UNIVERSITI PUTRA MALAYSIA

IMMUNOMODULATORY AND GENE EXPRESSION CHARACTERISATION OF HUMAN MESENCHYMAL STEM CELLS DERIVED FROM NON-OSTEOARTHRITIC AND OSTEOARTHRITIC CARTILAGE

SATAR JABBAR RAHI AL-GRAITTEE

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By

SATAR JABBAR RAHI AL-GRAITTEE

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

February 2018

DEDICATION

This thesis is dedicated to my parents and my ever-loving wife.

Abstract thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Doctor of Philosophy

IMMUNOMODULATORY AND GENE EXPRESSION CHARACTERISATION OF HUMAN MESENCHYMAL STEM CELLS DERIVED FROM NON-OSTEOARTHRITIC AND OSTEOARTHRITIC CARTILAGE

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February 2018

Chairman : Associate Professor Rajesh Ramasamy, PhD
Faculty : Medicine and Health Sciences

Osteoarthritis (OA) is a degenerative disease characterised by progressive loss of articular cartilage which affects millions of people globally. Although the leading causes of OA are still elusive, the increasing body of evidence indicates that the predisposing factors such as lifestyle, age, injuries and genetics associated with the onset of OA. The regeneration of the degraded cartilage tissue in OA is mediated by the tissue-resident stem cells. However, in advanced OA, the regenerative and tissue repair capability of tissue-resident stem cells is compromised as a result of diseases condition and leads to an unusual stem cell nature. Mesenchymal stem cells (MSCs) have been implicated in the pathogenesis of OA and, in turn, the progression of the disease could be therapeutically modulated by MSCs. However, it remains unclear whether the defective tissue-resident MSCs contributes to the pathogenesis of OA by a depleted stem cell pool or loss of the chondrogenic differentiation potential which impedes on the proper execution of stem cell functions. Therefore, this study aimed to explore the biological properties of human non-OA and OA cartilage-derived MSCs (C-MSCs) as well as to determine whether the defects in human OA C-MSCs are results of an inherent genetic make-up or acquired from the exposure of pathological OA inflammatory environment.

A small fraction of non-weight bearing human articular cartilage from non-OA subjects and OA patients were harvested during the arthroscopy session. Patients (n=11) were selected based on the grade 4 osteoarthritis according to the Kleegren and Lawrence score system, and five cartilage samples were obtained from non-osteoarthritic donors undergoing knee surgery or arthroscopy due to the sports injury. The optimised enzymatic digestion and serial plating methods were used to generate

cartilage-derived MSCs. The differences in biological features of OA compared to non-OA C-MSCs as well as that of non-OA C-MSCs cultured in OA synovial fluid were investigated through a series of proliferation, cell cycle and apoptosis assays. The secretome profile and the global gene expression were performed through cytokine antibody arrays and microarray, respectively.

Mesenchymal stem cells were successfully generated from the human OA cartilage tissues along with non-OA cartilage. As compared to the human non-OA C-MSCs, the counterpart from OA exhibited compromised cell qualities in term of ill-defined morphology specifically at late passages, lower colony forming ability, reduced chondrogenesis when induced, a higher tendency towards osteogenic and adipogenic differentiation. However, the immunophenotypic profile between these two groups remained relatively same. Additionally, human OA C-MSCs also demonstrated slower growth kinetics, prolonged doubling time, increased susceptibility to senescence especially at late passages, reduced proliferation and poor immunosuppressive ability against T cells. It was also observed that during the in vitro culture expansion, the human OA C-MSCs underwent escalated level of cellular senescence in late passage (80%), apoptosis (i.e. 18.33±0.1% early apoptosis, 6.46±0.2% late apoptosis at passage 3 and 20.09±0.1% early apoptosis, 8.42±0.2% late apoptosis at passage 6), exhibited G0/G1 cell cycle arrest (i.e. 78.68±3.17% of cells in G0/G1 phase, at passage 3 while passage 6 had 93.23±2.64% of cells in G0/G1 phase) with a secretome profile that reveals the downregulation of anti-inflammatory cytokines such as IL-1, IL-6, and IL-10, as well as aberrations in gene expression.

Analysis of OA synovial fluid indicated with presence of proinflammatory cytokines that associated with OA pathophysiology while pre-treated non-OA C-MSCs with OA synovial fluid exhibited increased apoptosis (i.e. 28.42±0.66% early apoptosis and 12.11±0.47% late apoptosis) and inhibition of proliferation via cell cycle arrest (i.e.78.62±4.38% of cells in G0/G1 phase and 12.42±1.53% of cells in S phase). These findings suggest that the catabolic and inflammatory agents in the synovial fluid could be implicated in cartilage tissue degradation, and may also be involved in the alteration of the inherent genetic makeup of cartilage tissue-resident MSCs which is evident from the aberrant gene expression. The microarray-based gene expression analysis of OA C-MSCs indicated dysregulation of essential genes of cell proliferation and survival, whereas the gene expression of non-OA MSCs treated with OA synovial fluid revealed dysregulation of cartilage metabolism. The KEGG pathway analysis based on the dysregulated gene expression showed the involvement of several key signalling pathways especially Wnt signalling, cell adhesion molecule pathway, Ras signalling pathway, cytokine-cytokine receptor interaction pathway.

In conclusion, the biological features of OA C-MSCs are negatively affected by OA disease. It could be possible that the inflammatory condition of OA synovial fluid impedes the functional properties of cartilage tissue-resident MSCs. Thus, treatment strategies for OA should be strategized by allotting an appropriate concern to the

inflammatory condition that limits the function of tissue stem cells and therapeutically transplanted stem cells.

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

IMUNOMODULATORI DAN EKSPRESI GEN OLEH SEL PUNCA MESENKIMAL MANUSIA DARIPADA RAWAN NON-OSTEOARTRITIS DAN OSTEOARTRITIS

Oleh

SATAR JABBAR RAHI AL-GRAITTEE

Februari 2018

Pengerusi : Profesor Madya Rajesh Ramasamy, PhD
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Osteoartritis (OA) adalah penyakit degeneratif yang menjejaskan berjuta-juta orang di dunia. Walaupun punca utama OA masih sukar difahami, kajian saintifik menunjukkan bahawa factor-faktor seperti penuaan, trauma dan kecederaan sering dikaitkan dengan permulaan OA. Walaupun pertumbuhan semula rawan akibat kecederaan dan trauma fizikal ditentukan oleh sel-sel punca tempatan, bagaimanapun keadaan-keadaan tertentu boleh menghalang pertumbuhan semula dan proses pembaikan yang lengkap. Ini mungkin disebabkan sel punca yang abnormal yang kemudiannya menjurus kepada penyakit degenerative. Sel-sel punca Mesenkimal (MSCs) telah dikaitkan dengan patogenesis OA, dan boleh dirawat dengan MSC. Walaubagaimanapun, penghausan rawan dalam penyakit OA samada disebabkan oleh pengurangan sel punca rawan tempatan ataupun penurunan tahap pembezaan kondrogenik oleh MSC masih belum jelas. Oleh itu, kajian ini bertujuan untuk mengkaji sifat MSC yang diterbitkan daripada rawan manusia normal dan diperolehi dari pesakit OA. Disamping itu, kajian ini juga bertujuan untuk menentukan sama ada keabnormalan yang diteliti pada MSC rawan OA adalah hasil daripada kelainan dalam eksperesi gen-gen MSC ataupun diaruhi oleh inflamasi dipersekitaran rawan.

Secebisan kecil rawan artikular manusia yang tidak menanggung berat badan dari pesakit osteoartritis dan juga penderma non-OA dituai semasa sesi artroskopi. Seramai sebelas pesakit (n= 11) telah dipilih berdasarkan sistem skor Kleegren dan Lawrence (osteoartritis gred 4) dan lima sampel rawan normal diperolehi daripada penderma sihat yang menjalani pembedahan lutut atau artroskopi akibat kecederaan sukan. Kaedah pencernaan enzim yang dioptimumkan dan kaedah kultur bersiri telah dipilih untuk menjana MSCs yang berasal dari tulang rawan. Indeks-indeks untuk mencirikan MSC termasuk pemerhatian morfologi, keupayaan pembentukan koloni, masa

penggandaan dan kinetik pertumbuhan, imunofenotaip dan pembezaan mesoderma telah dijalankan dan dibandingkan dengan MSCs dari rawan manusia normal. Perbezaan ciri-ciri biologi MSC OA dan normal telah ditentukan melalui proses percambahan, kesenesenan, kitaran sel dan apoptosis. Profil sekretom dan ekspresi gen global melalui mikroarray telah diteruskan untuk mengukur eksperesi protein and gen, masing-masingnya untuk merumus laluan isyarat yang terlibat. Pada masa yang sama, MSCs daripada non-OA dikulturkan dengan bendalir sinovial yang diperolehi dari pesakit OA untuk menentukan sama ada persekitaran inflamasi boleh mangaruh keabnormalan pada MSC non-OA.

Sel punca mesenkimal telah berjaya dijanakan daripada tisu rawan OA manusia dan rawan non-OA. Berbanding dengan non-OA C-MSCs, OA C-MSCs mempamerkan kualiti sel yang terkompromi dari segi morfologi terutamanya di passages lewat, keupayaan membentuk koloni yang lebih rendah, tahap kondrogenesis berkurangan apabila diaruh, serta kecenderungan lebih tinggi terhadap pembezaan osteogenik dan adipogenik. Walau bagaimanapun, profil imunofenotaip di antara kedua-dua kumpulan ini secara relatifnya kekal sama. Di samping itu, OA C-MSCs juga menunjukkan kinetik pertumbuhan yang perlahan; masa penggandaan yang berpanjangan; kecenderungan terhadap proses kesenesenan di sekitar passage lewat; dan kadar percambahan rendah dengan potensi imunosupresif yang lemah terhadap sel-sel T. Tambahan pula, OA C-MSCs juga mengalami proses apoptosis, perencatan kitaran sel di fasa G_0/G_1 dengan profil sekretom yang mirip kepada pro-inflamasi.

Analisis bendalir synovial OA menunjukan kehadiran sitokin-sitokin pro-inflamasi dan juga biomarkers OA. Apabila, non-OA C-MSCs dirawat dengan bendalir synovial OA, peningkatan apoptosis, pengurangan percambahan melalui hentian kitaran sel, dan tahap kesenesenan sel semakin meningkat. Penemuan ini menunjukkan bahawa ejen-ejen katabolisme dan inflamasi di persekitaran synovium terlibat dalam degradasi tisu rawan, dan mungkin punca kepada pengubahan ciri-ciri semulajadi MSCs serta penyerongan ekspresi gen. Hasil analisis mikroarray memaparkan disregulasi eksperesi gen-gen penting dalam metabolisme tulang rawan dan fungsi MSCs dan menjurus kepada perubahan dalam laluan isyarat utama terutama sekali pengisyaratan Wnt, laluan molekul lekatan sel, laluan pengisyasratan Ras, dan laluan interaksi sitokin-reseptor sitokin.

Kesimpulannya, kadar pertumbuhan sel yang perlahan, perubahan dalam morfologi, kecenderungan kepada kesenesenan awal dan kadar kondrogenesis yang berkurangan dalam OA C-MSCs mungkin berakarumbi daripada patologi and paras inflamasi yang tinggi di persekitaran OA. Berkemungkinan besar keadaan inflamasi di sekitar synovium menghalang fungsi MSCs tempatan. Perubahan dalam ciri-ciri biologi pada OA C-MSCs disokong dengan ekspresi gen yang mempengaruhi nasib sel melalui pelbagai laluan isyarat. Oleh itu, strategi rawatan OA perlu dikaji semula dengan memberi keprihatinan yang sesuai terhadap persekitaran mikro yang tidak-kondusif dan inflamasi yang menghadkan fungsi sel-sel punca tempatan dan juga sel-sel punca yang ditransplantasikan secara terapeutik.

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I certify that a Thesis Examination Committee has met on 8 February 2018 to conduct the final examination of Satar Jabbar Rahi Al-Graittee on his thesis entitled "Immunomodulatory and Gene Expression Characterisation of Human Mesenchymal Stem Cells Derived from Non- Osteoarthritic and Osteoarthritic Cartilage" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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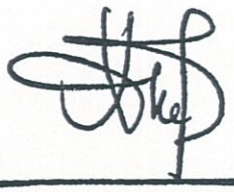

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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ABB	Annexin Binding Buffer
ACAN	Gene encoding aggrecan
ADAM TSs	Disintegrin metalloproteinases with thrombospondin
Akt	Serine-threonine kinase
ALK	Activin receptor-like kinases
Ang-1	Angiopoietin-1
ANGPTL4	Angiopoietin-like 4
APC	Adenomatous polyposis coli
BCL2	B cell Lymphoma 2
bFGF	Basic fibroblast growth factor
BGLAP	Aone gamma-carboxyglutamate protein
BM	Bone marrow
BM-MSCs	Bone Marrow Mesenchymal Stem cells
BMPs	Bone marrow Morphogenic Proteins
CAMs	Cell adhesion molecules
CCL2	Chemokine ligand 2
CDKs	Cyclin-dependent kinases
CFU-f	Colony Forming Unit- fibroblast
CKI	Casein kinase I
CKIs	CDK inhibitors
COL2A1	Collagen type II alpha 1 chain
COMP	Cartilage oligomeric matric protein
COX2	Cyclooxygenase 2
CSF-MSCs	Synovial fluid MSC
CX3CL1	CX3 motif chemokine ligand 1
Cy3	Cyanine- 3
DDR	DNA damage response
DIO2	Deiodinase, Iodothyronine, type II
DKK1	Dickkopf-related protein 1
EBs	Embryoid bodies
ECM	Extracellular matrix

EGF	Epidermal growth factor
ELN	A gene that encodes the protein Elastin
ENA-78	Epithelial-derived Neutrophil-Activating peptide 78
ERK	Extracellular signal-regulated kinase
FABP4	Fatty acid binding protein 4
FACS	Fluorescence Activated Cell Sorting
FADD	FAS Activated Death Domain
FGF	Fibroblast growth factor
FITC	Fluorescein Isothiocyanate
FRZB	Frizzled-related protein
GRO-a	Growth-Regulated Alpha protein
GSK3β	Glycogen synthase kinase 3β
GvHD	Graft versus Host Disease
HA	Hyaluronic acid
hC-MSCs	Human cartilage MSCs
HGF	Hepatocyte growth factor
HLA-G	Human leukocyte antigen G
HO-1	Heme oxygenase-1
HRP	Horse Radish Peroxidase
ICAM	Intercellular adhesion molecule
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
IGFs	Insulin-like Growth Factors
IL	Interleukin
IL-1Ra	Interleukin 1 receptor antagonist
IL-1α/β	Interleukin-1alpha/ beta
iNOS	inducible nitric oxide synthase
ISCT	International Society for Cellular Therapy
KEGG	Kyoto Encyclopaedia of Genes and Genome
KGF	Keratinocyte growth factor
LEP	Leptin
LIF	Leukaemia inhibitory factor
LPL	Lipoprotein lipase

LRP	Lipoprotein receptor-related protein
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MMPs	Matrix metalloproteinase
MSCs	Mesenchymal stem cells
NO	Nitric oxide
NTNG1	Netrin G1
OA	Osteoarthritis
OA C-MSCs	Osteoarthritis cartilage-derived MSCs
OSM	Oncostatin M
PBMCs	Peripheral Blood Mononuclear Cells
PDGF	Platelet-derived growth factor
PD-L1/2	Programmed cell death 1 ligand1/2
PDT	Population doubling time
PGE2	Prostaglandin E2
PHA	Phytohemagglutinin
PI3K	Phosphatidylinositol 3 kinase
RA	Rheumatoid arthritis
RIN	RNA integrity number
RTKs	Receptor tyrosine kinases
S1P	Sphingosine 1-phosphate
S1PR1	Sphingosine-1-phosphate receptor 1
SA-β-Gal	Senescence-Associated β-galactosidase
SAA1	Serum Amyloid A1
SDF -1	Stem cell-derived factor-1
SMOC-2	Secreted modular calcium-binding protein-2
Sox9	SRY-Box9
SPP1	Secreted phosphoprotein 1
sTNFR	Soluble tumour necrosis factor receptor
TGFs	Transforming Growth Factors
TIMPs	Tissue inhibitors of metalloproteinases
TNF	Tumour necrosis factor

TSG	TNF-α stimulated gene/protein
UC-MSCs	Umbilical cord-derived MSCs
VEGF	Vascular endothelial growth factor
VTCNT1	V-set domain-containing T-cell activation inhibitor 1
WNT	Wingless type MMTV integration site

CHAPTER 1

INTRODUCTION

The impact of 'regenerative medicine' has brought substantial changes and revamps in the practices of modern medicine. It has opened a new trend and opportunity to treat or control many degenerative diseases that were once considered as terminal illnesses. After many years of talk, with hopes and hypes, the uses of stem cells of embryonic origins in clinical applications have been rather limited by the ethical concerns and the risk of differentiating into dysplastic or even malignant cell lines by virtue of their pluripotency. Thus, in the past 10 years, the research focus for the potential therapeutic application has been shifted towards safer stem cells, especially the adult stem cells (Wiedemann *et al.*, 2004) ,.

Mesenchymal stem cells or mesenchymal stromal cells (MSCs) have seized the attention of many scientists worldwide because of their versatility in differentiating into many mature cell types and also the ability to modulate immune responses. These cells are not only considered as non-immunogenic or immune-privilege in the setting of allogeneic transplantation, they are also proven to be indispensable in tissue engineering and regenerative medicine. Under specific conducive conditions, MSCs can differentiate into chondrocytes, osteocytes, adipocytes, and myocytes among others. Nevertheless, the obvious challenge that could be encountered in the clinical application using MSCs is their generation from adult tissues and subsequent expansion to produce large cell numbers.

Many studies have successfully optimised the methods of isolating and expanding MSCs from adult tissues such as bone marrow (Ayatollahi *et al*., 2012), umbilical cord blood (Peters *et al.*, 2010), umbilical cord tissue (Yusoff *et al*., 2016), placenta tissue (Vellasamy *et al*., 2012), adipose tissues (Boquest *et al*., 2006), synovium (Harvanová *et al*., 2011) and cartilage (Grogan *et al*., 2009). Although the challenge in expanding MSC remains a significant problem, the potential usefulness of MSCs in the treatment of autoimmune diseases and inflammatory arthritic conditions like rheumatoid arthritis and osteoarthritis (OA) has been very promising (De Bari, 2015; Jo *et al*., 2014). Meanwhile, there are reports by previous studies on the poor quality and reduced, or impaired biological function of MSCs that are derived from tissues of patients with different disease conditions. Overproduction of IL-6 and reduced immunosuppressive efficiency have been reported in MSCs derived from the bone marrow of myeloma patients (Arnulf *et al*., 2007). Similarly, impaired proliferative capacity and a lower immunosuppressive potential have been observed in MSCs from the bone marrow of patients with immune thrombocytopenic purpura (Pérez-Simón et al., 2009) and severe aplastic anaemia (Bacigalupo *et al*., 2005), compared with MSCs from healthy donors. In systemic lupus erythematosus, early senescence-associated defective morphological and growth characteristics of bone marrow MSCs have been reported (Nie et al., 2010).

Although there are no specific nomenclatures for MSCs, the adherence to the plastic surface, tri-lineage differentiation ability (i.e. chondrogenesis, adipogenesis and osteogenesis) as well as the presence/ absence of specific cell surface markers have been the main criteria for classification of MSCs. The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) proposed the following as minimal criteria to define human MSCs (Dominici *et al*., 2006).

i. Ability to adhere to the plastic surface when maintained in a standard culture condition.
ii. Express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules.
iii. Differentiate to osteoblasts, adipocytes and chondroblasts *in vitro*.

The adult stem cells, particularly MSCs are very much implicated in the tissue specific degenerative diseases. One of the degenerative diseases that affect millions aged people is osteoarthritis. Osteoarthritis results from the degeneration of joint tissues, and often associated with severe pain and disability in adults (Control and Prevention, 2010). Osteoarthritis is reflected by wear and tear of the articular cartilage, and involves the action of inflammatory mediators at the joint, resulting an irregular remodelling of the joint tissues (Rahmati *et al*., 2016). There are several risk factors associated with OA. However, obesity, age, gender, prior joint injury and genetic history are among the most important ones (Blagojevic *et al*., 2010). Although OA has been identified as a complex condition with unknown aetiology, the damage or loss of articular cartilage accompanied by changes in the subchondral bone and synovial inflammation could serve as indicators of the development of the disease condition (Findlay, 2010). The synovial inflammation triggers the recruitment of immune cells to the synovium; induce secretion of proinflammatory cytokines and production of cartilage degenerating proteinases that elicit destruction of the cartilage (Scanzello *et al*., 2008; Mukundan Attur *et al*., 2010).

The physiological or a minute scale of tear and wear off of the cartilage tissue is well compensated by the tissue-resident MSCs, where they can differentiate into cells of mesodermal progenies (Alsalameh *et al*., 2004a; Pretzel *et al*., 2011). However, in a disease condition such as OA, the cartilage tissue-derived MSCs are inadequate or unable to execute the cartilage repair as the need of regeneration could not be reciprocated by tissue-resident stem cells (Mobasheri *et al*., 2014). It was also reported that the chondrocytes produce and release cartilage-degrading enzymes, proinflammatory cytokines, matrix metalloproteinase, aggrecanase, nitric oxide and prostaglandins during the progression of OA leading to progressive degeneration of cartilage tissue (Sokolove and Lepus, 2013). Under physiological condition, MSCs in the cartilage are expected to repair the degenerated cartilage. However, in OA, the capacity for cartilage to undergo a repair mechanism that mediated by MSCs is limited (Brandt and Mazzuca, 2006). Furthermore, the presence of inflammation in the synovial fluid has been associated with the progressive degeneration of cartilage in OA (Vangsness *et al*., 2011; Berenbaum, 2013) However, it remains unclear whether

the impairment of reparative abilities of the OA cartilage-derived MSCs is resulted from inherent defects of MSCs or induced by the synovial inflammation.

1.1 Problem statement

Osteoarthritis is the most common and important form of arthritis with features of articular cartilage degeneration, accompanied by subchondral bone sclerosis and synovial inflammation. The progressive destruction of articular cartilage stimulates synovial lining cells and articular chondrocytes within diseased cartilage to synthesize and secrete proteolytic enzymes: matrix metalloproteinase, aggrecanase, proinflammatory cytokines and mediators such as nitric oxide and prostaglandins which further aggravates the cartilage destruction.

The inability of cartilage MSCs to repair the lost cartilage tissue has been identified as the major challenge in OA. Thus, investigations should target whether the impaired reparative function of cartilage MSCs is a result of stem cell pool depletion or defective stem cells with less differentiation potential that prevent the proper execution of stem cell functions.

Besides the insufficient stem cells number and its respective qualities, the constant inflammatory milieu as well possess a new challenge in maintaining transplanted stem cells or expansion of the tissue-resident stem cells. This could be a result of interference with the normal stem cell function by the OA-associated inflammatory synovial fluid. Therefore, it is necessary to investigate whether the inflammatory synovial fluid which is known to be involved in cartilage tissue degradation can alter the inherent genetic nature of cartilage resident MSCs. Findings from this investigation will raise awareness on factoring the potential negative effects of synovial inflammation during stem cell-based therapy for OA patients.

1.2 Hypothesis

i. Mesenchymal stem cells can be generated from OA cartilage with immunophenotypic and biological properties similar to the non-OA C-MSCs.

ii. The inadequacy of OA cartilage-derived MSC to regenerate injured cartilage is due to the inflammatory microenvironment at the affected joint areas.

1.3 Objectives of the study

1.3.1 General objective

To evaluate the immunomodulatory and gene expression of human MSCs derived from OA and non-OA cartilage.

1.3.2 Specific objective

i. To optimise the generation and expansion of cartilage MSCs from OA and non-OA donors.
ii. To compare the biological features of OA and non-OA cartilage-derived MSCs.
iii. To determine the immunosuppressive activity and global gene expression profile of OA cartilage-derived MSCs.
iv. To investigate the impact of OA-synovial fluid on non-OA cartilage-derived MSCs.

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LIST OF PUBLICATIONS

Journal Publications

Mesenchymal Stem Cell-Mediated T Cell Immunosuppression **Satar Jabbar Rahi Algraittee**, Hamza Lawal, Rajesh Ramasamy Stem Cell Res Ther: SCRT-119. DOI: 10.29011/SCRT-119. 000019, 2017

Generation and Characterization of Human Osteoarthritis Cartilage-Derived Mesenchymal Stem Cells by Modified Sample Processing and Culture Method **Satar Jabbar Rahi Algraittee**, *Mohadese Hashem Boroojerdi, Vahid Hosseinpour Sarmadi, Maryam Maqbool, Fahrudin Che Hamzah, Shalini Vellasamy, Ling King Hwa, Rajesh Ramasamy* Manuscript has been submitted to **Stem Cells International (Q3)**

Immunomodulatory and Gene Expression Profile of Human Mesenchymal Stem Cells derived from Normal and Osteoarthritis Cartilages **Satar Jabbar Rahi Algraittee**, *Vahid Hosseinpour Sarmadi, Fahrudin Che Hamzah, Shalini Vellasamy, Ling King Hwa, Rajesh Ramasamy* Manuscript in preparation for **Cytotherapy (Q1)**

Review article: Osteoarthritis derived mesenchymal stem cells **Satar Jabbar Rahi Algraittee**, *Fahrudin Che Hamzah, Rajesh Ramasamy* Manuscript in preparation for **Stem Cell Research & Therapy (Q2)**

Characterisation and immunosuppressive activity of human cartilage-derived mesenchymal stem cells Sandrasaigaran, P., **Satar Jabbar Rahi Algraittee**., Ahmad, A. R., Vidyadaran, S., & Ramasamy, R. (2018).. Cytotechnology, 1-14.

The effect of umbilical cord-derived mesenchymal stem cells on leukemic cell growth: Lesson learned from global gene expression profiling *Vahid Hosseinpour Sarmadi,* **Satar Jabbar Rahi Algraittee**, *Mohadese Hashem Boroojerdi, , Maryam Maqbool, Ling King Hwa, Rajesh Ramasamy* Manuscript in preparation for **Leukemia (Q1)**

Mitogenic Activity of Human Mesenchymal Stem Cells on Haematopoietic Stem Cells through Modulation of Genes associated with Proliferation, Apoptosis and Signalling Pathways Mohadese Hashem Boroojerdi, Vahid Hosseinpour Sarmadi, Maryam Maqbool, **Satar Jabbar Rahi Algraittee**, Cini Mathew John, King-Hwa Ling, S. Khartini Abdul Wahab, Rajesh Ramasamy Manuscript submitted to **Stem Cell International (Q2)**

Conference Proceedings

1) **Satar Jabbar Rahi Algraittee**, Shalini Vellasamy, Fahrudin Che Hamzah, Ling King Hwa, Cini Mathew John, Rajesh Ramasamy
Human mesenchymal stem cells derived from Normal and Osteoarthritis Cartilage
4th International Conference on Nanomedicine and Tissue Engineering (ICNT2016)
12-14th August 2016, Mahatma Gandhi University, Kottayam, Kerala, India

2) **Satar Jabbar Rahi Algraittee**, Ling King Hwa, Fahrudin Che Hamzah, & Rajesh Ramasamy
A Comparison Study of Human Mesenchymal Stem Cells Derived from Normal and Osteoarthritis Cartilages
International Conference & Workshop: The Art of Stem Cell
8-10th April 2017, Sultan Agung Islamic University (UNSULA), Semarang, Indonesia

3) Haslinda Abdul Hamid, Mohd Kamarulzaki Mustafa, Azizi Miskon, **Satar Jabbar Rahi Algraittee**, Hamza Lawal & Rajesh Ramasamy
The Effects of Magnetic Field on in Vitro Culture of human Umbilical Cord Derived Mesenchymal Stem Cells
International Conference & Workshop: The Art of Stem Cell
8-10th April 2017, Sultan Agung Islamic University (UNSULA), Semarang, Indonesia

4) Hamza Lawal, Woo Yeng Fung, **Satar Jabbar Rahi Algraittee** & Rajesh Ramasamy
Ethanol Extract of Moringa Oleifera's Leaves Enhances the Viability and Expansion of Human Mesenchymal Stem Cells
International Conference & Workshop: The Art of Stem Cell
8-10th April 2017, Sultan Agung Islamic University (UNSULA), Semarang, Indonesia

5) Vigneshraaj Pushparajah, **Satar Jabbar Rahi Algraittee**, Collin Looi Seng Kim, Sharifah Roohi Ahmad, Rajesh Ramasamy
The Generation and Characterisation of Mesenchymal Stem Cells Derived from Goat's Bone Marrow and Mobilised Peripheral Blood
International Conference & Workshop: The Art of Stem Cell
8-10th April 2017, Sultan Agung Islamic University (UNISULA), Semarang, Indonesia

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