumour cell cycle revealed that UC-MSCs induced an arrest in G_0/G_1 and S phase of cell cycle. A subsequent microarray analysis showed that out of 3019 differentially expressed genes, 2000 and 1019 genes were up and down-regulated respectively in BV173 tumour cell line that were co-cultured with UC-MSCs. Besides, the microarray results also highlighted 380 altered genes with unknown function or unrelated association in BV173 cell line. When these dysregulated genes were analysed based on biological processes, the physiological functions such as cell adhesion, vasculature development, regulation of cell proliferation and regulation of cell migration processes were over-represented. In addition, the microarray analysis showed the most significant signalling pathways such as focal adhesion, ECM-receptor interaction, cytokine-cytokine receptor interaction, MAPK, p53 and TGF-β signalling pathway were dysregulated by UC-MSCs in BV173. The qPCR result confirmed the mRNA level some of the selected genes.

The present study indicated that UC-MSCs inhibit tumour cells proliferation by arresting in G_0/G_1 phase of cell cycle and this effect is mediated by cell-to-cell contact. Further gene profiling and signalling pathways revealed that anti-proliferative activity of UC-MSCs on tumour cell proliferation is associated with genes which are involved in cell cycle (CDK6, CCNE2 and CDKN1A), cell adhesion (TGFβI, MYO7A and CD82), metastasis (CCL2, TFPI2 and CXCR3), angiogenesis (PDGF, CXCL1 and PTX3) and regulation of cell proliferation (HECW1, SCIMP and ANXA1). The generalized tumour cells inhibition by UC-MSCs could be potentially exploited to treat various tumours. However, this anti-proliferative activity needs to be tested in *in-vivo* model and at protein level for their better understandings and validation.

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

PEMPROFILAN PERUBAHAN GEN DAN AKTIVITI ANTI-TUMOR OLEH SEL STEM MESENKIMA TERHADAP SEL-SEL TERBITAN TUMOR BV173

Oleh

VAHID HOSSEINPOUR SARMADI

Ogos 2016

Pengerusi: Profesor Madya Rajesh Ramasamy, PhD
Fakulti: Perubatan dan Sains Kesihatan

Pada tahun 2013, terdapat 8.2 juta kes kematian akibat kanser di seluruh dunia dan kanser adalah punca kedua utama kematian selepas penyakit kardiovaskular. Ia merupakan salah satu isu kesihatan yang kritikal dan perlukan perhatian yang teliti disebabkan rawatan semasa untuk membanteras sel-sel tumor seperti kemoterapi dan radioterapi kurang bermanfaat dan sering menjurus kepada petumbuhan semula sel-sel kanser. Perkembangan terbaru dalam penyelidikan sel stem mesenkima menjanjikan rawatan yang berkesan terhadap sel-sel kanser melalui beberapa mekanisme seperti pembantutan kitaran sel, pencetusan apoptosis dan aktiviti imunosupresif.

Sel stem mesenkima daripada tali pusat (UC-MSCs) merupakan sel stem dewasa yang ditemui dalam tisu Wharton jeli dan dianggap sebagai sumber menarik untuk terapi sel dan kejuruteraan tisu. Di samping, UC-MSCs juga mudah diperolehi dan dikembangkan tanpa menjejaskan potensi pembezaan. Kajian-kajian penyelidikan terdahulu menunjukkan bahawa, MSCs terbitan daripada sum-sum tulang menghalang pertumbuhan pelbagai jenis sel-sel tumor. Walau bagaimanapun, mekanisma molekul yang terlibat dalam kekangan ini masih belum dikenal pasti. Oleh itu, kajian ini bertujuan untuk mengkaji kesan perencatan UC-MSCs ke atas pertumbuhan *in vitro* sel-sel terbitan tumour dan juga menggariskan mekanisma molekul dan profil ekspresi gen yang berkaitan.

Tisu *Wharton jelly* dari tali pusat manusia diproses dengan enzim *collagenase* dan seterusnya dikultur untuk menghasilkan UC-MSCs. Sel-sel stem mesenkima dicirikan berdasarkan piawaian universal seperti

immunophenotyping dan pembezaan mesodermal. Sel-sel terbitan tumor *haematopoietic* HL-60, K562, Jurkat dan BV173 telah diperolehi dari ATCC. Sel-sel terbitan tumour dikultur bersama UC-MSCs dan kesan perencatan UC-MSCs terhadap percambahan sel-sel tumor, apoptosis, kitaran sel, ekspresi gen, proses biologi dan *'signalling pathways'* dinilai. Akhirnya, gen-gen yang terpilih telah disahkan menggunakan SYBER GREEN qPCR.

Didapati bahawa, UC-MSCs merencat percambahan sel-sel tumor mengikut dos apabila dikaji melalui pengambilan *^{3}H-thymidine* dan esei MTS. Esei transwell menunjukkan bahawa kesan perencatan oleh UC-MSCs memerlukan komunikasi secara langsung di antara sel-dengan-sel. UC-MSCs tidak mencetuskan apoptosis untuk merencat percambahan sel-sel tumor. Siasatan susulan menunjukkan bahawa UC-MSCs membantut pertumbuhan sel-sel tumor di fasa G_0/G_1 dan S. Analisis *microarray* menunjukkan bahawa daripada 3019 gen diubah ekspresi, 2000 dan 1019 gen ekpresinya ditingkatkan dan direndahkan masing-masing pada sel tumor BV173 apabila dikultur bersama UC-MSCs. Selain itu, keputusan microarray juga memaparkan sejumlah 380 gen diubah ekpresis tetapi fungsinya tidak diketahui. Tambahan pula, ekpresi gen yang diubah oleh UC-MSC pada BV173 dikait rapat dengan proses-proses biologi seperti lekatan sel, perkembangan salur, pengawalan percambahan dan pengawalseliaan penghijrahan sel. Di samping itu, analisis microarray juga menunjukkan *signalling pathways* yang penting seperti lekatan fokal, interaksi ECM-reseptor, interaksi reseptor cytokine-cytokine, MAPK, p53 dan isyarat laluan TGF-β telah diubah oleh UC-MSCs. Ekpresi gen-gen tertentu disahkan melalui qPCR.

Kajian ini menunjukkan bahawa UC-MSCs merencat percambahan sel-sel tumor melalui pembantutan kitaran sel di fasa G_0/G_1 menerusi komunikasi terus dengan sel-sel tumor. Pencirian gen dan *signalling pathways* mendedahkan bahawa aktiviti perencatan UC-MSCs terhadap percambahan sel-sel tumor dikaitkan dengan pengkawalaturan gen yang terlibat dalam kitar sel (CDK6, CCNE2 dan CDKN1A), lekatan sel (TGFβI, MYO7A dan CD82), *metastasis* (CCL2, TFPI2 dan CXCR3), *angiogenesis* (PDGF, CXCL1 dan PTX3) dan peraturan percambahan sel (HECW1, SCIMP dan ANXA1). Perencatan sel-sel tumor oleh UC-MSCs boleh dieksploitasi untuk merawat pelbagai jenis tumor. Walau bagaimanapun, aktiviti anti-proliferatif ini perlu diuji dalam model *in vivo* dan juga tahap protein gen yang berkenaan perlu dikaji demi pemahaman yang lebih baik.

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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 Doctor of Philosophy. The members of the Supervisory Committee are as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

^{3}H-TdR	Tritiated Thymidine
ACTB	Actin Beta
ALL	Acute Lymphoblastic Leukaemia
APC	Antigen Presenting Cell
APC	Allophycocyanin
ATP	Adenosine Triphosphate
BP	Biological Process
BM	Bone Marrow
BMP	Bone Morphogenetic Protein
BSA	Bovine Serum Albumin
CD	Cluster of Differentiation
CDC	Cell-Division Cycle
CDK	Cyclin Dependent Kinase
cDNA	Complementary Deoxyribonucleic Acid
CFU-F	Colony Forming Unit-Fibroblast
CKI	Cyclin-Dependent Inhibitors
CML	Chronic Myeloid Leukaemia
CPM	Count Per Minutes
DAVID	Database for Annotation, Visualization and Integrated Discovery
DC	Dendritic Cell
DKK	Dickkopf
DMEM	Dulbecco's Modified Eagle's Medium
ECM	Extracellular Matrix
ECS	Embryonic Stem Cell
EGF	Epidermal Growth Factor
EMT	Epithelial-Mesenchymal Transition
ER	Estrogen Receptor
ERK	Extracellular signal-Regulated Kinases
F	Forward primers
FACS	Fluorescence-Activated Cell Sorting
FBS	Foetal Bovine Serum
FC	Fold Change
FDR	False Discovery Rate
FGF	Fibroblast Growth Factor
FITC	Fluorescein Isothiocynate
G	Gap
GO	Gene Ontology
GVHD	Graft Versus Host Disease
HGF	Hepatocyte Growth Factor
HLA	Human Leucocytes Antigens
HSC	Haematopoietic Stem Cell
Hu	Human
IBMX	Isobutylmethylxantine
ICAM	Inter Cellular Adhesion Molecule
ICM	Inner Cell Mass
IDO	Indoleamine 2,3 Deoxygenase
IFN	Interferon

Ig	Immunoglobulin
IGF	Insulin-like Growth Factor
IL	Interleukin
INK	Inhibitor of Kinase
ISCT	International Society for Cellular Therapy
KEGG	Kyoto Encyclopaedia of Genes and Genomes
M	Mitosis
MAPK	Mitogen-Activated Protein Kinase
MHC	Major Histocompatibility Complex
mRNA	Messenger Ribonucleic Acid
miRNA	Micro-RNA
MSC	Mesenchymal Stem Cell
NK	Natural Killer
NO	Nitric Oxide
PD	Parkinson's Disease
PE	Phycoerythrin
PGE_2	Prostaglandin E_2
PI	Propidium Iodide
PPAR γ	Peroxisome Proliferators Activated Receptors γ
R	Reverse primers
RA	Rheumatoid Arthritis
Rb	Retinoblastoma
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RPMI	Roswell Park Memorial Institute
S	Synthesis
SD	Standard Deviation
SN	Supernatant
TBP	TATA Box Binding Protein
TβR	TGF-β Receptor
TGF-β	Transforming Growth Factor Beta
TNF	Tumour Necrosis Factor
TRAIL	Tumour Necrosis Factor-Related Apoptosis Inducing Ligand
TSG	Tumour Suppressor Gene
UC	Umbilical Cord
UCB	Umbilical Cord Blood
VCAM	Vascular Cell Adhesion Molecule
VEGF	Vascular Endothelial Growth Factor
WJ	Wharton's Jelly
Wnt	Wingless Signalling Pathway

CHAPTER ONE

INTRODUCTION

1.1 Stem cells

Stem cells have been described as primal undifferentiated cells that have the intrinsic capability to self-renew, and therefore to produce more stem cells, as well as to differentiate, giving rise to more specialized cell types (Lajtha, 1979). Nowadays, the use of stem cell is recognized as an important tool in the tissue repair, tissue regeneration and treatment of various malignancies. Stem cells are both present in the embryo during the blastocyst phase of embryological development as well as in the different adult tissues. Hence, adult stem cells are regarded as a potential alternative to embryonic stem cells due to their lesser ethical cues and genetic stability (Minguell *et al.*, 2000).

Since stem cells can generate different types of cells in the organs of human body, stem cell therapy is believed to have the potential to radically change the treatment of human disease. Despite the promising potentials and prospects, there are limited approved treatments or human trials using embryonic stem cells due to ethical concerns. However, adult stem cells treatments have been used for many years to successfully treat leukaemia and related bone or blood malignancies through bone marrow transplants (Lemischka, 1999; Metcalf, 1999; Gahrton and Bjorkstrand, 2000; McCulloch, 2003).

1.2 Mesenchymal stem cells

Adult stem cells are multipotent stem cells derived from peri- and post- natal tissues. The best characterized and clinically most advanced adult stem cells are mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). Mesenchymal stromal cells reside in the stroma of most organs. Mesenchymal stem cells can be readily isolated from different adult mesenchymal tissues, making MSCs one of the most available stem cell populations for research and transplantation (Zuk *et al.*, 2001; Phinney and Prockop, 2007). Mesenchymal stem cells constitute a rare non-haematopoietic population in the adult mesenchymal tissues which can be defined based on its ability to self-renew and differentiation into adipocyte, osteocyte and chondrocyte (Pittenger *et al.*, 1999). Due to a lack of a single marker to define MSCs and variation in MSCs derived from different sources, a set of criteria regarding differentiation potential, marker expression and *in vitro* culture capacity was adopted by the Mesenchymal and Tissue Stem

Cells Committee of the International Society for Cellular Therapy (Dominici *et al.*, 2006).

One of the best reservoirs of MSCs is umbilical cord MSCs (UC-MSCs) that are generated from umbilical cord. Umbilical cord is considered an appealing source of adult stem cells for cell therapy and tissue engineering due to the fact that they can be easily obtained and are expanded faster while maintaining their multi-lineage differentiation potential. Many studies have been conducted with bone marrow MSCs and less is known about UC-MSCs. Umbilical cord MSCs can be readily isolated from Wharton's jelly (WJ) by using enzymatic digestion and mechanical disassociation (Tong *et al.*, 2011).

In many instances, it has been shown that MSCs exhibit a potent immunosuppressive activity which targets almost all types of immune cells of both myeloid and lymphoid linage. The weak immunogenicity of MSCs is the most important characteristic of MSCs which makes them suitable for xenogeneic and allogeneic transplantation. Due to these characteristics, MSCs have been considered a suitable candidate for non-immunocompromised model of transplantation.

1.3 Tumour Cells and Interaction of UC-MSCs and Tumour cell

Cancer is a generic term for a large group of diseases that are characterized by the uncontrolled growth and spread of abnormal cells. Malignant tumours and neoplasms are other terms normally used to refer to cancer (Adami *et al.*, 2002). In 2012, there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide and it was the second leading cause of death after cardiovascular diseases (Global Burden of Disease Cancer, 2015). Environmental factors play an essential role in cancer development but cancer might also occur due to heredity (Anand *et al.*, 2008). The beginning of cancer, inside the cell, is most commonly dependent on a genetic mutation that occurs in the DNA of the cell. The genetic sequence change leads to production of a mutant protein. However, more commonly, when several mutations happen inside the DNA in the cell, a normal cell transforms to a cancerous one.

Current conventional cancer therapies such as radiotherapy, chemotherapy and surgery are, to a significant extent, symptomatic and passive in nature. Despite improved treatment models, many tumours remain unresponsive to conventional therapies. When fatalities occur, the majority of cancer patients die from the therapy-related life-threatening complications or recurrence of metastasis. The major obstacle limiting the effectiveness of conventional therapies for cancer is their tumour specificity. Therefore, it is critical to explore efficient treatment strategies that specifically target tumour cells.

Tumour progression and development are dependent on the interaction between tumour cells and the surrounding stroma (Mbeunkui and Johann, 2009). The mutual interactions of tumour cells and stromal cells through direct contact to various chemokines and cytokines in a paracrine manner are thought to modulate tumour progression (Orimo *et al.*, 2005; Karnoub *et al.*, 2007; Whiteside, 2008). Several studies have outlined MSCs promote tumour cells proliferation and metastasis (Yu *et al.*, 2008; Shinagawa *et al.*, 2010), whereas other studies have observed that MSCs display anti-tumour activities (Khakoo *et al.*, 2006; Gauthaman *et al.*, 2012b; Lee *et al.*, 2013). Therefore, these discrepancies requires further investigation.

The main source of MSCs is bone marrow (BM), but the collection of MSCs from BM are extremely difficult and also proliferation and mesodermal differentiation capacities of BM-MSCs decrease with aging (Rao and Mattson, 2001). Furthermore, most of the works were carried out using BM-MSCs instead of UC-MSCs and were very specific to certain types of tumour. However, umbilical cord collection is convenient and is not associated with any ethical or legal issue (Secco *et al.*, 2008). Baksh et al have confirmed that the proliferative and differentiation abilities of UC-MSCs are greater than BM-MSCs (Baksh *et al.*, 2007). Therefore, UC-MSCs are considered a promising source of stem cells for tumour cells treatment.

Some studies have shown that UC-MSCs target many primary tumours and their metastases (Ayuzawa *et al.*, 2009; Xu *et al.*, 2009). Umbilical cord MSCs have been found to reduce the growth of breast cancer cells via secreting of interferon-β (IFN-β) by inducing apoptosis (Rachakatla *et al.*, 2008). Furthermore, Ganta et al have shown that the intra-tumoural injection of rat UC-MSCs caused regression of rat mammary carcinomas (Ganta *et al.*, 2009). Consequently, the results showed that UC-MSCs exhibit an anti-tumour effect. However, it is necessary to explore this aspect with a different type of tumours since different tumour lineage employs different mechanism for their own survival. Furthermore, the molecular mechanism and signalling pathway of UC-MSCs on tumour cells remains unclear. Therefore, a better understanding of the molecules, mechanism and signals that regulate the proliferation, migration and invasion of hematopoietic tumour cells are essential to the development of novel effective therapies. Thus, the present study is mostly to focus on the molecular mechanism/s and signalling pathway/s underlying these effects.

1.4 Objectives of the study

The present study aims to follow the following research objectives:

General Objective

To decipher the anti-tumour activity of human UC-MSCs on haematopoietic tumour cell lines.

Specific Objectives:

- To generate and characterize mesenchymal stem cells derived from human umbilical cord tissue (UC-MSCs).
- To elucidate the inhibitory/anti-tumour effect of UC-MSCs on haematopoietic tumour cell line.
- To profile the global gene expression changes inflicted by UC-MSCs in BV173 cell line.
- To decipher the potential biological process/es and signalling pathway/s that mediate(s) the anti-tumour activity of UC-MSCs

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LIST OF PUBLICATIONS

Published:

Mesenchymal Stem Cell Inhibit Proliferation of Lymphoid Origin Haematopoietic Tumour Cells by Inducing Cell Cycle Arrest
VH Sarmadi, C K Tong, S Vidyadaran, M Abdullah, H F Seow, R Ramasamy
Malaysian Journal of Medicine and Health Sciences, Vol. 65 (3) September 2010

Under Review:

Umbilical cord derived mesenchymal stem inhibit leukemic cells proliferation: reveal global genes expression
Vahid Hosseinpour Sarmadi, Heng Fong Seow, King Hwa Ling, Aishah Adamand Rajesh Ramasamy

The role of umbilical cord derived mesenchymal stem cells in Lymphatic origin tumour cells proliferation
Vahid Hosseinpour Sarmadi, Salma Ahmadloo, Heng Fong Seow, King Hwa Ling, Aishah Adamand Rajesh Ramasamy

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