UNIVERSITI PUTRA MALAYSIA

INFLUENCE OF GENDER AND GENETIC POLYMORPHISM OF NATURAL KILLER CELL GENES ON ACUTE LYMPHOBLASTIC LEUKAEMIA

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FPSK(P) 2018 17

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By

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

September 2017

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

INFLUENCE OF GENDER AND GENETIC POLYMORPHISM OF NATURAL KILLER CELL GENES ON ACUTE LYMPHOBLASTIC LEUKAEMIA

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September 2017

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Acute lymphoblastic leukaemia (ALL) is characterized by an over-proliferation of immature lymphoblasts in the bone marrow. It is the most common cancer in children but affects adults as well. The majority of ALL are B cell lineage however approximately 15% are of T-cell origin. ALL predominates among males, from 1.2 times in B-cell lineage to 2.2 in T-cell ALL. Natural killer (NK) cells are significant players of the innate immune response characterised by cytolytic activity against virus-infected and tumour cells. The role of NK cells in immune surveillance and the tumour microenvironment are supported by earlier studies. Furthermore, like ALL it appears to be increased in the male gender. The activity of NK cells is regulated by groups of inhibitory and activating receptors. The role of NK cells in the leukaemogenesis is still unclear.This study hypothesise that variation in NK cell associated genes may affect functional killing activities of NK cells and influence leukeamogenesis. The objective of this study is to investigate genetic polymorphisms and variations in NK cell associated genes in of ALL patients and contrast between sexes.

The percentage of NK cells (CD56+) in peripheral blood mononuclear cells were compared between gender in B-cell and T-cell ALL and compared with healthy controls. The average percentage of NK cells in mononuclear cells was higher in male subjects including normal, B-ALL and T-ALL male compared to female subjects. Gene expression frequencies of activating and inhibitory killer cell immunoglobulin-like receptors (*KIR*), commonly studied were also compared between these samples. Significant absence in expression of *KIR2DL1-L4, 3DL3, 2DS2* and *S4* ($p<0.04$) were observed in ALL patients. The expression of *KIR2DL1, 2DL3, 2DL4, 3DL3* and *2DS4* were significantly absent in T-ALL male patients

when compared with normal male controls. Genetic mutation and polymorphism, particularly single nucleotide polymorphism (SNPs) and small variants were then examined for NK-related genes in ALL samples via next-generation sequencing (NGS). Significant small variants present in specific gender and groups were identified. The consequences of these small variants to amino acid coding were predicted. These small variants have potential effects to the NK cells of individuals. The effects of selected small variants identified by NGS on gene expression levels were also investigated using qPCR. Small variants present in *KIR3DL2, KLRC1, KLRC2* and *LILRB1* were found to be significantly associated with the downregulation of gene expressions. Gene copy number variations (CNVs) defined by deletion or amplification in NK cells associated genes were also identified following next-generation sequencing and further validated using real-time quantitative polymerase chain reaction (qPCR). In ALL patients, amplification was detected in *LAIR2, KLRC1, NCR1, NCR3, KLRC2, KLRC3* and *KLRC4* while deletion was detected in *CD69* and *KLRD1*. Gene copy numbers of KLRC2 and *KLRD1* were positively and significantly correlated with gene expression level. Lastly, the most common mechanism in epigenetic modification that is DNA methylation was investigated in the promoter regions of KIR. Hypermethylation or higher methylation index of KIR genes were observed in most ALL patients. Of these genes, *KIR2DL4* showed significant negative correlation between methylation index and gene expression (r_s= -0.610, $p< 0.001$). This study showed significant differences in genetics of NK cell related genes between ALL patients and healthy controls. There were also significant differences when genders were compared. These implied differences in function and activity of NK cells in the various groups and influence of gender from the variation in NK cell related genes may potentially affect leukaemogenesis on ALL. All the data from this fundamental study will lead to a better understanding on the innate immunity particularly the NK cell's arm in ALL patients and normal individuals on gender basis. The new insight on the genetic polymorphism, gene copy number variation and DNA methylation in ALL may be used to associate ALL with leukaemogenesis for better diagnosis and therapy in future. This study showed influence of gender in terms of genetic polymorphism, DNA methylation and gene copy number variations on ALL.

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

PENGARUHAN JANTINA DAN POLIMORFISME GENETIK BAGI GEN-GEN SEL PEMUSNAH SEMULAJADI TERHADAP LEUKEMIA LIMFOSITIK AKUT

Oleh

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Leukemia limfositik akut (ALL) dicirikan oleh proliferasi sel progenitor lymphoid secara melampau dalam sumsum tulang. Ia adalah kanser yang paling biasa ditemui dikalangan kanak-kanak. Kebanyakkan ALL adalah keturunan dari jenis sel-B (B-ALL) walaubagaimanapun kira-kira 15% adalah berasal dari sel-T (T-ALL). ALL lebih kerap terjadi di kalangan lelaki, 1.2 kali dalam ALL jenis sel-B dan 2.2 kali dalam ALL jenis sel-T. Sel pemusnah semulajadi (sel NK) adalah sejenis sel immune yang dapat dicirikan oleh aktiviti pembunuhan sel-sel yang dijangkiti oleh virus dan juga tumor. Peranan sel-sel NK dalam pengawasan imun dan persekitaran mikro tumor disokong oleh kajian terdahulu. Tambahan pula, seperti dalam ALL ia ternyata meningkat di golongan jantina lelaki. Aktiviti sel-sel NK dikawal oleh kumpulan-kumpulan reseptor penghalang dan pengaktif. Peranan sel NK dalam pembentukkan ALL masih kurang dikaji. Hipotesis kajian ini adalah variasi dalam gen-gen sel NK yang berkaitan berkeupayaan mempengaruhi fungsi kemusnahan sel NK dan berperanan dalam proses pembentukkan ALL. Objektif kajian ini adalah menyelidik poliformisme dan variasi genetic dalam gen-gen sel NK yang berkaitan dan membeza akan jantina.

Peratus sel NK (CD56+) dalam sel-sel mononuklear darah periferi dibandingkan antara jantina dalam sel-B dan sel-T ALL dan juga kumpulan kawalan yang sihat. Purata peratus sel-sel NK dalam sel-sel mononuklear adalah lebih tinggi dalam subjek lelaki termasuk dalam kumpulan kawalan, B-ALL dan T-ALL berbanding dengan subjek wanita. Frekuensi ekspresi gen-gen penghalang dan pengaktif reseptor killer cell immunoglobulin-like receptor (*KIR*) juga dibandingkan antara sampel-sampel. KEtakhadiran yang signifikan dalam ekspresi *KIR2DL1-L4, 3DL3, 2DS2* dan *S4* ($p<0.04$) diperhatikan dalam pesakit ALL. Ekspresi *KIR2DL1, 2DL3,*

2DL4, 3DL3 dan *2DS4* juga lebih rendah secara signifikan di pesakit lelaki T-ALL berbanding dengan kawalan normal. Mutasi genetik dan polimorfisme, terutamanya polimorfisme nukleotida tunggal (SNP) dan varian kecil dalam gen-gen sel NK telah diperiksa melalui penjujukan generasi baru (NGS). Varian kecil yang signifikan dalam jantina dan kumpulan tertentu telah dikenal pasti. Akibat daripada varian kecil dalam pengkodan asid amino telah diperiksa. Varian kecil mempunyai potensi berkesan kepada sel-sel NK dalam individu. Kesan varian kecil yang dikenal pasti daripada NGS di peringkat ekspresi gen telah disiasat menggunakan qPCR. Varian kecil di dalam *KIR3DL2, KLRC1, KLRC2* dan *LILRB1* didapati berkait secara signifikan dengan pegawalaturan menurun ekspresi gen. Variasi salinan gen (CNVs) yang ditakrifkan sebagai penghapusan atau amplifikasi dalam gen-gen sel NK juga disiasat dengan cara NGS dan seterusnya disahkan menggunakan qPCR. Dalam pesakit ALL, amplifikasi dikesan di *LAIR2, KLRC1, NCR1, NCR3, KLRC2, KLRC3* dan *KLRC4* manakala penghapusan dikesan di *CD69* dan *KLRD1*. CNV dalam gen *KLRC2* dan *KLRD1* berhubung secara positif dan signifikan dengan ekspresi gen. Akhir sekali, mekanisma yang paling biasa dalam pengubahsuaian epigenetik iaitu metilasi DNA telah disiasat di kawasan promoter gen-gen *KIR*. Hypermetilasi atau metilasi indeks gen *KIR* yang tinggi diperhatikan dalam kebanyakan pesakit ALL. Gen *KIR2DL4* menunjukkan hubugan negative yang signifikan antara indeks metilasi dan ekspresi gen (r_s= -0.610, $p< 0.001$). Kajian ini menunjukkan perbezaan yang signifikan dalam genetic gen yang berkaitan dengan sel NK antara pesakit ALL dan kawalan yang sihat. Terdapat juga perbezaan yang signifikan apabila jantina dibandingkan. Perbezaan tersirat dalam fungsi dan aktiviti sel-sel NK dalam pelbagai kumpulan dan juga jantina akibat variasi dalam gen-gen sel NK, maka berpotensi mempengaruhi pembentukkan ALL. Semua data dari kajian asas ini akan membawa kepada pemahaman yang lebih mendalam mengenai imuniti semula jadi terutamanya dari lengan sel NK dalam pesakit ALL dan individu normal mengikut jantina. Wawasan baru dari polimorfisme genetik, variasi salinan gen dan metilasi DNA dalam ALL boleh digunakan untuk mengaitkan ALL dengan leukaemogenesis untuk menambahbaik diagnosis yang lebih baik dan terapi pada masa depan. Kajian ini menunjukkan pengaruh jantina dari segi polimorfisme genetik dan variasi salinan gene pada ALL.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Assoc. Prof. Dr. Maha Abdullah for her guidance, advice, patience and encouragement throughout this project. A special note thanks to Prof. Dr. Seow Heng Feng, Dr. Michael Ling King Hwa and Dato' Dr. Chang Kian Meng as my co-supervisors for their invaluable advice.

In addition, I am thankful for the technical support from Malaysia Genome Institute (MGI). I owe special thanks to fellow scientists from MGI especially Pn. Irni Suhayu Sapian and En. Mohd Noor Mat Isa for all their constructive feedback and constant guidance.

In addition, I would like to express my sincere gratitude and appreciation to all who have directly and indirectly assisted me especially my fellow labmates. Most importantly, I would like to thank my family for their endless support and sacrifice. To my parents, thank you for understanding me throughout these years.

Thank you.

I certify that a Thesis Examination Committee has met on 20 September 2017 to conduct the final examination of Lee Le Jie on his thesis entitled "Influence of Gender and Genetic Polymorphism of Natural Killer Cell Genes on Acute Lymphoblastic Leukaemia" 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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ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
AR	Androgen receptor
BLAST	Basic local alignment search tool
bp	Base pair
CD	Clusters of differentiation
cDNA	Complementary DNA
CLEC	C-type lectin domain
CLL	Chronic lymphoblastic leukaemia
CML	Chronic myeloid leukaemia
CNV	Copy number variations
CR	Complete remission
DEPC	Diethylpyrocarbonate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dsDNA	Double stranded DNA
EDTA	Ethylenediaminetetraacetic
ESR	Estrogen receptor
FAB	French-American-British
FISH	Fluorescence *in situ* hybridisation
FU	Fluorescent unit
gDNA	Genomic DNA
HLA	Human leukocyte antigen
HSCT	Haematopoietic stem cell transplantation

IFN- γ	Interferon gamma
IL	Interleukin
ITAM	Immunoreceptor tyrosine-based activation motifs
ITGAL	Integrin alpha L
ITIM	Immunoreceptor tyrosine-based inhibitory motifs
KIR	Killer cell immunoglobulin-like receptors
KLR	C-type lectin-like receptors
LAIR	Leucocyte-associated inhibitory receptor
LCR	Leucocyte receptor complex
LILR	Leucocyte immunoglobulin-like receptor
M-MLV	Moloney murine leukaemia virus
MNP	Multiple nucleotide polymorphism
MOH	Ministry of Health
MRD	Minimal residual disease
mRNA	Messenger RNA
NCBI	National Center for Biotechnology Information
NCR	Natural cytotoxic receptors
NGS	Next-generation sequencing
NK cell	Natural killer cell
NTC	No-template control
PAS	Period acid-Schiff
PBS	Phosphate buffered saline
PGR	Progesterone receptor
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid
RPMI	Roswell Park Memorial Institute

RT	Room temperature
SEM	Standard error of mean
SNP	Single nucleotide polymorphism
TNF-α	Tumour necrosis factor
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

According to National Cancer Registry year 2011, leukaemia is the 7th most common cancer in Malaysia. Leukaemia is the haematological malignancy of blood or bone marrow, characterised by the production of large number of abnormal and immature white blood cells. Acute leukaemia is the aggressive type of leukaemia where the primary diagnosis and classification of acute leukaemia relied on cytomorphological, cytochemical and immunophenotype of leukaemic cells. Acute lymphoblastic leukaemia (ALL) is characterised by the over proliferation of immature and cancerous lymphocytes known as lymphoblast. ALL is a common pediatric leukaemia with peak incidence around two to five years old while another peak incidence appears in old age. There are generally few types of ALL which include B-cell lineage and T-cell lineage. The higher incidence of acute lymphoblastic leukaemia in male has been reported in Malaysia and other studies across the world.

The etiology of acute leukaemia is still unclear. Immune surveillance protects the body from cancer formation. Mechanisms in which tumour cells evade immune eradication include hijacking immune suppressive pathways as well as maintaining immune ignorance via both innate and adaptive immune systems (Gaiewski et al., 2013).

Natural killer (NK) cells are significant players of the innate immune response characterized by cytolytic activity against virus-infected and tumour cells (Lorenzo, 2007). The major function of NK cells in fighting cancer is to be in surveillance and elimination of cells that become malignant. NK cell function and detection systems are regulated by a group of inhibitory and activating receptors and also their ligand. Major NK cell receptors include killer cell immunoglobulin-like receptors (KIRs), natural cytotoxic receptors (NCRs) and C-type lectin-like receptors (KLRs). The ligands for NK cell receptors were reported be HLA class I, however, majority of the specific ligands for NK cells receptors are yet to be identified. Apart from specific NK cells receptors, other system such as Fas and Fas ligand and sex hormones are also important factors in cytotoxicity mediated by NK cells (Chua et al., 2004). NK cells were reported to be predominant in male (Oshimi et al., 1980; Santoli et al., 1976; Kennichi et al., 2003; Reichert et al., 1991). For instance, in a study of gender effect on *in vitro* lymphocyte subset levels, Abdullah et al. (2012) reported a higher percentage and absolute count of NK cells in blood of healthy male.

As the incidence of ALL was reported to be higher in male and NK cells were also found to in be higher percentage and activity in male. However, the association between the higher incidence of ALL and NK cells activity in male remains unknown. it is hypothesised NK cell variations at genetic level are present in ALL cases and is gender biased.

There are several potential factors causing the dysfunction of NK cells related genes in ALL including genetic factors such as mutations, genetic polymorphisms, and gene copy number variations (CNV). The sources of genetic polymorphism include single nucleotide polymorphism (SNPs), sequence repeats, insertions, deletions and recombination. SNP is the most common sequence variation in human genome (Risch, 2001). Associations of small variants with leukaemia prognosis, survival, therapy and replapse have been described in some studies. However, the association between small variants in genes coded for NK cell receptors and with its function has yet to be identified. Other than small variant, CNV has emerged as another crucial research area in leukaemia and other diseases as CNVs are present in human population with high frequency and potentially explain more variation than SNPs (Pang et al., 2010). This is because large scale variations with possible deletions of tumour suppressor genes or amplifications of oncongenes are often found in cancer genome. Lastly, epigenetic modification such as DNA methylation may be one of the factors causing irregular gene expression of NK cell receptors. DNA methylation in the promoter region of a gene can suppress transcription events and thus reduce gene expression (Stirzaker et al., 2004). Cancer-associated hypomethylation and hypermethylation in different extent, frequency and types of cancers had been described; however, more studies on the role of DNA methylation in tumourgenesis and tumour progression need to be carried out (Ehrlich, 2009). Study involved all four aspects (genetic polymorphism, gene expression, gene copy number and DNA methylation) in NK cells and ALL has not been substantiated by others.

The general objective of this study is to investigate the association between genetic variations in NK cell related genes in ALL patients and gender bias.

The specific objectives of this study are:

1. To compare gene expression of NK cell receptors and percentage of NK cells in ALL patients and healthy controls of different genders.
2. To investigate genetic polymorphisms and gene copy number variation in NK cell related genes in ALL patients and healthy controls of different genders.
3. To study the effects of genetic polymorphism on NK cell genes expressions in ALL patients and healthy controls of different genders.
4. To identify DNA methylation and its correlation with gene expression levels of NK cell related genes in ALL patients and healthy controls of different genders.

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