UNIVERSITI PUTRA MALAYSIA

IN vitro MODULATORY EFFECTS OF MICROGLIA ON NEUROEPITHELIAL CELL NEURODIFFERENTIATION

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By

TONG CHIH KONG

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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Specially dedicated to my beloved parents, family, and friends.

For their unconditional love, understanding, patience, support and constant faith.

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

In Vitro MODULATORY EFFECTS OF MICROGLIA ON NEUROEPITHELIAL CELL NEURODIFFERENTIATION

By

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Chairman : Sharmili Vidyadaran, PhD
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Neural precursor cells (NPC) give rise to neurons and glial cells during embryonic brain development. Dysregulation of NPC growth and function can cause brain deformities and result in psychiatric and behavioural deficits later in life. Recent discoveries reveal that microglia are involved in modulating neurogenesis during embryonic brain development. This study explores the role of microglia in regulating NPC proliferation and neural differentiation using an in vitro cell culture approach. For this, BV2 microglia-conditioned media from cultures treated acutely and chronically with 1µg/ml lipopolysaccharide were collected and incubated with the NE-4C neuroepithelial cell line. NE-4C cultures were either non-induced or induced into neural differentiation using a retinoid analogue, EC23. The effects of microglia on NPC were elucidated by examining proliferation, cell death, pluripotency and cell adhesion markers, as well as early and terminal neural differentiation. Firstly, it was shown that BV2 soluble factors, regardless of activation status, significantly reduced the proliferation of NE-4C cells at all time points examined (from 24 to 96 hours). For instance, at 24 hours, unstimulated BV2-conditioned media reduced non-induced NE-4C proliferation by 83.00 ± 4.43% ($p<0.001$). DAPI/PI staining and Annexin-V/PI assays showed no increase in apoptotic cells in the presence of BV2 microglia-conditioned media, confirming that the reduced proliferation of NE-4C is unrelated to apoptosis. By immunophenotyping and RT-qPCR analysis, it was shown that BV2 microglia-conditioned media does not alter the expression of pluripotency markers (SSEA-1 and CD133) and neural commitment and maintenance factors (HES1, HES3, HES5, MASH1, SOX1, NGN2, and PAX6) in NE-4C neuroepithelial cells at the early phase of neural differentiation. Immunocytochemical studies showed that BV2 microglia-conditioned media inhibited the production of RC2+ radial glial cell and

TUJ1+ neurons during the early phase of neural differentiation. This was accompanied by the reduced formation of neural aggregates. Next, western blot studies showed that BV2 microglia-conditioned media up-regulate the expression of E-cadherin, beta-catenin, and CDC42 but down-regulate the expression of N-cadherin in NE-4C cells. The alteration of the expression of these molecules in NPC may arrest the cells in an undifferentiated state and therefore fail to commit into neural differentiation. Subsequently, the present study elucidated whether microglia-derived soluble factors can impact the terminal production of neuronal cells. The results demonstrate that unstimulated BV2 microglia-conditioned media reduced $TUJ1^+$ neuron production in EC23-induced NE-4C cultures by 58.6% ($p<0.001$). However, there were no significant changes in the percentage of $GFAP^+$ astrocytes. BV2-conditioned media also did not affect the expression of the mature neuron marker MAP2 and synapse marker SYT1 in NE-4C derived neurons. This study then evaluated the effects of BV2-conditioned media on neurite complexity. BV2-conditioned media significantly reduced the number of neurites from 9169 ± 1735 in untreated cultures to 1362 ± 117.6 ($p<0.001$). Total neurite length was also significantly decreased from 5246 ± 924.7px in untreated cultures to 1026 ± 203.6px ($p<0.001$). Neurite attachment points were also reduced from 3115 ± 451.5 in untreated cultures to 1310 ± 356.8 ($p<0.001$). Also, the number of neurite end points were significantly reduced from 7776 ± 1845 in untreated cultures to 4060 ± 952.1 ($p<0.001$). There was no neural differentiation observed in non-induced NE-4C cultures suggesting that BV2 soluble factors do not contribute to the initiation of neurogenesis. Also, the activation status of microglia had no effect on NE-4C neural differentiation in any of the parameters examined, indicating that ubiquitous microglial soluble factors are responsible for the effects described here. To conclude, the primary finding of this study is that microglia exert inhibitory effects on the neural differentiation of NPC.

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

KESAN MODULASI *In Vitro* MIKROGLIA PADA NEURODIFERENSIASI SEL NEUROEPITELIAL

Oleh

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Sel induk neural (NPC) berperanan untuk menghasilkan sel-sel neuron dan glial semasa perkembangan otak embrionik. Penyisihan pertumbuhan dan fungsi NPC boleh menyebabkan kecacatan otak dan mengakibatkan defisit psikiatri dan tingkah laku pada tahap kehidupan selanjutnya. Penemuan baru-baru ini mendedahkan bahawa mikroglia terlibat dalam mengubah neurogenesis NPC semasa perkembangan otak embrionik. Kajian ini mengeksplorasi peranan mikroglia dalam mengawal selia proliferasi NPC dan diferensiasi neural dengan menggunakan pendekatan kultur sel in vitro. Untuk ini, media BV2 mikroglia dari kultur yang dirawat dengan 1µg/ml lipopolysaccharide secara akut dan kronis dikumpulkan dan digunakan untuk diinkubat bersama sel neuroepitelial NE-4C. Kultur NE-4C sama ada tidak diinduksi atau diinduksi untuk diferensiasi neural dengan menggunakan analog retinoid, EC23. Kesan mikroglia pada NPC akan dijelaskan dengan memeriksa proliferasi, kematian sel, pluripotency and adhesi sel, serta diferensiasi neural awal dan terminal. Pertama, ditunjukkan bahawa factor larutan BV2, tanpa mengira status pengaktifan, mengurangi proliferasi sel neuroepitelial NE-4C secara mendadak pada semua titik masa yang dikaji (dari 24 hingga 96 jam). Contohnya, media BV2 yang tidak distimulasi mengurangkan proliferasi kultur NE-4C yang tidak diinduksi sebayak 83.00 ± 4.43% ($p<0.001$) pada titik masa 24 jam. Keputusan dari pewarnaan DAPI/PI dan ujian Annexin-V/PI menunjukkan bahawa tidak terdapat peningkatan sel apoptotik dalam kehadiran media BV2 mikroglia, seterusnya mengesahkan bahawa penurunan kadar proliferasi NE-4C tidak berkaitan dengan apoptosis. Dengan menggunakan analisis flow cytometry dan RT-qPCR, ditunjukkan bahawa media BV2 mikroglia tidak mengubah ekspresi penanda pluripotency (SSEA-1 dan CD133) serta faktor komitmen dan pemeliharaan neural (HES1, HES3, HES5, MASH1, SOX1, NGN2, dan PAX6) dalam sel-

sel neuroepitelial NE-4C pada peringkat awal diferensiasi neural. Kajian immunocytochemical menunjukkan bahawa media BV2 mikroglia menghalang penghasilan produksi $RC2^+$ sel radial glial dan neuron $TUJ1^+$ semasa fasa awal diferensiasi neural. Ini disertai dengan berkurangnya pembentukan agregat neural. Seterusnya, kajian western blot menunjukkan bahawa media BV2 mikroglia menaikkan ekspresi E-cadherin, beta-catenin dan CDC42 tetapi menurunkan ekspresi N-cadherin dalam sel NE-4C. Pengubahan ungkapan molekul-molekul ini dalam NPC boleh menahan sel-sel dalam keadaan yang tidak berdiferensiasi dan oleh itu gagal melakukan mode diferensiasi neural. Selanjutnya, kajian ini membuktikan sama ada faktor larutan BV2 dapat mempengaruhi produksi sel-sel terminal neuron. Hasilnya menunjukkan bahawa media BV2 yang tidak distimulasi mengurangkan produksi neuron $TUJ1^+$ di dalam kultur NE-4C yang diinduksi dengan EC23 sebanyak by 58.6% ($p<0.001$). Walau bagaimanapun, tiada perubahan signifikan dalam peratusan $GFAP^+$ astrocytes dan $nestin^+$ sel progenitor. Juga diketahui bahawa media BV2 tidak mempengaruhi ekspresi penanda neuron matang MAP2 dan penanda synapse SYT1 dalam neuron keturunan NE-4C. Kajian ini kemudiannya menilai kesan media BV2 pada kompleksiti neurit. Media BV2 mengurangkan bilangan neurit secara medadak dari 9169 ± 1735 dalam kultur tidak dirawat kepada 1362 ± 117.6 ($p<0.001$). Panjang keseluruhan neurit juga menurun secara signifikan dari 5246 ± 924.7px dalam kultur yang tidak dirawat kepada 1026 ± 203.6px ($p<0.001$). Titik pelekatan neurit juga dikurangkan dari 3115 ± 451.5 dalam kultur tidak dirawat kepada 1310 ± 356.8 ($p<0.001$). Selain itu, bilangan titik akhir neurit juga berkurangan secara signifikan dari 7776 ± 1845 kultur tidak dirawat kepada 4060 ± 952.1 ($p<0.001$). Tiada diferensiasi neural yang dilihat di NE-4C kultur yang tidak diinduksi dan ini mencadangkan bahawa faktor lautan BV2 tidak menyumbang kepada permulaan neurogenesis. Selain itu, status pengaktifan mikroglia tidak mempunyai kesan yang berbeza terhadap diferensiasi neural NE-4C dalam mana-mana parameter yang diperiksa dan ini mencadangkan bahawa faktor larutan mikroglia setiasa ada yang bertanggunjawab terhadap kesan yang dijelaskan di sini. Kesimpulannya, penemuan utama kajian ini adalah mikroglia melakukan kesan perencatan terhadap diferensiasi neural oleh NPC.

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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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This is to confirm that:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AGM	aorta–gonad–mesonephros
ANOVA	analysis of variance
BDNF	brain derived neurotrophic factor
BLBP	brain lipid-binding protein
BP	basal progenitor
C1q	a subcomponent of complement C1
C3	complement component 3
CA1	C-shaped Cornu ammonis area 1
CA3	C-shaped Cornu ammonis area 3
CD11b	integrin αM
CD133	prominin-1
CD14	cluster of differentiation 14
CD45	cluster of differentiation 45, a receptor type protein tyrosine phosphatase protein
cDNA	complementary DNA
c-kit	mast/stem cell growth factor receptor (SCFR), also known as proto-oncogene c-Kit
CNS	central nervous system
CNTF	Ciliary Neurotrophic Factor
CR3	complement receptor 3
CSF-1R	Colony Stimulating Factor 1 Receptor
CX_3CR1	fractalkine receptor
DAP12	DNAX activation protein of 12kDa
DAPI	4',6-diamidino-2-phenylindole, ihydrochloride
DLX1	Distal-Less Homeobox 1
DLX2	Distal-Less Homeobox 2
EC23	synthetic retinoid analogue of all-trans retinoic acid
ECM	extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor

EMX1	empty spiracles homeobox 1
ER81	a member of the ETS family of transcription factors
ESC	Embryonic stem cell
FGF-2	fibroblast growth factor 2
GCV	ganciclovir
GFAP	Glial fibrillary acidic protein
GLAST	astrocyte-specific glutamate transporter
GSH1	GS Homeobox 1
GSH2	GS Homeobox 2
GSK-3β	Glycogen synthase kinase 3 beta
Hbms	hydroxymethylbilane synthase
HES1	Hairy and enhancer of split 1 Drosophila
HES3	Hairy and enhancer of split 3 Drosophila
HES5	Hairy and enhancer of split 5 Drosophila
Hoxb8	Homeobox B8
^{3}H-TdR	tritium thymidine
IGF1	Insulin-like growth factor
IL-1	Interleukin1
IL-1β	Interleukin1 beta
IL-6	Interleukin 6
INM	interkinetic nuclear migration
iNOS	Inducible Nitric oxide synthases
IPC	Intermediate progenitor cells
kDa	Kilo dalton
LIF	Leukaemia inhibitory factor
LPS	bacterial endotoxin lipopolysaccharide
MAP2	Neuronal dendritic marker
MASH1	Mammalian Achaete Scute Homolog-1
MHC II	Major histocompatibility class II
MMP	matrix metalloproteases
Myb	Myb proto-oncogene, transcription factor
NFIA	Nuclear factor 1 A-type

NGF	Nerve growth factor
NGN2	neurogenin 2, neurog2
NKX2.1	NK2 Homeobox 1
Noxa	Phorbol-12-myristate-13-acetate-induced protein 1
NPC	Neural precursor cell
OCT-4	octamer-binding transcription factor 4
OLIG2	Oligodendrocyte transcription factor
PAX6	Paired box protein 6
PBS	Phosphate-buffered saline
PET	positron emission tomography
Pgk1	Phosphoglycerate Kinase 1
PI	propidium iodide
Psmb2	Proteasome subunit beta type-2
PU.1	an ETS-family transcription factor
Puma	p53 upregulated modulator of apoptosis)
PVDF	polyvinylidene difluoride
RC2	radial glial cell marker
RG	Radial glial cells
ROS	reactive oxygen species
xg	Gravity force
Runx1	runt-related transcription factor 1
S100β	S100 calcium-binding protein B
SD	Standard deviation
SDS-PAGE	sodium dodecyl sulphate polyacrylamide gel electrophoresis
SGZ	subgranular zone
SOX1	SRY-related HMG-box 1
SOX9	SRY-related HMG-box 9
SP8	specificity protein 8, transcription factor
SSEA-1	stage-specific embryonic antigen1
SVET1	subventricular expressed transcript 1
SVZ	subventricular zone

synCAM-1	Synaptic cell adhesion molecule 1
SYT1	Synaptotagmin 1
Tbr2	T-box brain protein 2
TGF-β	Transforming growth factor beta
TN-C	Tenascin C
TNFR	tumor necrosis factor receptor
TNF-α	tumor necrosis factor aplha
TUJ1	Neuron-specific Class III β-tubulin
v-myc	viral-myc gene, myelocytomatosis viral oncogene
v-raf	viral raf gene

CHAPTER 1

INTRODUCTION

The brain consists of complex neural circuits made up of neurons and glia. This complex organ exerts centralised control over every aspect of an organism, including basic physiological functions, rudimentary reflexes, cognition, and intellect. During embryonic development, the brain derives from neural precursor cells (NPC) that are highly plastic, proliferative, possess the ability to differentiate into different cell types and eventually acquire regional identities (Gotz & Huttner, 2005; Taverna et al., 2014). Development of the brain is a highly coordinated process that requires precise spatiotemporal regulation of NPC self-renewal and pluripotency in order to generate the right amount and right type of neuronal cells at the right time. Dysregulation of NPC function at embryonic developmental stages can result in brain malformations and later lead to neurodevelopmental disorders (Ernst, 2016).

Microglia are specialised tissue macrophages in the brain that play important roles including provide immune defences, tissue repair and maintaining brain homeostasis (Wolf et al., 2017). Emerging data shows that microglia are actively involved in shaping the development of the prenatal and perinatal brain (Paolicelli et al., 2011; Schafer et al., 2012; Cunningham et al., 2013; Arno et al., 2014). During embryonic development, yolk sac-derived microglia progenitors invade the developing brain and strategically take residence at neurogenic areas (Ginhoux et al., 2010; Cunningham et al., 2013; Swinnen et al., 2013). The invasion of microglia into the brain rudiment, their positioning patterns, and maturation timeline coincides with many embryonic brain development milestones including brain vascularisation, appearance of developmental apoptosis death, neuroepithelial to radial glial transformation, neuronal migration, and myelination (reviewed in (Harry & Kraft, 2012)). Given the time and space correlation of microglia development and important neurogenesis milestones, it is tempting to speculate that microglia are capable of modulating the process of embryonic neurogenesis.

The present study aims to elucidate the effects of microglia on NPC neural differentiation. It was hypothesised that microglia affect the neural differentiation outcome of NPC. For this purpose, the study employed a cell culture approach using the NE-4C neuroepithelial cell line as a model of NPC and BV2 microglia cell line as a model of microglia. BV2 microglia-conditioned media from different culture conditions (unstimulated, acute and chronically activated using lipopolysaccharide; LPS) were collected and used to treat NE-4C neuroepithelial cells under non-induced and retinoic acid-induced neural differentiation conditions. Microglia acquire distinct phenotypes upon acute or chronic immune stimulation (Cacci et al., 2008). It

had been demonstrated that these phenotypes have different effects on NPC properties (Battista et al., 2006; Cacci et al., 2008; Guadagno et al., 2013). Here, the effects of distinct microglia phenotypes (non-activated, acute or chronically activated) were examined. As retinoic acid is important for both *in vitro* and *in vivo* neurogenesis, the effects of microglia in the presence and absence of this neural inducer was explored to deduce their role in induced neurogenesis and whether their effects are independent of retinoic acid-induction. With this approach, firstly the potential of microglia to induce neural differentiation and to regulate NPC biology during the early phase of retinoic acid-induced neural differentiation were determined by examining NE-4C proliferation, cell death and radial glia marker. Next, the expression of cell adhesion-related molecules in NPC were examined. Finally, the production of neurons was measured to further characterise the effects of microglia on NPC terminal neuronal differentiation.

General Objective

The general objective of this project is to determine the effects of microglia on neural differentiation of NPC.

Specific Objectives

The specific objectives are:

1. To examine the effect of microglia on the proliferation of neuroepithelial cells.

2. To evaluate the effect of microglia on neuroepithelial cells differentiation to produce radial glial cells, neurons and astrocytes.

3. To determine the effects of microglia on the expression of cell adhesion-related molecules during neuroepithelial cell differentiation.

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LIST OF PUBLICATIONS

Chih Kong Tong, Sharmili Vidyadaran: Role of microglia in embryonic neurogenesis. Experimental Biology and Medicine 08/2016; 241(15). DOI:10.1177/1535370216664430
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Chih Kong Tong, Md Shariful Hasan Sumon**,** Sharmili Vidyadaran, Norshariza Nordin**:** Functions of microglial cells on neurogenesis, synaptic pruning and neurotransmission: a brief review. Regenerative Research 08/2015; 4(1).

Shalini Vellasamy, **Chih Kong Tong**, Nur Atiqah Azhar, Radha Kodiappan, Soon Choy Chan, Abhi Veerakumarasivam, Rajesh Ramasamy: Human mesenchymal stromal cells modulate T-cell immune response via transcriptomic regulation. Cytotherapy 08/2016; 18(10). DOI:10.1016/j.jcyt.2016.06.017
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Randy Tatt Yhew Haw, **Chih Kong Tong**, Andrew Yew, Han Chung Lee, James B Phillips, Sharmili Vidyadaran: A three-dimensional collagen construct to model lipopolysaccharide-induced activation of BV2 microglia. Journal of Neuroinflammation 07/2014; 11(1). DOI:10.1186/1742-2094-11-134
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