UNIVERSITI PUTRA MALAYSIA

COMPARATIVE ANALYSIS OF PATHOGENICITY PROFILES AND ANTITUMOUR EFFECTS OF WILD AND MUTANT STRAINS OF SALMONELLA ENTERICA SEROVAR AGONA

GWEE CHIN PIAW

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By

GWEE CHIN PIAW

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GWEE CHIN PIAW

October 2015

Chair: Cheah Yoke Kqueen, PhD
Faculty: Medicine and Health Sciences

The fight against cancer has been a never ending battle. Cancer remains a major threat to human life. Limitations of conventional therapies included lack of selectivity, poor penetration and highly toxic to the host. One of the innovative approaches which have gained the interest of scientists from past few decades is the use of live, genetically modified bacteria as tumour therapy agent. Engineered bacteria possess unique features to overcome the limitations of conventional therapies. Low virulence and highly tolerability of *Salmonella* spp. in animals and humans make it as a most studied pathogen in regards to antitumour therapy. Genetically modified *S.* Typhimurium has been constructed as direct tumouricidal agent or as drug delivery vector in many researches. Main objective of this study is to construct genetically modified *S.* Agona as antitumour agent. A powerful genetic manipulation tool is needed in order to meet the requirements as tumouricidal agent in experimental and clinical research. Group II intron mutagenesis technology was exploited in current study to inactivate the metabolic genes in *S.* Agona. Group II intron technology has been shown to be able to insert at desired DNA at high frequency and specificity. In this study, *LeuB* and *ArgD* metabolic genes in *S.* Agona were successfully knockout at frequency of 15% and 3% respectively. Non-reverting and high stability of intron insertion was proven with a stability passage assay of 30 days culture. The constructed knockout *S.* Agona has become auxotrophic for leucine and arginine. Inactivation of *LeuB* and *ArgD* genes leads to a significant growth defect in M9 minimal media. *Salmonella* is a natural pathogen of mice, thus, mouse model was used to evaluate the potential pathogenicity and antitumour activity of engineered *S.* Agona in present work. Quadruple knockout BDLA exhibited highest safety among all of the strains in all tested parameters including bacterial colony forming units, immunity profile and histopathology studies. Tumour growth inhibition study was divided into two groups, which are small tumour model with size approximately 250 mm^3 and large tumour model with size approximately 450 mm^3 in comparison with each other.

Results have shown that all of the stains are able to delay the growth of the small and large solid tumour as compare to the negative control, with better efficacy shown by auxotrophic knockout strain LA and BDLA. Interestingly, tumour growth inhibition noticed on small tumour is not as effective as seen on large tumour, might be due to the better hypoxia or nutrient conditions available in microenvironment of big tumour. Furthermore, findings from this study showed that the treated groups with repeated treatment did not show any significant improvement in tumour growth delay, in both big and small solid tumour models. Overall, the virulence of BDLA knockout strain was reduced and antitumour effect was successfully enhanced. The results obtained from current work suggest a great potential of auxotrophic quadruple knockout *S.* Agona as antitumour agent.

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

PERBANDINGAN ANALISIS DALAM PROFIL KEPATOGENAN DAN KESAN ANTITUMOUR ANTARA JENIS LIAR DAN STRAIN MUTAN *SALMONELLA ENTERICA* SEROVAR AGONA

Oleh

GWEE CHIN PIAW

Oktober 2015

Pengerusi: Cheah Yoke Kqueen, PhD
Fakulti: Perubatan dan Sains Kesihatan

Perlawanan menentang kanser telah menjadi pertempuran yang tidak berkesudahan. Kanser kekal menjadi ancanman utama kepada kehidupan manusia. Had-had terapi konvensional termasuk kekurangan selektiviti, penembusan yang lemah dan sangat toksik kepada tuan rumah. Salah satu cara inovatif yang mendapat minat daripada saintis-saintis dari beberapa dekad yang lepas ialah penggunaan bakteria yang hidup dan diubahsuai secara genetik sebagai agen terapi tumor. Bakteria yang telah diubahsuai mempunyai ciri-ciri unik untuk mengatasi batasan yang didapati dalam terapi konvensional. Tahap virulensi yang rendah dan toleransi yang tinggi pada haiwan dan manusia telah membolehkan *Salmonella* spp. Di antara patogen yang paling banyak dikaji dalam bidang terapi antitumor. *S.* Typhimurium yang diubahsuai secara genetik telah dihasilkan sebagai agen "tumouricidal" secara langsung atau sebagai vektor penyampai ubat dalam banyak kajian. Objektif utama kajian ini adalah untuk menghasilkan *S.* Agona pengubahsuaian genetik untuk dijadikan agen antitumor. Alat manipulasi genetik yang berkuasa diperlukan supaya dapat memenuhi syarat-syarat sebagai agen "tumouricidal" dalam kajian eksperimental dan percubaan klinikal. Dalam kajian ini, teknologi mutagenesis Intron Kumpulan II telah dieksploitasi untuk menyahaktifkan gen metabolik dalam *S.* Agona. Kaedah Teknologi Intron Kumpulan II telah terbukti berjaya dapat memasukkan DNA yang diingini pada frekeunsi and spesifikasi yang tinggi. Dalam kajian ini, gen metabolik *LeuB* dan *ArgD* dalam *S.* Agona telah berjaya disingkir keluar secara genetik pada frekuensi 15% dan 3% masing-masing. Kemasukkan intron dengan kestabilan tinggi dan tanpa pengembalian ke asal telah terbukti dengan ujian kestabilan (stability passage assay) pada kultura sehingga 30 puluh hari. *S.* Agona yang diubah suai secara genetik telah menjadi auksotrofik kepada leusina dan arginina. Keupayaan pertumbuhan ganda dua mutan Δ*LeuB*Δ*ArgD* (LA) dan ganda empat mutan Δ*SopB*Δ*SopD*Δ*LeuB*Δ*ArgD* (BDLA) dalam M9 media minumum telah berjaya dilumpuhkan. Oleh kerana *Salmonella* merupakan patogen semula jadi yang didapati dalam tikus, maka model tetikus telah digunakan untuk menilai tahap kepatogenan dan potensi antitumor aktiviti

kejuruteraan *S.* Agona dalam kajian ini. Mutant ganda empat BDLA dapat menunjukkan tahap keselamatan yang tertinggi di antara semua jenis *Salmonella* dalam semua parameter yang diuji, termasuk unit pembentukkan koloni bakteria, profil imuniti and juga kajian histopatologi. Kajian perencatan pertumbuhan tumor telah dibahagikan kepada dua kumpulan,iaitu tumor besar (~450 mm^3) dan tumor kecil (~250 mm^3). Keputusan dalam kajian ini telah menunjukkan semua jenis *Salmonella* dapat melambatkan pertumbuhan tumor kecil and besar berbanding dengan kumpulan kawalan negatif, dengan keberkesanan yang lebih baik ditunjukkan oleh LA dan BDLA mutan auksotrof. Yang menariknya ialah pencegahan pertumbuhan tumor pada tumor kecil tidak begitu baik seperti yang dapati dalam tumor besar, kemungkinan ini disebabkan oleh keadaan hipoksia dan nutrien yang lebih baik didapati dalam tumor besar. Tambahan pula, keputusan menunjukkan bahawa kumpulan dengan ulangan rawatan tidak menunjukkan sebarang peningkatan yang ketara dalam pencegahan pertumbuhan tumor sama ada tumor kecil atau besar. Secara keseluruhan, virulensi BDLA mutan dapat dikurangkan dan kapasiti perencatan tumor tidak terjejas, sebaliknya ia menunjukkan peningkatan dalam efikasi terhadap tumor besar. Sebagai kesimpulan, keputusan kajian ini menunjukkan bahawa mutan *S.* Agona auksotrofik dengan ganda-empat berpotensi tinggi sebagai agen perencat tumor.

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I certify that a Thesis Examination Committee has met on 7 October 2015 to conduct the final examination of Gwee Chin Piaw on his thesis entitled "Comparative Analysis of Pathogenicity Profiles and Antitumour Effects of Wild and Mutant Strains of *Salmonella enterica* Serovar Agona" 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:

Roslida binti Abd Hamid @ Abdul Razak, PhD
Associate Professor
Faculty of Medicine and Health Science
Universiti Putra Malaysia
(Chairman)

Son Radu, PhD
Professor
Faculty of Food Science and Technology
Universiti Putra Malaysia
(Internal Examiner)

Samuel Lihan, PhD
Senior Lecturer
Universiti Malaysia Sarawak
Malaysia
(External Examiner)

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

Date: 17 November 2015

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

Cheah Yoke Kqueen, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Sabrina Sukardi, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
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Committee: _____

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Name of
Member of
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Committee: _____

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LIST OF ABBREVIATIONS/ SYMBOLS, UNITS AND TERMS

ATCC	American Type Culture Collection
bp	Base pair
CFU	Colony forming unit
DNA	Deoxyribonucleic acid
dNTP	Deoxyribonucleotide triphosphate
h	Hour
IPTG	Isopropyl-Beta-D-Thiogalactopyranoside
kb	Kilobase pair
LB	Luria Bertani
mL	Mililiter
mm	Millimeter
min	Minute
MOI	Multiplicity of infection
OD	Optical density
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
RPM	Revolutions per minute
s	Second
X-gal	5-Bromo-4-Chloro-3-Indolyl-Beta-D-Galacto-Pyranoside
XLD	Xylose lysine deoxycholate
Δ	Mutant
ºC	Degree celcius
%	Percentage
µg	Microgram
µM	Micromolar
µl	Microliter

CHAPTER 1

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide. Most of the patients are found at the late stage of disease and more than half of the patients diagnosed with cancer eventually die from this disease (Jemal et al., 2011). Conventional anticancer therapies, such as chemotherapy, radiotherapy and surgery often encounter significant side effects and fail to achieve complete tumour remission. These standard therapies do not target tumour tissue specifically and do not successfully penetrate deep into tumour tissue (Jain, 1998; Tannock et al., 2002), which ultimately leads to loss of local control and tumour recurrence (Davis and Tannock, 2002). A new paradigm for cancer drug development is therefore urgently needed.

The use of bacteria in the tumour regression in certain forms of cancer has been recognized for more than a century. Certain live, attenuated non-pathogenic bacteria such as *Salmonella, Bifidobacterium, Clostridium, and Listeria* possess unique features to overcome all these limitations (Pawelek et al., 2003; Morrissey et al., 2010; Taniguchi et al., 2010). Tumour microenvironment is often characterized by mass and abnormal tissue architecture, leads to disorganized and variable blood flow, which eventually creates heterogeneous microenvironment, including gradients chemical concentration and also hypoxia regions, make it particularly resistant to systemic treatment (Klemm and Joyce, 2014; Cairns et al., 2006). Bacteria are able to survive and proliferate within tumour microenvironment with very little oxygen whereby most of the times radiotherapy and chemotherapy are unsuccessful. Bacteria mostly are motile, able to penetrate into tumour tissue (St Jean et al., 2008; Lee, 2012). Although several bacteria species has been reported as anticancer agent, however, most of the current approaches are focused on *Salmonella* strains.

Salmonella characteristics such as motility, propagation control with antibiotics, genetic stability, environmental sensing, native cytotoxicity, low cost of production and safety make it a suitable choice as anticancer agent (Chorobik et al., 2013). *Salmonella* is able to produce certain virulence factors that lead to cytotoxicity and induce innate immunity to target tumour which helps in further tumour regression (Lee et al., 2008; Lee, 2012; Kaimala et al., 2014). Besides that, unlike other therapeutic agents, *Salmonella* can be delivered in low dose follow by proliferation to an effective dose within the target tumour (Forbes et al., 2003). An advantage of *Salmonella* to obligate anaerobes, the growth of facultative bacteria is not restricted to hypoxic environment. Therefore, this pathogen are able to colonize large and small tumour, and even accumulate within metastases after systemic administration (Leschner and Weiss, 2010; Yam et al., 2010).

The virulence of *Salmonella* is attenuated in some genetic modification. It was reported that *Salmonella* auxotroph with the deletion of *msb*B and *pur*I gene would preferentially replicate within tumours when inject into tumor-bearing mice, showing tumour to normal tissue ratio exceeding 1000:1. The accumulation of *Salmonella* in tumour is accompanied by delaying the growth of tumour (Pawelek et al., 1997). In order to enhance their oncolytic effects, *Salmonella* strains were engineered as delivery vector to express effector genes such as those encoding angiogenic inhibitors (Lee et al., 2005) or prodrug converting enzymes (Pawelek et al., 1997; King et al., 2002).

Altogether, bacterial anticancer therapy has made great steps in past decades. In spite of the advantages and potential for live bacteria as antitumour agent, it is clear that in many cases fundamental work and issues are need to be addressed in order to limit the side-effects and to improve the efficacy of the system. Apparently, a powerful genetic engineering tool is desirable in order to reduce toxicity on host and meanwhile develop or enhance therapeutic activity. This study describes the use of group II intron technology for genetic manipulation of metabolic genes in *Salmonella* Agona. Mouse as natural host for *Salmonella* serovars was used as ideal experimental model for *in vivo* antitumour study and toxicity assay in present work. The constructed genetically modified *S.* Agona leucine and arginine auxotroph was expected to exhibit lower virulence in terms of bacterial colony forming unit, immunity profile and also histopathological analysis as compared to wild-type *S.* Agona. In addition, this particular knockout auxotrophic strain will be attracted by tumour microenvironment which is high in nutrient and subsequently exhibit higher antitumour efficacy. By taking initiative of constructing genetically modified *Salmonella* Agona and *in vivo* assay, it will greatly improve our understanding regarding the principle of group II intron genetic modification tool, the contribution of metabolic genes on antitumour activity and toxicity, and also novel use of *S.* Agona as antitumour agent.

Objectives of the study

The study was undertaken with the following objectives:

1. To construct genetically modified *S.* Agona by further inactivation of *LeuB* and *ArgD* metabolic genes

2. To investigate cytotoxic effects of engineered *S.* Agona *in vivo*

3. To evaluate the antitumour activity of engineered *S.* Agona *in vitro* and *in vivo*

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