IDENTIFICATION OF DISRUPTED MOLECULAR NETWORKS INVOLVED IN BRAIN MATURATION AND FUNCTION IN THE TS1CJE MOUSE MODEL OF DOWN SYNDROME

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By

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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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April 2016

Chairman : Cheah Pike See, PhD
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Down syndrome (DS) is a chromosomal disorder resulted from trisomy of human chromosome 21 (HSA21). Cognitive impairment is the general feature for all DS individual. To date, there are no answers for the neuropathogenesis in DS individuals which can aid in determining targets for therapeutic interventions. Syntenically conserved HSA21 in mouse chromosome (MMU) 16, MMU17 and MMU10 enabled the generation of DS mouse models with different genetic content for scientific studies. However, insufficient understanding of the neuropathology mechanism in these mouse models impede the effort to unravel the trisomy secret in DS individuals. This study uses Ts1Cje, mouse model of DS with a triplicated region of MMU16 to identify neuropathological mechanisms of defective neurogenesis and neuronal development. We hypothesised that the trisomic genes in MMU16 are over-expressed and disrupts the functional molecular networks, leading to neuropathologies in Ts1Cje mouse brain. In order to prove the hypothesis, transcriptomic analysis comparing Ts1Cje and wild type control on three brain regions (cerebral cortex, cerebellum and hippocampus) across four postnatal (P) time-points (P1, P15, P30 and P84) by using microarray technology to identify the differentially-expressed genes (DEGs) and determination of the potential disrupted molecular network were performed. A total number of 317 DEGs were selected based on a stringent criteria and all the selected trisomic DEGs were up-regulated in their gene expression profiles. Functional clustering analysis of these 317 DEGs showed seven significant pathway clusters including interferon (IFN)-related signalling pathways. Validation of selected DEGs on their gene and protein expression profiles were performed by using quantitative real time polymerase chain reaction (RT-qPCR) and western blotting technique. Results demonstrated over-expression of the trisomic IFN receptor genes [IFN alpha or beta receptor subunit 1 (*Ifnar1*), IFN alpha or beta receptor subunit 2 (Ifnar2), and IFN gamma subunit 2 (*Ifngr2*)] and associated DEGs in IFN-induced Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signalling pathway [Leptin receptor (*Lepr*), and *Stat1*] on cerebral cortex and cerebellum at P84. Supported by previous study, IFN-induced JAK-STAT signalling pathway is selected to functionally characterise its role in gliogenic shift of DS brains. Preliminary study was conducted with Ifnar1 antagonist treatment on differentiating neural stem cell which was obtained via adult neurosphere

culture of Ts1Cje mouse brain. Restoration of defective neurogenesis and neuronal development were determined by RT-qPCR on gene expression profiles of neural stem markers, neuronal markers and glial markers. The result showed that the Ifnar1 antagonist treatment on differentiating neurospheres derived from Ts1Cje was able to revert the aberrant expression of *Stat1* to a level that was similar to those derived from wild type control. Collectively, the findings showed the over-expression of IFN receptors particularly *Ifnar1* which was due to trisomic segment of MMU16, disrupted IFN-induced JAK-STAT signalling pathway and may also dysregulate the neurogenesis and neuronal development in Ts1Cje mouse brain. Furthermore, the preliminary antagonisation study demonstrated a feasible direction to attenuate neurological abnormalities in DS individuals. This study suggests the potential of IFN-induced JAK-STAT signalling pathway as targets for therapeutic intervention in DS individuals.

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

PENGENALPASTIAN JARINGAN MOLEKUL TERGANGGU YANG TERLIBAT DALAM PEMATANGAN DAN FUNGSI OTAK MODEL MENCIT SINDROM DOWN TS1CJE

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Sindrom Down (DS) merupakan kecacatan kromosom yang disebabkan trisomi kromosom 21 manusia (HSA21). Ketakmampuan kognitif merupakan ciri umum semua individu dengan DS. Mekanisme neuropatologi yang boleh menentukan sasaran untuk rawatan terapeutik dalam individu dengan DS masih belum dikenalpasti sehingga kini. HSA21 yang terpelihara dari segi sinteni di dalam kromosom mencit (MMU) 16, MMU17 dan MMU10 menghasilkan beberapa model mencit DS dengan kandungan genetik yang berbeza bagi kajian sains. Namun begitu, kekurangan pemahaman mengenai mekanisme neuropatologi dalam beberapa model mencit DS ini menghalang usaha penyelidik untuk memahami kesan trisomi dalam individu dengan DS. Kajian ini menggunakan Ts1Cje, sejenis model mencit DS yang mempunyai tiga salinan bahagian MMU16 untuk mengenal pasti mekanisme neuropatologi yang menyebabkan kecacatan neurogenesis dan perkembangan neuron. Hipotesis kajian ini adalah ekspresi gen dengan trisomi MMU16 lebih tinggi dalam otak mencit Ts1Cje berbanding dengan mencit biasa, serta mengganggu jaringan molekul yang berfungsi, yang menyebabkan neuropatologi dalam otak mencit Ts1Cje. Untuk membuktikan hipotesis ini, analisis transkriptom dijalankan pada tiga bahagian otak (korteks serebrum, serebelum dan hipokampus) yang membandingkan antara mencit Ts1Cje dan mencit biasa pada peringkat umur P1, P15, P30 dan P84 hari selepas lahir. Teknik jujukan mikro digunakan untuk menentukan gen yang mempunyai ekspresi berbeza (DEG) dan jaringan molekul yang berpotensi terganggu dalam otak mencit Ts1Cje. Sebanyak 317 DEG ditentukan berdasarkan kriteria yang ketat dan semua DEG dalam trisomi MMU16 menunjukkan profil peningkatan ekspresi. Analisis pengelompokan berfungsi mengenal pasti tujuh kelompok lintasan yang signifikan, termasuk lintasan pengisyaratan yang berkaitan dengan interferon (IFN). Pengesahan DEG yang terpilih dijalankan atas ekspresi gen dan protein dengan mengunakan tindak balas berantai polimerase yang kuantitatif pada masa nyata (RT-qPCR) dan pemendapan *Western*. Keputusan menunjukkan peningkatan ekspresi gen reseptor IFN yang trisomi pada MMU16 [reseptor subunit 1 alfa atau beta IFN (*Ifnar1*), reseptor subunit 2 alfa atau beta IFN (*Ifnar2*), dan subunit 2 gamma IFN (*Ifngr2*)] dan DEG yang berkaitan dengan lintasan pengisyaratan *Janus kinase (JAK)*-transduser dan pengaktif isyarat transkripsi *(STAT)* yang dirangsang oleh IFN [reseptor leptin *(Lepr)* dan *Stat1*] dalam korteks

serebrum dan serebelum pada P84. Kajian penyelidikan sebelum ini menyokong pemilihan lintasan pengisyaratan *JAK-STAT* yang dirangsang oleh IFN dalam kajian ini untuk mencirikan peranannya dalam peralihan kepada penghasilan glia (gliogenesis) di dalam otak DS. Kajian awal dijalankan dengan ujian antagonis melibatkan *Ifnar1* terhadap sel punca saraf yang membeza, yang diperoleh daripada kultur neurosfera otak mencit Ts1Cje dewasa. Teknik RT-qPCR yang mengenal pasti profil ekspresi gen penanda sel punca saraf, neuron dan glia digunakan untuk menentukan pemulihan kecacatan neurogenesis dan perkembangan neuron. Keputusan kajian awal ini mendedahkan bahawa ujian antagonis *Ifnar1* mampu menurunkan ekspresi *Stat1* yang tinggi terhadap sel punca saraf Ts1Cje yang membeza sehingga tahap yang sama dalam sel punca saraf mencit biasa. Sebagai ringkasan, dapatan ini menunjukkan peningkatan ekspresi reseptor IFN terutamanya *Ifnar1* yang disebabkan trisomi gen pada MMU16, mengganggu lintasan pengisyaratan *JAK-STAT* dirangsang oleh IFN dan mungkin juga mengganggu pengawalaturan neurogenesis dan perkembangan neuron dalam otak mencit Ts1Cje. Tambahan lagi, keputusan daripada kajian awal yang menggunakan antagonis *Ifnar1* menunjukkan bahawa cara ini boleh dilaksanakan untuk mengurangkan keadaan otak yang tidak normal dalam otak DS. Kajian ini menawarkan potensi lintasan pengisyaratan *JAK-STAT* sebagai sasaran untuk rawatan terapeutik kepada individu dengan DS.

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The 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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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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LIST OF ABBREVIATIONS

Abcb5	ATP-binding cassette, sub-family B (MDR/TAP), member 5
ATP	Adenosine triphosphate
Atp5o	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit
bFGF	Basic fibroblastic growth factor
BMP	Bone morphogenetic proteins
Brwd1	Bromodomain and WD repeat domain containing 1
Casp3	Caspase 3, Apoptosis-Related Cysteine Peptidase
Cbr1	Carbonyl reductase 1
Cbr3	Carbonyl reductase 3
cDNA	Complementary deoxyribonucleic acid
Cq	Quantification cycle
cRNA	Complementary ribonucleic acid
Cryzl1	Crystallin, zeta (quinone reductase)-like 1
Dab1	Disabled-1
DAVID	Database for Annotation, Visualisation and Integrated Discovery
DEG	Differentially-expressed gene
DG	Dendate gyrus
DNA	Deoxyribonucleic acid
Dnah11	Dynein axonemal heavy chain 11
Donson	Downstream neighbor of SON
Dopey2	Dopey family member 2
DS	Down syndrome
DSCR	Down Syndrome Critical or Chromosomal Region
Dyrk1a	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1a
E	Embryonic
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
EMX2	Homeobox protein EMX2
Erdr1	Erythroid differentiation regulator 1
ESC	Embryonic stem cell
FDA	Food and Drug Administration
Gfap	Glial fibrillary acidic protein
Grik1	Glutamate receptor, ionotropic, kainate 1
HCl	Hydrochloric acid
Hes5	Hes family bHLH transcription factor 5
Hmgn1	High mobility group nucleosomal binding domain 1
HSA21	*Homo sapiens* autosome 21
ICC	Immunocytochemistry
IFN	Interferon
Ifnar1	Interferon (alpha and beta) receptor subunit 1
Ifnar2	Interferon (alpha and beta) receptor subunit 2
Ifngr2	Interferon gamma receptor subunit 1
IQ	Intelligence quotient
Irf3	Interferon regulatory factor 3
Irf7	Interferon regulatory factor 7
Irf9	Interferon regulatory factor 9
Itgb8	Intergrin beta 8

Itsn1	Intersectin 1
JAK	Janus kinase
JAK-STAT	Janus kinase-signal transducer and activator of transcription
Lepr	Leptin receptor
LTD	Long-term depression
LTP	Long-term potentiation
Macc1	Metastasis associated in colon cancer 1
MECP2	Methyl CpG binding protein 2
MMU	Mouse chromosome
MMU10	Mouse chromosome 10
MMU12	Mouse chromosome 12
MMU16	Mouse chromosome 16
MMU17	Mouse chromosome 17
Morc3	Microrchidia 3
mRNA	Messenger ribosomal nucleic acid
Mrps6	Mitochondrial ribosomal protein S6
mTOR	Mammalian target of rapamycin
Neo	Neomycin
NeuroD1	Neurogenic differentiation factor 1
Ngn1	Neurogenin 1
Ngn2	Neurogenin 2
NMDA	N-methyl-D-aspartate
NMDA-LTD	N-methyl-D-aspartate-receptor dependent long-term depression
Notch	Neurogenic locus notch homolog protein
NPC	Neural progenitor cell
Nrp2	Neuropilin 2
NSC	Neural stem cell
Oct4	POU class 5 homeobox 1
P	Postnatal
PAX6	Paired box protein PAX6
Paxbp1	PAX3 and PAX7 binding protein 1
PBS	Phosphate buffered saline
PBST	Phosphate-buffered saline/Tween 20
PCR	Polymerase chain reaction
Pgk1	Phosphoglycerate kinase 1
Pigp	Phosphatidylinositol glycan anchor biosynthesis, class
Prox1	*prospero*-related homeobox gene 1
Psmb2	Proteasome subunit beta type-2
Psmg1	Proteasome (prosome, macropain) subunit, alpha type 2
PVDF	Polyvinylidene fluoride
Rcan1	Regulator of calcineurin 1
RIPA	Radioimmunoprecipitation assay
RMS	Rostral migration stream
RNA	Ribosomal nucleic acid
RT-qPCR	Real time quantitative polymerase chain reaction
S100β	S100 calcium binding protein B
SDS	Sodium dodecyl sulphate
SDS-PAGE	Sodium docecyl sulphate-polyacrylamide gel electrophoresis
SH2	Src Homology 2
Smad	Downstream mediator of activated BMP receptors
Sod1	Superoxide dismutase 1

Son	Son cell proliferation protein
Sp4	Trans-acting transcription factor 4
Sp8	Trans-acting transcription factor 8
STAT	Signal transducer and activator of transcription
Stat1	Signal transducer and activator of transcription 1
SVZ	Subventricular zone
TAP	Transit-amplifying progenitors
Tmem196	Transmembrane protein *Mus musculus* 196
Tmem50b	Transmembrane protein 50b
TrkB	Tropomyosin-related kinase receptor type B
Ttc3	Tetratricopeptide repeat domain 3
Tuj1	β class III tubulin
UPL	Universal ProbeLibrary
Wrb	Tryptophan rich basic protein
Znf295	Zinc finger protein 295

CHAPTER 1

INTRODUCTION

1.1 Background

Down syndrome (DS) is a genetic disorder which results from trisomy or partial trisomy of human chromosome 21 [also known as *Homo sapiens* autosome 21 (HSA21)]. It is a form of non-heritable genetic disease that causes intellectual disabilities (Babiloni *et al.*, 2010) and more than 80 clinical manifestations including craniofacial features, cognitive impairment, cardiac diseases, hypotonia and early onset Alzheimer's disease (Van Cleve *et al.*, 2006; Van Cleve & Cohen, 2006). The prevalence rate of DS is approximately one in 750 live births (Antonarakis *et al.*, 2004). Intellectual disability is the general feature for all DS individual as they have an average value of 50 in Intelligence Quotient (IQ) (Vicari *et al.*, 2005) and also learning impairment that involves both long-term and short-term memory (Brown *et al.*, 2003). DS individuals demonstrate various central nervous system abnormalities such as reduction in brain size, brain weight, brain volume, neuronal density, neuronal distribution and also neuronal and synaptic abnormalities (Marin-Padilla, 1976; Becker *et al.*, 1986; Ferrer & Gullotta, 1990; Wisniewski, 1990; Aylward *et al.*, 1997; Kaufmann & Moser, 2000; Kates *et al.*, 2002).

Exploration of mouse genome showed significant genetic homology between HSA21 and mouse chromosome (MMU) 16, MMU17 and MMU10 (Pletcher *et al.*, 2001) which enable the generation of mouse model for DS. Ts1Cje was developed in the year 1998 by Sago and colleagues based on C57BL/6J mouse genetic background (Sago *et al.*, 1998). This mouse model is also known as T(12;16)1Cje as it carries an extra segment of MMU16 which is synteny to HSA21. The extra segment of MMU16 is translocated onto MMU12 and spans from superoxide dismutase I (*Sod1*) gene to zinc finger protein 295 (*Znf295*) gene (Laffaire *et al.*, 2009). Furthermore, Ts1Cje mouse exhibits craniofacial defects (Sago *et al.*, 1998; Richtsmeier *et al.*, 2002) and also learning and memory impairment (Siarey *et al.*, 2005; Belichenko *et al.*, 2007; Fernandez & Garner, 2007) resembling DS individuals.

To date, there are limited reports on the neuropathology mechanism in DS individuals which can aid to determine targets for therapeutics intervention. There is limited access to human brain samples as they can only be collected from aborted foetus and post mortem DS individuals, therefore, scientists opt for DS models to study the effect of trisomy in brain.

Two major hypotheses have been proposed to explain the trisomy effect of HSA21 which leads to DS. These hypotheses are also applicable on Ts1Cje mouse model. The first hypothesis is called "dosage imbalance hypothesis" which implies that the increased dosage of HSA21 genes results in DS-related abnormalities, while the second hypothesis is "amplified developmental instability hypothesis" that states that the trisomy of a small number of genes results in disruption of weakly buffered or feedback developmental

mechanisms and subsequently affects global gene expression and signalling pathways (Shapiro, 1975; Contestabile *et al.*, 2010). However, these genetic hypotheses still controversial and demand more systematic work on both genomic and proteomic expression to facilitate better understanding of the neuropathology mechanism in the DS mouse models including Ts1Cje.

This study is mainly supported by the findings of Hewitt and colleagues (2010) on adult Ts1Cje mouse brain. They reported that defective neurogenesis and neuronal development are the potential culprit of causing cognitive impairment in Ts1Cje mouse (Hewitt *et al.*, 2010). Thus, by exploring the effects of trisomic MMU16 genes on global gene expression in Ts1Cje mouse brain, this mouse model serves as an ideal model to study the neuropathological networks which then enables us to further extend the findings to DS individuals.

1.2 Hypothesis

The identified DEGs and IFN-induced JAK-STAT pathway are involved in defective neurogenesis and neuronal development.

1.3 Objectives

The present study was designed to meet the following objectives.

General objective:

- To identify disrupted molecular pathways that underlie defective neurogenesis and neuronal development in Ts1Cje mouse.

Specific objectives:

- To identify the DEGs by comparing transcriptomes from different brain regions at different developmental time-points between the Ts1Cje mice and their disomic littermates.
- To determine the disrupted molecular networks via gene ontology and functional clustering with pathway enrichment analysis for DEGs.
- To quantitatively validate the messenger ribosomal nucleic acid (mRNA) and protein expression of DEGs by using RT-qPCR and western blotting method respectively.
- To determine the role of Ifnar1 on neurogenesis and neuronal development in adult neural stem cells by using Ifnar1 antagonists.

1.4 Significance of study

The current study improves understanding of the mechanisms, particularly JAK-STAT signalling pathway which is associated with defective neurogenesis and neuronal development.

Restoring functional neurogenesis and neuronal development in DS NPCs through JAK-STAT antagonist can be improved and adapted as JAK-STAT signalling blocker treatment in DS individuals.

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BIODATA OF STUDENT

Tan Kai Leng was born on the 13th of December, 1987. Her primary education from 1994 to 1999 was completed at Sabah with 5As in Ujian Pencapaian Sekolah Rendah (UPSR) examination. She continued her secondary education at Sekolah Menengah Kebangsaan Agaseh, Sabah from 2000 to 2003 and passed the Penilaian Menengah Rendah (PMR) with 7As, among the top scorer in the school. In 2004, she moved to Johor together with her family and continued her Sijil Pelajaran Malaysia (SPM) studies at Sekolah Menengah Kebangsaan Dato' Syed ESA. She pursued her Sijil Tinggi Pelajaran Malaysia (STPM) studies and scored with cumulative grade point average (CGPA) 3.75. Upon completing her STPM in 2006, she was accepted to further her education in the field of Biomedical Sciences at the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia (UPM). She obtained her Bachelor of Science degree (First Class) in the year 2011.

Miss Tan found her passion in research when she was working on her Bachelor's degree final year project with skin cancer mouse model. Upon completing her Bachelor's degree, she joined the Genetic & Regenerative Medicine Research Centre (GRMRC), Faculty of Medicine and Health Sciences, UPM as a Doctor of Philosophy (PhD) candidate. She pursued her postgraduate studies in the field of neuroscience under the supervision of Dr. Cheah Pike See. She was granted with MyBrain15 scholarship in PhD category and also awarded to attend 2nd IBRO (International Brain Research Organisation)-APRC School of Neuroscience in 2011. In November 2013, Miss Tan was awarded a one-year Sub-project grant (Geran Putra-IPS) from Universiti Putra Malaysia based on her current research findings. Miss Tan had presented poster and oral presentation in five local conferences and four international conferences. Recently, she awarded FENS-IBRO/PERC travel grant to attend FENS Forum 2016, Denmark. To date, she had published five journals and currently in preparation of one manuscripts for publication.

LIST OF PUBLICATIONS

Publication:

Han-Chung Lee,**Kai-Leng Tan**,Pike-See Cheah and King-Hwa Ling. Potential role of JAK-STAT signaling pathway in the neurogenic-to-gliogenic shift in Down syndrome brain. 2016. *Neural Plasticity*. doi: 10.1155/2016/7434191. IF: 3.59.

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Kai-Leng Tan, Jia-Wen Leong, King-Hwa Ling, Mei-I Lai, Sharmili Vidyadaran and Pike-See Cheah.
Restoration of neurogenesis and neuronal development via Ifnar1 antagonist in Ts1Cje mouse model.

Proceedings:

Kai-Leng Tan, Han Chung Lee, King-Hwa Ling, Chelsee A. Hewitt, Hamish S. Scott, Mei-I Lai, Sharmili Vidyadaran, Pike-See Cheah. Overexpressed IFN alpha or beta receptors in the brain of adult Ts1Cje mouse model of Down syndrome.
The 12th Meeting of the Asian-Pacific Society for Neurochemistry (APSN) 2014, Taiwan. 23th- 26th August 2014.

Oral presentation:

3N-2014 Nanosymposium - Disrupted IFN-induced JAK-STAT signalling pathway in adult Ts1Cje mouse model of Down syndrome. Kuala Selangor, 3th May 2015.

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