UNIVERSITI PUTRA MALAYSIA

MODULATION OF C5A RECEPTOR IN MAMMARY GLAND TUMOUR BY EP54 AND PMX205 PEPTIDES

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By

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MODULATION OF C5A RECEPTOR IN MAMMARY GLAND TUMOUR BY EP54 AND PMX205 PEPTIDES

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June 2015

Chairman: Mohd Hezmee Mohd Noor, PhD
Institute: Veterinary Medicine

Drug resistance has become the main issue in cancer therapy field. This situation causes the increasing number of cancer related disease in the world. The usage of complement 5a has become a new method of therapy against cancer by following agonist-antagonist treatment. This project was mainly about the agonist (EP54) and antagonist (PMX205) modulate the expression of C5aR causing the regression of mouse mammary gland tumour. The objectives of this project were to determine the expression of C5a receptor on 4T1 cell line, to determine the mechanism of mouse mammary gland tumour cell death after treatment with respective peptides, determine the effect of the peptides on mouse mammary gland tumour cell, and to determine the effect of EP54 and PMX205 on the liver and kidneys of mice with 4T1-induced mammary gland tumour. Several methods were conducted such as immunoflourescence staining, PCR, ELISA (TNF-α, VEGF, Caspase 3 and C5a), acridine orange and propidium iodide double staining and serum biochemical analysis. The results showed that the presence of C5a receptor on 4T1 cell line was based on the immunoflourescence staining and PCR. The presence of the receptor showed that the 4T1 cell was suitable to be used with those peptides. The mechanism was determined by using ELISA. Based on ELISA results, it showed that the apoptosis becomes the underlying pathway that is used in mammary gland tumour regression for both environments *in vitro* and *in vivo*. These findings showed that the apoptosis is an important process involved in most organisms for survival. In order to validate the findings, acridine orange/propidium iodide staining (AO/PI) and cell viability assay were conducted. Besides, tumour measurements also were used as to validate the mechanism proposed. Both peptides showed capability to present apoptosis based on the AO/PI result. While in the cell viability assay (Alamar Blue & MTT) in which it represents data *in vitro*, it showed that PMX205 showed greater potential in treating the cancer compared to EP54 group. In Alamar Blue assay, the result showed that the absorbance PMX205 was lower compared to EP54 group. Similar trend could also be found from the MTT assay. Tumour measurement recorded from the *in vivo* experiment, shows that the size of tumour decreased in EP54 group whereas the PMX205 group, the tumour maintain its own size. In the serum biochemical analysis, no significant effects were obtained on the liver and kidney of the animal. Based on these results, it showed that EP54 and PMX205 could modulate the expression of

C5aR causing the regression of mouse mammary gland tumour. Apoptosis was the underlying mechanism involved during the treatment and the treatment did not produce significant effects on the organ of the animal.

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

PEMODULATAN RESEPTOR C5A DALAM TUMOUR KELENJAR MAMA OLEH PEPTIDA EP54 DAN PMX205

Oleh

NURNEQMAN NASHREQ BIN KOSNI

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Rintangan dadah menjadi isu utama dalam bidang terapi kanser. Keadaan ini menyebabkan peningkatan jumlah penyakit kanser yang berkaitan di dunia. Penggunaan pelengkap 5a menjadi satu kaedah terapi baharu melawan kanser dengan mengikuti rawatan agonis-antagonis. Projek ini adalah terutamanya mengenai agonist yang (EP54) dan antagonis (PMX205) memodulasi ungkapan C5aR menyebabkan regresi tumour tikus kelenjar mama. Objektif projek ini adalah untuk menentukan ungkapan C5a reseptor pada sel 4T1, untuk menentukan mekanisme kematian tumour tikus kelenjar mama selepas rawatan dengan peptida, menentukan kesan peptida pada sel tumour tikus kelenjar mama, dan untuk menentukan kesan EP54 dan PMX205 pada hati dan buah pinggang mincit dengan sel 4T1- penyebab tumour kelenjar mama. Beberapa kaedah telah dijalankan seperti pewarnaan immunoflourescence, PCR, ELISA (TNF-α, VEGF, Caspase 3 dan C5a), acridine orange dan propidium iodida pewarnaan berganda dan analisis serum biokimia. Hasil kajian menunjukkan bahawa terdapat kehadiran reseptor C5a pada sel 4T1 berdasarkan pewarnaan immunoflourescence dan PCR. Kehadiran reseptor C5a menunjukkan bahawa sel 4T1 adalah sesuai digunakan dengan peptide tersebut. Mekanisme telah ditentukan dengan menggunakan ELISA. Berdasarkan keputusan ELISA, ia menunjukkan bahawa apoptosis menjadi laluan asas yang digunakan dalam regresi tumour kelenjar mama untuk kedua-dua persekitaran *in vitro* dan *in vivo*. Penemuan ini menunjukkan bahawa apoptosis adalah satu proses penting yang terlibat dalam organisma untuk hidup. Untuk mengesahkan penemuan tersebut, acridine orange/propidium iodida pewarnaan (AO/PI) dan asai sel kebolehhidupan telah dijalankan. Selain itu, ukuran tumour juga telah digunakan untuk mengesahkan mekanisme yang dicadangkan. Kedua peptida menunjukkan keupayaan untuk menghasilkan apoptosis berdasarkan hasil AO/PI. Walaupun dalam asai sel kebolehhidupan (Alamar Blue & MTT) yang mewakili data *in vitro*, ia menunjukkan PMX205 mempunyai potensi yang lebih besar dalam merawat kanser berbanding dengan kumpulan EP54. Di Alamar Blue asai, hasil menunjukkan bahawa absorbans PMX205 adalah lebih rendah berbanding kumpulan EP54. Aliran yang sama juga boleh didapati dari asai MTT itu. Ukuran tumour direkodkan daripada eksperimen *in vivo*, saiz tumour telah menurun dalam kumpulan EP54 manakala kumpulan PMX205, tumour mengekalkannya saiz sendiri. Dalam

analisis biokimia serum, tiada kesan yang penting telah diperolehi pada hati dan buah pinggang haiwan. Berdasarkan keputusan ini, ia menunjukkan bahawa EP54 dan PMX205 boleh memodulasi ungkapan C5aR menyebabkan regresi tumour kelenjar mama tikus. Apoptosis adalah mekanisme asas yang terlibat dalam rawatan dan daripada rawatan tersebut ia tidak menghasilkan kesan yang besar ke atas organ haiwan.

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I certify that a Thesis Examination Committee has met on (date of viva voce) to conduct the final examination of (student's name) on his (her) thesis entitled ("Title of Thesis") 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 (insert the name of relevant degree).

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LIST OF ABBREVIATIONS

bp	base pair
BCA	Bicinchoninic acid
CO2	Carbon dioxide
Caspase	cysteine-dependent aspartate-directed proteases
dH2O	distilled water
DEPC	DiethylenePyrocarbonate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
FBS	Fetal bovine serum
µg/ml	microgram per mililiter
g	gram
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
h	hour
HCL	Hydrochloric acid
IBS	Institute of Bioscience
IC50	half maximal inhibitory concentration
kDa	Kilodalton
L	Litre
M	molar
min	Minute
mins	Minutes
ml	Mililiter
mM	Milimolar
MTT	Methylthiazol Tetrazolium
NaCl	Sodium Chloride
NaOH	Sodium Hydorxide
NCR	National Cancer Registry
PBS	Phospate Buffer Saline
PCR	Polymerase Chain Reaction
PI	Propidium Iodide
RNA	ribonucleic acid
rpm	rotated per minute
RPMI	Roswell Park Memorial Institute
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
Sec	Seconds
TNF-α	Tumour Necrosis Factor
UPM	Universiti Putra Malaysia
µl	microliter
mg/ml	milligram per mililiter
v/v	volume over volume
w/v	weight per volume
˚C	Degree Celcius

CHAPTER 1

GENERAL INTRODUCTION

Breast cancer is a combination of the most notorious cancers on earth (about 22% of all type of cancers), followed by a malady of the prostate, colon, lung and ovaries, accordingly. According to Parkin et al. (2005), mammary gland disease is also associated with a 14% from cases of all deaths from cancer among women worldwide, and also known as the most common cancer for women in both developing and developed countries. Evidence in 2003 from the National Cancer Registry of Malaysia recorded that about 3738 new cases associated with breast cancer were recorded to the registry on that year, producing an age standardized incidence rate (ASR) of 46.2 per 100,000 women. This mechanism focuses 1 in 20 women in Malaysia purposefulness transport breast cancer in their lifetime (Yip et al., 2006).

There are different types of treatment that can be used to treat breast cancer such as surgery, radiation therapy, hormone therapy, chemotherapy and targeted therapy. Each of these treatments has its own positive or negative effects. For example, in chemotherapy, several kinds of drugs are used during a session. The problem is when certain kind of drugs was introduced to the cancer cell, it will cause some genetic alterations in the cancer cell (Gottesman, 2002), which later causes failure of the respective drugs to work against cancer cells. This situation is known as drug resistance which has also become one of the most common problems that usually occur in cancer therapy.

The study on possible mechanism of tumour regression especially in malignant mammary tumour has gained some focus lately, as it is capable of promoting the development of new drugs or peptides that are useful to be used for cancer therapy as well as yielding a wealth of information about complement therapies in treating cancer diseases. From past to present, it is recorded that the resistance of certain type of tumour towards commercial cancer therapy medicine has become a major problem (Dexter and Leith, 1986). The resistance of tumour towards drugs occurred due to few factors such as host factor and genetic alterations in cancer cells (Gottesman, 2002). Both of these factors contributed towards the failure of cancer therapy.

The complement C5a system has become a potential treatment to be applied in cancer therapy based on its involvement in immune defence mechanism, where it acts as a protector for an organism against the presence of any foreign substances inside an organism. In addition, the expression of complement C5a receptor is not just restricted on myeloid cells such as macrophages (McCarthy and Henson, 1979), basophils and neautrophils (Hook et al., 1975) and eosinophils (Kay et al., 1973), but it is also expressed on non-myeloid cells such as epithelial, endothelial and smooth muscle cells in the human liver and lung (Zwirner et al., 1999). The widespread expression of C5a receptor suggested more of its general and systemic functionality.

The experiment was planned to observe the expression of complement C5a receptor on malignant type of breast cancer model cell that is known as 4T1 cells. Further experiments were constructed to see the effects or interactions between complement peptides, agonist (EP54) and antagonist (PMX205) with 4T1 cell line *in vitro* and *in vivo*.

The hypothesis of this study was agonist (EP54) and antagonist (PMX205) modulate expression of C5aR causing regression of mouse mammary gland tumour. The objectives of this study were to determine the:

1) expression of C5a receptor on 4T1 cell line.
2) mechanism of mouse mammary gland tumour cell death after treatment with EP54 and PMX205 peptides.
3) effect of EP54 and PMX205 peptides on mouse mammary gland tumour cell.
4) effect of EP54 and PMX205 on the liver and kidney of mice with 4T1-induced mammary gland tumour.

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