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MODULATION OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS SIGNAL TRANSDUCTION PATHWAY AS THERAPEUTIC OPTION FOR MALARIA THERAPY

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By

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April 2015

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Receptor for advanced glycation endproducts (RAGE), an important receptor in the regulation of innate immune response, has been associated with many inflammatory related diseases such as septicaemia, rheumatoid arthritis, and arteriosclerosis. Malaria is also considered as an inflammatory disease involving excessive inflammatory response towards parasite invasion and severe systemic inflammation occurred during the infection has been closely linked to morbidity and mortality of the disease. However, RAGE involvement during malaria infection has yet to be revealed. In this study, the role and involvement of RAGE during malaria infection was investigated and the effects of modulating RAGE on the course of the infection, the release of major inflammatory cytokines and the histopathological consequences in major affected organs during malaria were evaluated. *Plasmodium berghei (P. berghei)* ANKA infection in male ICR mice was used as a model for malaria infection. The mice were inoculated intraperitoneally with 2×10^7 parasite-infected red blood cells (PRBCs) whereas the control mice received an equivalent dilution of normal RBCs. The plasma levels of RAGE in malarial mice were measured by ELISA. Results showed that RAGE was upregulated during malaria especially at the late critical phase of infection and there is a positive correlation between RAGE concentration and parasitaemia development suggesting that RAGE could be one of the important factors in mediating the severity of the infection.

Modulation of RAGE expression was carried out by treatment of malarial mice with recombinant mouse RAGE Fc chimera (rmRAGE/Fc Chimera) or mouse RAGE polyclonal antibody (mRAGE/pAb) intravenously. Both treatments did not affect the parasitaemia development during malaria infection. Blocking RAGE signaling pathway during the infection period significantly result in an elevation in the plasma levels of interleukin (IL)-4 and IL-17A, a further increase in IL-10 and IL-2 plasma levels, and reduced secretion of interferon (IFN)-γ in the plasma. But no effect on the release of tumor necrosis factor (TNF)-α and IL-6 was observed. Histopathological examination was performed on five major organs affected during malaria including liver, spleen,

brain, kidney, and lung. The results showed that modulation of RAGE expression improve the histopathological conditions of malaria to some degree. Both treatment groups showed an overall better outcome in histopathological conditions of all five organs despite the lack of effect on the course of the parasitaemia. In conclusion, the findings from this study showed that RAGE is involved during immune response towards malaria infection and blocking of RAGE may prove beneficial by reducing tissue injury to a lesser degree. Hence, this suggests the potential of RAGE as an immunotherapeutic target in malaria, in which the host may benefit from its inhibition.

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MODULASI *RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS* SEBAGAI SASARAN TERAPEUTIK UNTUK TERAPI MALARIA

Oleh

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Receptor for Advanced glycation endproducts (RAGE), suatu reseptor penting dalam pengawalaturan gerakbalas imun semulajadi, telah dikaitkan dengan banyak penyakit berkaitan inflamasi seperti septisemia, artritis reumatoid dan arteriosklerosis. Malaria juga dianggap sebagai suatu penyakit inflamasi melibatkan gerakbalas inflamasi yang berlebihan terhadap pencerobohan parasit dan inflamasi sistemik tenat yang berlaku semasa jangkitan telah dikaitkan secara rapat dengan morbiditi dan mortaliti penyakit. Walau bagaimanapun, penglibatan RAGE semasa jangkitan malaria belum lagi dirungkaikan. Dalam kajian ini, peranan dan penglibatan RAGE semasa jangkitan malaria diselidiki dan kesan-kesan modulasi RAGE ke atas keadaan jangkitan, pembebasan sitokin inflamasi utama dan kesan histopatologi dalam organ-organ utama yang terkesan semasa jangkitan dinilai. Jangkitan *Plasmodium berghei (P. berghei)* ANKA dalam mencit ICR jantan telah digunakan sebagai model bagi jangkitan malaria. Mencit diinokulasi secara intraperitoneum dengan 2×10^7 sel-sel darah terjangkit parasit, manakala mencit kawalan menerima pencairan setara sel-sel darah normal. Tahap plasma RAGE dalam mencit malaria diukur menggunakan ELISA. Keputusan menunjukkan bahawa RAGE meningkat dalam mencit malaria pada fasa kritikal akhir jangkitan dan terdapat korelasi positif antara kepekatan RAGE dan perkembangan parasitaemia, yang mencadangkan RAGE mungkin salah satu faktor penting dalam memperantarakan jangkitan yang tenat.

Modulasi ekspresi RAGE dijalankan dengan merawat mencit malaria dengan RAGE Fc kimera mencit rekombinan (rmRAGE/Fc Chimera) atau antibodi poliklonal mencit (mRAGE/pAb) secara intravena. Kedua-dua rawatan tidak memberikan kesan ke atas perkembangan parasitaemia semasa jangkitan malaria. Merencat RAGE semasa jangkitan menyebabkan peningkatan secara signifikan interleukin-4 dan IL-17A pada tahap plasma, meningkatkan lagi tahap plasma IL-10 dan IL-2, dan mengurangkan pembebasan IFN-γ dalam plasma. Tetapi tiada kesan ke atas TNF-α dan IL-6 diperhatikan. Pemeriksaan histopathologi telah dijalankan ke atas lima organ utama yang terkesan semasa jangkitan malaria termasuk hati, limpa, otak, ginjal dan paru-paru. Keputusan menunjukkan modulasi ekspresi RAGE mampu memperbaiki keadaan

histopatologi malaria. Kedua-kedua kumpulan rawatan menunjukkan hasil keseluruhan yang lebih baik ke atas keadaan histopatologi kelima-lima organs walaupun tiada kesan ke atas parasitemia. Kesimpulannya, dapatan dari kajian ini menunjukkan bahawa RAGE terlibat semasa gerakbalas imun terhadap jangkitan malaria dan merencat RAGE mungkin berfaedah dengan mengurangkan kecederaan tisu ke tahap lebih rendah. Jadi, ini mencadangkan potensi RAGE sebagai sasaran imunoterapeutik dalam malaria, di mana hos mungkin mendapat faedah dari perencatannya.

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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:

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ADCI	antibody-dependent cellular inhibition
ALI	acute lung injury
ANOVA	one-way analysis of variance
APCs	antigen-presenting cells
ARDS	acute respiratory distress syndrome
B cells	B lymphocyte cells
CBA	cytometric bead array
cRAGE	cleaved RAGE
CTL	cytotoxic T cells
DCs	dendritic cells
DNA	deoxyribonucleic acid
Na_2HPO_4	disodium hydrogen phosphate anhydrous
ELISA	enzyme-linked immunosorbent assay
esRAGE	endogenous secretory RAGE
et al.	and others
fl-RAGE	full length, membrane-bound form RAGE
GPI	glycosylphosphatidylinositol
GM-CSF	granulocytes macrophage-colony stimulating factor
Ig	immunoglobulin
ICAM-1	intercellular adhesion molecule-1
IFN-γ	interferon-gamma
IL-	interleukin
i.p.	intraperitoneal
i.v.	intravenous

JAK	janus kinase
µg	microgram
µL	microliter
µm	micrometer
mM	milimolar
min	minute
mRAGE/pAb	mouse RAGE polyclonal antibody
ng	nanogram
nm	nanometer
NaN_3	sodium azide
NaCl	sodium chloride
NK cells	natural killer cells
NMD pathway	nonsense-mediated decay pathway
NO	nitric oxide
iNOS	nitric oxide synthase
NF-κB	nuclear factor kappa B
n	number of observation
PfEMP-1	*P.falciparum*-encoded erythrocyte membrane protein-1
PRBCs	parasite-infected red blood cells
PBS	phosphate buffer saline
pg	pictogram
P.	*Plasmodium*
KCl	potassium chloride
KH_2PO_4	potassium dihydrogen phosphate anhydrous
PGE_2	prostaglandin E_2
RAGE-/- mice	homozygous RAGE deficient mice

RBCs	red blood cells
rmRAGE/Fc Chimera	recombinant mouse RAGE Fc chimera
rpm	revolution per minute
sRAGE	soluble RAGE
STAT	signal transducer and activator of transcription
s.e.m.	standard error of the mean
Th1	T-helper type 1
Th2	T-helper type 2
T_h cells	T helper cells
TLR	toll-like receptor
TGF-β	tumor growth factor-beta
TNF-α	tumor necrosis factor-alpha
T_{regs}	Regulatory T cells
VCAM-1	vascular cell adhesion molecule-1
w/v	weight per volume

CHAPTER 1

INTRODUCTION

1.1 Background

Although being investigated for over hundreds years, malaria still remains a tough challenge to mankind, creating an enormous social, economic, and health burden. According to World Malaria Report 2012, malaria is reported as being endemic in over 104 countries and territories, spanning all continents of the world except Antarctica and Australia, with 99 of these countries had on-going malaria transmission. Despite the extensive efforts in controlling and eradicating malaria since 1955, half of the world population or approximately 3.3 billion people remain at risk of this parasitic infection. In 2010, there were an estimated 219 million cases of malaria, causing 660 000 deaths (WHO, 2012). Every year, malaria imposes huge financial costs on afflicted persons as well as the governments of the endemic countries, putting an immense economic burden on those countries (WHO, 2012; Roll back malaria, 2010).

In Malaysia, the national malaria eradication program has been a success in recent decades, steadily reduces the incidence of malaria from 59208 cases (29.7 per 10,000 populations) in 1995 to 6650 cases (2.4 per 10,000 populations) in 2010 (Lokman, 2011). The reported malaria death cases also remain steady within 20-40 cases annually for the last decade (Western Pacific Region WHO, 2012). The majority of malaria incidences in Malaysia are reported in both Sabah and Sarawak of Malaysian Borneo, accounted for 38% and 33% respectively of all reported cases (Ministry of Health Malaysia, 2011). Noteworthy, most of the malaria cases are confined to rural and semi-rural areas no matter in Peninsular Malaysia or Malaysian Borneo (Rundi, 2011) and largely concentrated among immigrant workers (legal/illegal), workers in land schemes, and hinterland aborigines who are mostly socio-economically disadvantaged (Ministry of Health Malaysia, 2011).

The appearance of first drug resistant case to one of the most common antimalarial drug, chloroquine, along the Thai-Combodian border in late 1950s, has indicated the start of a new chapter in the history of combating malaria. Since then, more and more cases reporting the resistance of the malaria parasites to anti-malarial chemotherapy were detected worldwide. To date, resistance *in vivo* has been observed in almost all currently used antimalarial drugs, including chloroquine, quinine, sulphadoxine-pyrimethamine, and mefloquine (Farooq & Mahajan, 2004). To make the situation worse, not only drug resistance of malaria parasites is widespread, the vector *Anopheles* mosquitoes themselves also have developed resistance to insecticide used for malaria control (WHO, 2012). Since no vaccine is yet fully available and new antimalarial agents will be facing resistance problem eventually, the need to develop a new therapeutic option for malaria therapy by targeting the immune system is great indeed.

Excessive inflammatory response to the parasite invasion is the disastrous endpoint of an overstimulated immune reaction, which in turn lead to malaria susceptibility, severe immunopathological conditions, septic shock and multi organ failure due to end organ damage (Plebanski & Hill, 2000). Although not much is known for the mechanisms in the pathogenesis of severe malaria, considerable evidences have revealed that high levels of pro-inflammatory cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1) are correlated with severity of malaria and hyperinflammation is implicated in the development of severe malaria (Lyke *et al.*, 2004; Artavanis-Tsakonas, Tongren & Riley, 2003). These findings suggest an idea that using immunomodulatory approach to reduce the overproduction pro-inflammatory cytokines and limiting the hyperactivated immune response may be beneficial in reducing morbidity and mortality due to severe malaria. In this case, receptor for advanced glycation end products (RAGE) has potential to be an attractive immunomodulatory target because RAGE signaling and its downstream pathways has been identified to be essential in perpetuation and amplification of inflammatory reactions (Bierhaus *et al.*, 2005) as well as in the production of various pro-inflammatory cytokine, including TNF-α, IFN-γ, and IL-6 (Lotze & Tracey, 2005; Treutiger *et al.*, 2003).

The receptor of advanced glycation endproducts (RAGE) is a newly identified multi-ligand receptors and a member of the immunoglobulin superfamily. It is involved in the signal transduction from pathogen substrates to cell activation during the onset and perpetuation of inflammation. The binding of RAGE ligands, including advanced glycation endropducts (AGEs) and high mobility group box protein 1 (HMGB1), to their receptor has been found to initiate a series of intracellular signal transduction pathways that leads to a sustained inflammatory reaction (Lander *et al*. 1997; Wautier *et al.* 2001*;* Ishihara *et al*. 2003; Huang *et al.* 2001) as well as amplify the cytokine cascade during systemic inflammation (Andersson *et al.* 2000).

Upregulation of RAGE occurred in the blood vessels, neurons and transformed epithelial during many inflammatory-related pathologic conditions such as septicaemia, rheumatoid arthritis, inflammatory kidney disease, arteriosclerosis, and inflammatory bowel disease (Bierhaus *et al.* 2005).The potential of RAGE as therapeutic target in disease conditions has been demonstrated in several studies. Blocking of RAGE signal transduction pathway for example can increase survival in experimental sepsis (Wang *et al*. 1999; Yang *et al*. 2004), reduce the signs of lung damage in acute inflammation during lung injury (Abraham *et al*. 2000) and increase survival after massive liver resection (Cataldegirmen *et al.* 2005*).* The most interesting finding was that RAGE knockout mice were protected from lethal septic shock as compared with the wild-type controls (Liliensiek *et al.* 2004*).*

Most data from the previous studies suggest that RAGE perpetuates and amplifies inflammatory reactions and targeting this receptor might help curbing the hyperinflammatory responses that occur in many inflammation-associated conditions. Since malaria is also considered as an inflammatory disease involving excessive inflammatory response towards parasite invasion and severe systemic inflammation has been closely linked to morbidity and mortality of the disease, it is necessary to investigate whether modulation of RAGE signaling pathway would produce any

beneficial outcomes during malaria infection. If modulation of RAGE signaling pathways can produce impact on the pathological conditions seen during malaria infection then targeting RAGE would be beneficial and it can represent a promising new therapeutic option for malaria therapy. This can at least reduce the morbidity and mortality associated with malaria infection and may be a breakthrough in the effort of treating the disease.

1.2 Hypotheses

In this study, it is hypothesized that RAGE is involve in malaria infection and modulating the RAGE signaling pathway would give a positive impact on the pathophysiology of the disease.

1.3 Objectives

The general objective of this research is to study and determine the possible roles and involvement of RAGE during malaria infection. The specific objectives of this study are listed as follows:

1) To investigate the involvement of RAGE during malaria infection by determining its expression at systemic level.
2) To modulate the expression of RAGE *in vivo* by means of neutralizing antibody against RAGE and chimera binding protein as an antagonist to RAGE ligands.
3) To evaluate the effects of RAGE pathway modulation on the pathological changes seen during malaria infection, whether blocking of RAGE pathway would improve the pathological conditions associated with disease.
4) To evaluate the modulatory effects of RAGE on the pattern of major cytokines release during the infection. This includes the pro-inflammatory cytokines IL-2, IL-6, IL-17A, TNF-α and IFN-γ, and the anti-inflammatory cytokines IL-10 and IL-4.

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