UNIVERSITI PUTRA MALAYSIA

COMPARISON BETWEEN SEVERE AND SURVIVAL MODELS OF MALARIA INFECTION FOR BETTER UNDERSTANDING OF THE UNDERLYING DISEASE PATHOGENESIS

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By

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Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in fulfillment of the Requirements for the Degree of Master of Science

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

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November 2013

Chair: Associate Professor Rusliza Basir, PhD

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Different host-parasite combination will result in varied malaria presentation and outcome. In this preliminary study, ICR mice and *Sprague dawley* rats were inoculated intraperitoneally with 2 x 10^7 parasitized red blood cells (pRBCs) obtained from donor mouse pre-infected with *P. berghei* ANKA (PbA). Control to malaria-infected animals received an equivalent volume and dilution of normal RBC through the same route of administration. The susceptible mice which serve as severe model demonstrated a parasitaemia level of approximately 75% together with a progressive decrease in body weight and temperature before succumb to the infection. Malarial rats that survived the infection developed moderate level of parasitaemia (45%) and insignificant changes in terms of illness symptoms and behavioural responses followed with gradual resolution. Multiple organ dysfunctions is also an important contributor towards malaria-associated mortality, hence histopathological examination

was performed on H&E stained tissue obtained from five vital organs including brain, liver, spleen, kidney and lung. Some of the major histopathological alterations observed in both mice and rats including sequestration of pRBCs, accumulation of hemozoin pigment and macrophage engulfing elements in microvasculature, disorganization of spleen architecture, and hyalinized membrane in alveolar wall.Systemic concentration of pro-inflammatory cytokines (TNF-α, IFNγ and IL-1α) and anti-inflammatory cytokines (IL-10, IL-4 and IL-13) were also quantified in mice and rats by using commercial ELISA kit. A distinctive difference obtained from analyzed data showed significant elevation of plasma TNF-α in malarial mice which contradict with low production of TNF-α along with significant concentrations of IL-10, IL-4 and IL-13 in serum of malarial rats. Thispattern of cytokine release has tipped towards the regulation of inflammatory response and survival during malaria infection. The protective role of the above said anti-inflammatory cytokines is not well elucidated, nor is there a relevance of these cytokines with the disease pattern or extent of vital organ dysfunction during the infection. Hence, the effects of systemic augmentation of IL-10, IL-4 and IL-13 on pathological conditions of malaria were investigated. *P. berghei* ANKA (PbA)-infected mice were treated with either the recombinant mouse (rm) IL-10, rmIL-4 or rmIL-13 and treatment with these cytokines has successfully delayed the mortality rate in all malarial mice with development of parasitaemia was reduced to as much as 20% during peak parasitaemia in relative to malaria mice receiving PBS. Body weight and rectal temperature also showed lesser extent of reduction. Results revealed the amelioration of malaria histopathological conditions in all examined organs upon treatment. Sequestration of pRBCs was

reduced in the brain tissue. Hypertrophied Kupffer cells and sinusoids dilatation that were significant during malaria infection was lessen by treatment. The red and white pulp elements and central germinal structure were regained in spleen. Glomerular and tubular appearance of the treated malarial kidney appeared to be normal whilst the lung tissue of treated malarial mice were revealed to be normal without formation of hyalinized membrane and pigment deposition in alveolar septa. Taken together, it can be concluded that IL-10, IL-4 and IL-13 play significant role(s) during malaria infection and they may well serve as potential immunotherapeutic target strategy in malaria therapy.

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

PERBANDINGAN ANTARA MODEL JANGKITAN MALARIA TENAT DAN BERDAYA HIDUP UNTUK PEMAHAMAN YANG LEBIH BAIK TENTANG PATOGENESIS YANG MENDASARI PENYAKIT

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Kombinasi hos-parasit yang berbeza akan menghasilkan jenis malaria yang berlainan. Dalam kajian awal ini, mencit ICR dan tikus *Sprague dawley* diinokulasikan secara intraperiteum dengan 2 x 10^7 sel-sel darah merah berparasit (pRBCs) yang diperolehi dari mencit penderma yang dijangkiti terlebih dahulu dengan *P. berghei* ANKA (PbA). Kawalan kepada haiwan terjangkit menerima isipadu dan pencairan sel-sel darah merah normal yang setara melalui cara administrasi yang sama. Mencit rentan yang berfungsi sebagai model tenat mempamerkan tahap parasitemia lebih kurang 75% beserta dengan pengurangan berat dan suhu badan yang progresif sebelum tewas terhadap jangkitan. Tikus malaria yang mampu bertahan terhadap jangkitan menghasilkan tahap parasitemia yang sederhana dan perubahan-perubahan yang tidak ketara dari segi simptom penyakit dan gerakbalas-gerakbalas tingkahlaku diikuti dengan penyembuhan secara beransur-ansur. Kegagalan fungsi organ berganda juga adalah merupakan penyumbang penting kepada mortaliti yang dikaitkan dengan

malaria, jadi pemeriksaan histopatologi dilakukan ke atas tisu terwarna H&E yang diperolehi daripada lima organ utama termasuk otak, hati, limpa, ginjal dan paru-paru. Perubahan-perubahan histopatologi utama yang diperhatikan dalam kedua-dua tikus dan mencit termasuklah sekuestrasi pRBCs, longgokan pigmen hemozoin dan elemen-elemen diliputi makrofaj di dalam mikrovaskulatur, arkitektur limpa yang berselerak dan membran terhialin dalam dinding alveolar. Kepekatan sistemik sitokin-sitokin proinflamasi (TNFα, IFNγ dan IL-1α) dan sitokin-sitokin antiinflamasi (IL-10, IL-4 dan IL-13) di dalam mencit dan tikus juga ditentukan menggunakan peralatan ELISA komersil. Perbezaan ketara diperolehi dari data yang dianalisis menunjukkan peningkatan signifikan TNFα plasma dalam mencit malaria di mana ini berlawanan dengan pengeluaran TNFα yang rendah beserta dengan kepekatan IL-10, IL-4 dan IL-13 yang signifikan dalam serum tikus malaria. Corak pembebasan sitokin ini memberikan petunjuk terhadap pengawalaturan gerakbalas inflamasi dan kelangsungan hidup semasa jangkitan malaria. Fungsi perlindungan sitokin-sitokin antiinflamasi yang disebutkan di atas tidak diterangkan dengan baik, dan tiada hubungkait sitokin-sitokin ini dengan corak penyakit atau kegagalan fungsi organ utama semasa jangkitan. Oleh yang demikian, kesan penambahan sistemik IL-10, IL-4 dan IL-13 ke atas keadaan patologi malaria diselidiki. Mencit terjangkit *P. berghei* ANKA (PbA) dirawat dengan rekombinan mencit (rm) IL-10, rmIL-4 atau rmIL-13 dan rawatan dengan ketiga-ketiga sitokin ini telah berjaya melewatkan kadar mortaliti dalam kesemua mencit malaria dengan perkembangan parasitemia berkurangan sebanyak 20% berbanding mencit malaria yang dirawat dengan PBS. Berat dan suhu badan juga menunjukkan kadar pengurangan yang rendah. Keputusan menunjukkan

pembaikan keadaan histopatologi malaria di dalam kesemua organ-organ yang diperiksa selepas rawatan. Sekuestrasi pRBC berkurangan di dalam tisu otak. Sel-sel kupffer yang terhipertrofi dan dilatasi sinusoid yang signifikan semasa jangkitan malaria berkurangan dengan rawatan. Elemen-elemen palpa merah dan putih dan juga struktur pusat germinal di dalam limpa pulih semula. Keadaan glomerulus dan tubul ginjal malaria yang dirawat kelihatan normal, manakala tisu paru-paru mencit malaria yang dirawat kelihatan normal tanpa pembentukan membran terhialin dan longgokan pigment di dalam septa alveolar. Secara keseluruhan, ianya boleh disimpulkan bahawa IL-10, IL-4 dan IL-13 memainkan peranan yang signifikan semasa jangkitan malaria dan mungkin boleh menjadi sasaran imunoterapeutik yang berpotensi dalam terapi malaria.

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I certify that a Thesis Examination Committee has met on 21 November 2013 to conduct the final examination of Chong Wing Chui on her thesis entitled "Comparison between survival and severe models of malaria infection for better understanding of the underlying disease pathogenesis" 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.

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted to any other degree at Universiti Putra Malaysia or at any other institution.

CHONG WING CHUI

Date: 21 November 2013

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ACT	:	artemisinin-based combination therapies
ACUC	:	animal care and use committee
ADCC	:	antibody dependent cellular cytotoxicity
ADCI	:	antibody dependent cellular inhibition
APC	:	antigen presenting cells
ARDS	:	acute respiratory distress
ATN	:	acute tubular necrosis
BBB	:	blood brain barrier
^{o}C	:	degree Celcius
CM	:	cerebral malaria
CSA	:	chondroitin sulphate A
dH_2O	:	deionized water
DNA	:	double helix nucleic acid
ELISA	:	Enzyme Linked Immunosorbent Assay
et al	:	elsewhere or and others
etc	:	et cetera
g	:	gram
GPI	:	glycosyl phosphotidyl inositol
H&E	:	hematoxylin and eosin
HLA	:	human leukocyte antigen
hr	:	hour

HRP	:	horseradish peroxidase
ICAM-1	:	intercellular adhesion molecule-1
ICR mice	:	imprinting control region mice
IFNγ	:	interferon gamma
Ig	:	immunoglobulin
IL-	:	interleukin
IL1R1	:	Interleukin1 receptor 1
iNOS	:	inducible nitric oxide synthase
i.p	:	intraperitoneal
i.v	:	intravenous
kDa	:	kilodalton
kg	:	kilogram
L	:	liter
LPS	:	lipopolysaccharide
MHC	:	major histocompatibility complex
min	:	minute
mL	:	milliliter
mm	:	millimeter
mmol	:	millimolar
n	:	number of observation
ng	:	nanogram
NK Cells	:	Natural Killer cells
NKT	:	Natural Killer T lymphocyte

nm	:	nanometer
NO	:	Nitric Oxide
PbA	:	*Plasmodium berghei* ANKA
PBS	:	phosphate buffered saline
%	:	percent
pg	:	picogram
pRBC	:	parasitized red blood cell
RBC	:	red blood cell
RNI	:	reactive nitrogen intermediates
ROI	:	reactive oxygen intermediates
rpm	:	revolution per minute
rmIL-4	:	recombinant mouse Interleukin-4
rmIL-10	:	recombinant mouse Interleukin-10
rmIL-13	:	recombinant mouse Interleukin-13
S.E.M	:	standard error of the mean
Stat6	:	signal transducer and activator of transcription 6
TGF-β	:	transforming growth factor-beta
Th_1	:	T helper type 1
Th_2	:	T helper type 2
TNF-α	:	tumor necrosis factor-alpha
TNFR2	:	tumor necrosis factor receptor 2
Treg cells	:	T regulatory cells
µg	:	microgram

μL	:	microliter
VCAM-1	:	vascular cell adhesion molecule-1
WHO	:	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

The contest between malaria and human has begun since mankind evolved, and it continues unabated till present, with no resolution in sight (Mohr, 2002). In the company of more than 200 million clinical cases and estimated 700000 deaths per annum, malaria is one of the major vectorborne diseases which now rivals HIV/AIDS as the world most deadly infection (Guerin *et al*., 2002; WHO, 2010). To date, there are five *Plasmodium* protozoa namely *Plasmodium vivax* (*P. vivax*), *Plasmodium falciparum* (*P. falciparum*), *Plasmodium malariae* (*P. malariae*), *Plasmodium ovale* (*P. ovale*), and the recent discovered simian *Plasmodium knowlesi* (*P. knowlesi*) that infect human with malaria through the Anopheles mosquito (Campbell, 2009; Lee *et al.*, 2011; White 2008). Infections caused by *P. vivax* and *P.falciparum* are reported extensively worldwide, along with its high mortality rate and drug resistance. Until recently, *P. knowlesi* infection in human has become a significant malaria infection in Southeast Asia that may lead to deadly complications (Cox-Singh *et al.*, 2008; Snow *et al.*, 2005). With widespread air travel, malaria is now prevailing and threatening developed countries too, with two-thirds of the global population at risk (Vernick*et al*., 2004).

Once malaria parasite intrudes successfully into the host, liver cells are the bed where they first grow and multiply. Then they multiplies asexually in the red blood cells at

which most of the clinical symptoms such as chills, headaches and fever begin to occur (Davis, 2010). Pathogenesis of malaria can be divided into severe and survival model (Craig *et al*., 2012). It is noteworthy that the relationship between the host's genetic profile and the susceptibility towards malaria is intricately interwined. Conferred genetic resistance of malaria not only enhanced by modifications of immune system such as the major histocompatibility complex gene, but also by certain haemoglobin inherited disorders or erythrocyte polymorphisms (Lopez *et al*., 2010). It is also believed that the involvement of environmental factors, parasite genetic factor, and multi-gene interaction play pivotal rolesas well (Kwiatkowski, 2005).

Control of malaria infection is critical due to rapid increment of mosquito insecticide resistance and parasite drug resistance. To date, many attempts have been made to facilitate the development of a more effective treatment and efficacious malaria vaccine. Incomplete understanding of protective immunity and its core induction process has hindered the progress of effective malaria control measures (Kumar *et al*., 2002; Richie *et al*., 2002). In this regard, a greater effort on investigating prospective targets and mechanisms of immunity to malaria on both severe and survival models may provide better description on pathological versus protective responses and this provide more efficacious immunological interventions (Langhorne *et al*., 2008).

Animal models have been principal, in that they provide much valuable information to understanding malaria, particularly the accumulation of infected red blood cells in a number of organs and microvascular obstruction induced by cytoadherence and

inflammation (Craig *et al*., 2012). To date, most of the current anti-malarial strategies are targeting on *Plasmodium* parasites, however malaria remained to be endemic due to anti-malarial drug resistance (Lee *et al*., 2013). To solve this problem, it is hypothesized that cytokines may be one of the potential targets for immunotherapeutic strategy in malaria. Albeit the well-documented pathogenesis studies in malaria infection, there is still a large gap to be filled for the understanding of the host's immune responses during malaria infection. In accordance with this, two different models of mice and rats representing the severe and survival mode of pathogenesis, respectively were conducted throughout this research to add evidence to immunological studies of the infection. With that, the development of future malaria treatment and vaccines are plausible.

1.2 Objectives

The main objective of this study isto investigate the effectiveness of anti-inflammatory cytokines in preventing severe malarial infection.

The specific objectives are:

i. to establish survival and severe models in mice and rats, respectively.

ii. to determine and differentiate behavioural, clinical, histopathology, pro- and anti-inflammatory cytokine levels and survival in these models.

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