UNIVERSITI PUTRA MALAYSIA

REGRESSION OF MOUSE MAMMARY TUMOUR THROUGH COMPLEMENT-MEDIATED INFLAMMATION OF C5A/C5AR AXIS

NURUL HAZWANI BINTI KAMARUDIN

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By

NURUL HAZWANI BINTI KAMARUDIN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirement for the Degree of Master of Science

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DEDICATION

This thesis is specially dedicated to my beloved parents, Kamarudin bin Hj Sabli and Habibah binti Osman and family for their endless love and who continuously pray for my success, for the patience and encouragement throughout my life.

Abstract of thesis prepared to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

REGRESSION OF MOUSE MAMMARY TUMOUR THROUGH COMPLEMENT MEDIATED INFLAMMATION OF C5A/C5AR AXIS

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NURUL HAZWANI BINTI KAMARUDIN

Chairman: Dr.Mohd Hezmee Bin Mohd Noor, PhD
Faculty: Veterinary Medicine

Complement component 5a (C5a) is a potent inflammatory chemoattractant that are triggered by the activation of the complement system. This complement might be a beneficial therapeutic target for the initiation of an effective anti-tumour response. The functional effect of C5a is exerted via its receptor, C5aR and this interaction of C5a/C5aR signaling is widely used in pharmaceutical studies. In the current study, C5aR was found to be expressed abundantly on the cell membrane of EMT6 cell line. C5a agonist, EP54 and antagonist, PMX205 were shown to be able to trigger the modulation of C5a by either promoting or inhibiting tumour development ofEMT6 murine mammary cancer cells through *in vitro* and *in vivo*experiments. In the *in vitro* study, the cells treated with EP54haveasignificant reduction in cells proliferation with a low absorbance and percentage value in both Alamar Blue and MTT assay respectively as compared to PMX205 and chemotherapy drug, Tamoxifen which acts as a positive control. C5aR agonism and Tamoxifen treatments both contribute to the apoptotic activity as shown with the acridine orange (AO) and propidium iodide (PI) experiment. For the *in vivo* study, a group of female Balb/c mice injected with EMT6 cells line and treated daily with EP54 peptide showed a regression of tumour size after day 8 to day 14 post-treatment while for the group with PMX205 treatment showed an increased in tumour size. In order to analyze the role of C5a agonist and antagonist towards treated cultured cells and liver tissues, Enzyme Linked Immunosorbent Assay (ELISA) was conducted to quantify the levels of TNF-α, Caspase 3, C5a and Vascular Endothelial Growth Factor A (VEGF-α) signals following treatments. The data showed that EP54 significantly promoted high number and concentration of signaling proteins except VEGF-α, suggesting that the treatment diminishes tumour development and simultaneously generate activation of apoptotic activity. Both C5aR agonism and antagonism peptides might be suggested affecting several tissues in mice as treatments by both peptides have resulted in high concentration levels of the aspartate aminotransferase (AST), Urea, Creatinine and Creatine Kinase (CK) enzymes compared to the normal mice. In summary, C5a agonist, EP54 has a potential to minimized mammary tumour growth by activating the C5a/C5aR signaling and promotes apoptosis.

Abstrak tesis yang telah dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

REGRESI TUMOR MAMMA TIKUS MELALUI PERANTARA TINDAK BALAS INFLAMATORI KOMPLEMEN PAKSI C5A/C5AR

By

NURUL HAZWANI BINTI KAMARUDIN

Pengerusi: Dr.MohdHezmee Bin Mohd Noor, PhD
Fakulti: PerubatanVeterinar

Komplemenkomponen C5a merupakan pengkemotarik inflamasi kuat yang dicetuskan oleh pengaktifan system komplemen. Komponen ini boleh menjadi ajen terapeutik yang bermanfaat untuk aruhan tindak balas anti tumor yang berkesan. Kesan fungsi C5a di dorong melalui reseptornya, C5aR dan interaksi pengisyaratan C5a/C5aR digunakan secara meluas dalam kajian farmaseutikal. Dalam kajian ini, ekspresi C5aR banyak ditemui pada membrane sel titisan sel EMT6. Agonis C5a, EP54 dan antagonis C5a, PMX205 telah menunjukkan dapat mengesan mekanisme sama ada menggalakan atau menghalang perkembangan tumor, kanser sel mamma murin, EMT6 melalui kajian secara *in vitro* dan *in vivo*. Dalam kajian *in vitro*, sel yang dirawat dengan EP54 nyata sekali mengurangkan percambahan sel dalam kedua – dua asai Alamar Blue dan MTT dengan nilai bacaan keserapan dan peratusan yang rendah berbandingdengan PMX205 dan kawalan positif ubat kemoterapi, Tamoxifen. Rawatan agonisme C5aR dan Tamoxifen secara serentak menyumbang kepada aktiviti apoptosis, di mana kemunculan warna jingga, pengecutan sel dan kecai asid deoksibonukleik terhasil selepas pewarnaan berganda dengan akridina jingga (AO) dan iodide propidium (PI). Bagi kajian in vivo, kumpulan tikus Balb/c betina yang disuntik dengan titisan sel EMT6 dan dirawat harian dengan rawatan EP54 menunjukkan regresi keluasan tumor selepas hari kelapan sehingga hari ke 14 manakala kumpulan dengan rawatan PMX205 menunjukkan peningkatan keluasan tumor. Bagi menganalisis peranan C5a agonis dan antagonis terhadap kultur sel dan tisu hati yang telah dirawat, asai immunoserapterangkai ensim (ELISA) dijalankan untuk mengukur paras TNF-α, Caspase 3, C5a and, factor pertumbuhan endothelial vaskular A, VEGF-A sesudah rawatan. Data menunjukkan EP54 dengan ketaranya menggalakkan jumlah dan kepekatan yang tinggi bagi semua asai isyarat protein kecuali asai VEGF-A, maka menandakan rawatan tersebut dapat mengurangkan pertumbuhan tumor dan pada masa yang sama menjana pengaktifan aktiviti apoptosis. Agonis dan antagonis C5aR menunjukkan kesan perubahan terhadap beberapa tisu yang terdapat di dalam badan tikus, di mana kedua-dua peptida member bacaan kepekatan yang tinggi bagi aspartate aminotransferase (AST), urea, kreatinina dan kreatina kinase (CK) berbanding kumpulan normal. Konklusinya, agonis C5aR, EP54 mempunyai keupayaan untuk meminimumkan pertumbuhan tumor mamma dengan mengaktifkan isyarat C5a/C5aR dan pengaktifan apoptosis aruhan.

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I certify that a Thesis Examination Committee has met on 17 September 2015 to conduct the final examination of Nurul Hazwani binti Kamarudin on her thesis entitled "Regression of Mouse Mammary Tumour Through Complement-Mediated Inflammation of C5a/C5aR Axis" 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 Master of Science.

Members of the Thesis Examination Committee were as follows:

Md Zuki bin Abu Bakar @ Zakaria, PhD
Professor
Institute of Bioscience
Universiti Putra Malaysia
(Chairman)

Muhajir bin Hamid, PhD
Associate Professor
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Internal Examiner)

Vasudevan Mani, PhD
Associate Professor
Universiti Teknologi MARA
Malaysia
(External Examiner)

ZULKARNAIN ZAINAL, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 5 November 2015

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

Mohd Hezmee bin Mohd Noor, PhD
Senior Lecturer
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Intan Shameha binti Abdul Razak, PhD
Senior Lecturer
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Abdul Rahman bin Omar, PhD
Professor
Institute of Bioscience
Universiti Putra Malaysia
(Member)

BUJANG KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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This is to confirm that:

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
AO	Acridine orange
AST	Aspartate aminotransferase
ATCC	American Type Culture Collection
BCA	Bicinchoninic acid
BSA	Bovine serum albumin
C1	Complement component 1
C3	Complement component 3
C3a	Complement component 3a
C3b	Complement component 3b
C5	Complement component 5
C5a	Complement component 5a
C5b	Complement component 5b
C5aR	Complement component 5a receptor
Caspase	Cysteine-dependent aspartate-directed proteases
CDK	Cyclin dependent kinase
CK	Creatine kinase
CRD	Carbohydrate recognition domain
DAPI	4’6-diamidino-2-phenylindole
DMSO	Dimethyl sulfoxide
ELISA	Enzyme-linked immunosorbent assay
EP54	C5a agonist
FBS	Fetal bovine serum
FITC	Fluorescein isothiocyanate
IACUC	Institutional Animal Care and Use Comittee
LAFAM	Laboratory Animal Facility and Management
M	Mitotic phase
MAC	Membrane attack complex
MASP	MBL-associated protein
MBL	Mannose binding lectin
MDSC	Myeloid-derived suppressor cells
MTT	MethylthiazolTetrozolium
PAMP	Pathogen-associated molecular pattern
PBS	Phosphate buffer saline
PI	Propidium iodide
PMX205	C5a antagonist
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
rpm	Rotation per minute
S	Synthetic phase
SPF	Specific pathogen free
TNF-α	Tumour necrosis factor alpha

UiTM	UniversitiTeknologi Mara
VEGF	Vascular endothelial growth factor

CHAPTER 1

INTRODUCTION

It is becoming increasingly apparent that breast cancer is a primary cause of cancer-associated death in women of all ethnic background worldwide especially in United States with 40,000 numbers of deaths reported annually in 2014 (Siegel et al., 2014). However, according to National Cancer Research, Ministry of Health Malaysia, in the year 2006 and 2007, the percentage of women with breast cancer have increased from 29.9% with 3034 patients to 32.1% with 3242 patients respectively (Ariffin et al., 2006, Ariffin & Saleha, 2011). The development of breast cancer usually arised from familial history,age of menopause, nulliparity and parity after the age of 30 and frequent use of post menopausal hormone (Gupta & Kuperwasser, 2004; Sprengart et al., 1998). The public awareness in regards to this disease is very low especially in the much younger generation. Generally, cancer occurred due to the mutation of normal cell and uncontrolled cell growth which then leads to the capability of the mutated cells to outsmart and escape the immune system surveillance (Dunn et al., 2004; Grivennikov & Karin, 2010).

Inflammation is usually related to tumour development but the specific functional role of inflammation remains unclear. In the past, Colombo &Forni, 1997 suggested that inflammatory responses could promote tumour regression and thereby providing a potential therapeutic alternative in combating tumour immunity (Colombo & Forni, 1997).As a complex biological process, inflammation is responsible to destroy pathogens that cause tissue injury, as well as a first defence response that is also known as acute inflammation (Nathan, 2002; Newton & Dixit, 2012). However, the failure of acute inflammation to eliminate the infections, may lead to chronic inflammation resulting in the process that will initiate the pathogenesis of numerous diseases, including cancer(Le Bitoux & Stamenkovic, 2008; Nathan, 2002). Complement is usually involved in inflammation and biochemical cascade that essential in innate immune response (Carroll, 2004; Tamamis et al., 2014) using cleaved C5 that generates a potent inflammatory peptide which is C5a (Drouin et al., 2001a). The inflammatory function of C5a is initiated by interaction with its receptor, C5aR that belongs to the rhodopsin family of seven transmembrane G protein coupled receptors (Guo & Ward, 2005).

C5a involvement have been reported in many animal diseases especially in cancer (Markiewski et al., 2008a), but the exact functional role of the in cancer immunotherapy is not fully understood. Previous study has stated the excessive activation of C5a could be harmful to the immune system and simultaneously induce tumourigenesis. Corrales and colleagues has demonstrated in a syngeneic mouse model of lung cancer that C5a promotes tumour development by minimizing myeloid-derived suppressor cells that expressed the receptor of C5a(Corrales et al., 2012). In opposite to this finding, Kim et al., 2005 has found that the over-expression of C5a in mouse mammary tumour is able to block the progression of the tumour cell cycle and suggested that subsequent tumour challenge could heighten adaptive immunity and promote tumour regression (Kim et al., 2005). Kim et al., 2005 also found that C5aR expressed in mouse mammary carcinoma cell line (Kim et al., 2005).

Macor and Tedesco, 2007 emphasizes that complement components contribute to direct tumourigenesis and potentially modulate complement pathways that can improve the potency of immunotherapeutic strategies (Macor & Tedesco, 2007). Studies have been conducted to explore whether the combination of chemotherapeutic drugs with other substances could provide a much better treatment with low toxicity in breast cancer cases (Åberg et al., 2011; Kumar et al., 2013; Rajput et al., 2013; Sarkar et al., 2011). Other treatment likes the use of small peptides C5a agonist and antagonist, EP54 and PMX205 has been tested on the receptors in these murine mammary cancer cell lines. Both of these peptides were used in this study since they act as a molecular adjuvant for cancer therapy, which activate and inhibit the merging of C5a to C5aR respectively. C5a agonist, EP54 selectively and solely interacts with C5aR to augment the activity of immune system in contrast to that of C5a antagonist, PMX205. Previously, mammary tumour tissue has been reported to expressed complement activation products (Niculescu et al., 1992) and C5aR was also found to be expressed in mouse mammary carcinoma cell line (Kim et al., 2005) but the potential mechanisms that might be involved in the use of these peptides to promote tumour regression are not fully understood especially in breast cancer. Therefore, the present study was conducted with the following hypothesis and objectives:

The hypothesis of this study was:

1) C5a production is a part of the inflammatory responses that particularly contributes to chronic inflammation

2) C5aR agonism action will be beneficial in causing successful tumour reduction via induction of apoptosis following C5aR agonism

The objective of this study:

1) To determine the expression of C5aR in EMT6 mouse mammary cancer cell line.

2) To determine the effects of C5aR agonism and antagonism on the development and regression of mouse mammary tumour in a mice model and cell line.

3) To determine the possible mechanism of tumour remission following the action of C5aR agonism/antagonism.

4) To determine the effects of C5aR agonism on vital organs.

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