ROLE OF HLA-DR IN DYSREGULATION OF B CELL HOMEOSTASIS IN *Dermatophagoides pteronyssinus*-INDUCED ALLERGIC RHINITIS AMONG MALAYS

By

VIVEK PRASAD A/L JANA MONEY

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

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DEDICATION

This thesis is dedicated to everyone who has been there for me throughout this long and winding journey in the quest for knowledge beyond books.

May God bless you all.

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Chair : Professor Maha binti Abdullah, PhD
Faculty : Medicine and Health Sciences

Allergic rhinitis (AR) is an IgE-mediated nasal inflammatory disorder, commonly triggered by house dust mite, *Dermatophagoides pteronyssinus*. Der p 1 is a dominant allergenic protein derived from this species. The highly polymorphic human leukocyte antigen (HLA) genes were linked to AR predisposition/protection in different ethnicities. Variation in this gene alters epitope-binding affinities for HLA molecule, causing polarization of immune responses due to differential cytokines and antibodies secretions. The relationship between HLA and Der p 1 epitopes in the induction of specific cytokines and antibodies is unclear. During allergies, B cells perform various effector and regulatory functions. Dysregulation of B cells with Der p 1 stimulation under HLA regulation, remains unknown. This study aimed to use *in silico* approaches to predict relationship between Der p 1 epitopes and HLA-DR serotypes in cytokines/antibodies induction and evaluate *in vitro* changes in B and T cells of Der p 1-stimulated peripheral blood mononuclear cells (PBMCs) from AR patients and controls with selected *HLA-DRB1* alleles. Full amino acid sequence of Der p 1 (NCBI protein database) was submitted into TepiTool, NetMHCIIpan 4.0, PREDIVAC and ABCpred, BCPREDS, BepiPred 2.0 to predict T and B cell epitopes, respectively. AllerTOP 2.0, AllergenFP 1.0 and AlgPred determined allergenicities of predicted peptides. IL4Pred, IL-10Pred and IFNepitope assessed T cell epitopes' cytokine-inducing properties, while Bcipep and IgPred evaluated B cell epitopes' antibody isotype secretions. Needleman-Wunsch alignment tool (NCBI BLAST) identified overlapping sequences between T and B cell epitopes. For *in vitro* study, Malay adults were recruited and screened for *HLA-DRB1* alleles via polymerase chain reaction with sequence-specific primers using buccal DNA samples. Three subjects per HLA group for patients (DR7 and DR13) and controls (DR15) were selected for skin prick testing and blood sample collection. Der p 1-stimulated PBMCs were analyzed for B and T cells via flow cytometry. *In silico* analysis identified 32 $CD4^+$ T cell epitopes, mostly IL-4 inducers (n = 11) and associated with allergenicity (p = 0.049). DR13 preferentially bound IL-4-inducing epitopes (75.00%) whereas DR7 mostly bound IL-10/IFN-γ-inducing epitopes (70.59%). DR15 bound almost equally IL-4 (42.86%) and IL-10/IFN-γ-inducing peptides (57.14%). From 13

predicted B cell epitopes, majority induced either IgE only (n = 4) or both IgE and IgA (n = 4). DR13-associated epitopes, cross-matched between T and B cell peptides for at least 60% similarities, were mostly IgE-inducing. Day 3 Der p 1-stimulated PBMCs showed lower percentages of IL-10-secreting T cells in AR patients (DR7+ and DR13+) compared to controls (DR15+) (27.08% vs 43.97%; p = 0.025). Memory B cell percentages were higher in DR13+ than DR7+ group (63.00% vs 10.77%; p = 0.022) whereas regulatory B cells were greater in DR7+ than DR13+ group (88.63% vs 32.53%; p = 0.022). In conclusion, *in silico* and *in vitro* studies supported HLA-DR13 as AR predisposing due to increased bindings of IL-4 and IgE-inducing epitopes, causing proliferation of memory B cells. Conversely, HLA-DR7 protected against AR via selective presentation of IL-10/IFN-γ-inducers, triggering differentiation of regulatory B cells. The DR15 controls maintained a healthy immune profile, suggesting a neutral outcome.

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

PERANAN HLA-DR DALAM KETIDAKATURAN HOMEOSTASIS SEL B DALAM ALAHAN RINITIS CETUSAN *Dermatophagoides pteronyssinus* DI KALANGAN ORANG MELAYU

Oleh

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Pengerusi : Profesor Maha binti Abdullah, PhD
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Alahan rinitis (AR) ialah masalah keradangan hidung yang dimediasikan oleh IgE, biasanya dicetuskan oleh hama habuk rumah, *Dermatophagoides pteronyssinus*. Der p 1 merupakan protein yang dominan dalam alergen ini. Gen antigen leukosit manusia (HLA) yang amat polimorfik telah dikaitkan dengan kecenderungan/perlindungan daripada AR dalam pelbagai kumpulan etnik. Variasi dalam gen ini boleh mengubah kecenderungan pengaitan epitop oleh molekul HLA dan mengundang polarisasi dalam tindak balas imun disebabkan oleh perbezaan dalam rembesan sitokin dan antibodi. Hubungkait antara epitop, HLA dan Der p 1 dalam induksi sitokin dan antibodi tertentu masih tidak jelas. Semasa alahan, sel-sel B melaksanakan pelbagai fungsi efektor dan regulatori. Disregulasi sel-sel B dalam rangsangan Der p 1 di bawah pengaruh HLA masih tidak diketahui. Kajian ini bertujuan untuk menggunakan pendekatan *in siliko* untuk meramalkan hubungkait antara epitop-epitop Der p 1 dan serotaip HLA-DR dalam rembesan sitokin/antibodi dan menilai perubahan *in vitro* dalam sel-sel B dan T dari kultur sel mononuklear darah periferal (PBMC), yang dirangsang dengan Der p 1, daripada pesakit AR dan kumpulan kawalan yang mempunyai alel *HLA-DRB1* tertentu. Urutan asid amino penuh Der p 1 (pangkalan data protein NCBI) telah dimasukkan ke dalam TepiTool, NetMHCIIpan 4.0, PREDIVAC, ABCpred, BCPREDS dan BepiPred 2.0 untuk ramalan epitop sel T dan B. AllerTOP 2.0, AllergenFP 1.0 dan AlgPred menentukan alergenisiti epitop. IL4Pred, IL-10Pred dan IFNepitope menilai sifat pencetus sitokin epitop sel T, manakala Bcipep dan IgPred menilai rembesan isotip antibodi epitop sel B. Sistem penjajaran Needleman-Wunsch (NCBI BLAST) mengenal pasti pertindihan jujukan antara epitop sel T dan B. Untuk kajian *in vitro*, orang dewasa Melayu telah disaring untuk mengenal pasti alel *HLA-DRB1* melalui reaksi rantai polimerase dengan urutan primer spesifik menggunakan sampel DNA pipi. Tiga subjek bagi setiap kumpulan HLA untuk pesakit AR (DR7 dan DR13) dan kawalan (DR15) telah dipilih untuk ujian cucuk kulit dan pengumpulan sampel darah. Sel-sel PBMC yang dirangsang dengan Der p 1 telah dianalisa untuk menentukan perubahan dalam sel-sel B dan T melalui sitometri aliran. Analisis *in siliko* mengenal pasti 32 epitop sel $CD4^+$ T, kebanyakannya penginduksi IL-4 (n = 11) dan dikaitkan dengan sifat alergenik (*p* =

0.049). DR13 lebih mengait epitop penginduksi IL-4 (75.00%) manakala DR7 lebih mengait epitop penginduksi IL-10/IFN-γ (70.59%). DR15 mengait penginduksi IL-4 (42.86%) dan IL-10/IFN-γ (57.14%) secara hampir sama rata. Daripada 13 epitop sel B yang diramalkan, majoriti mendorong rembesan sama ada IgE sahaja (n = 4) ataupun kedua-dua IgE dan IgA sekali (n = 4). Padanan silang epitop sel T dan B dengan pertindihan jujukan lebih daripada 60% menunjukkan kebanyakan daripada epitop yang dikaitkan oleh DR13 sebagai perembes IgE. Sel-sel PBMC yang dirangsang dengan Der p 1 selama 3 hari menunjukkan kekurangan dalam peratusan sel-sel T yang merembeskan IL-10 dalam pesakit AR (DR7+ dan DR13+) berbanding dengan kumpulan kawalan (DR15+) (27.08% lwn 43.97%; $p = 0.025$). Peratusan sel B memori adalah lebih tinggi dalam DR13+ berbanding kumpulan DR7+ (63.00% lwn 10.77%; $p = 0.022$) manakala sel B regulatori adalah lebih tinggi dalam DR7+ berbanding kumpulan DR13+ (88.63% lwn 32.53%; $p = 0.022$). Kesimpulannya, kajian *in siliko* dan *in vitro* menyokong HLA-DR13 sebagai faktor predisposisi AR disebabkan oleh peningkatan pengaitan epitop penginduksi IL-4 dan IgE, justeru mengakibatkan perkembangan sel B memori. Sebaliknya, HLA-DR7 melindungi daripada AR melalui pengaitan epitop penginduksi IL-10/IFN-γ dan mencetuskan peningkatan sel B regulatori. DR15 sebagai kawalan mengekalkan profil imun yang sihat dengan hasil neutral.

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When I first entered the Immunology Lab at the Faculty of Medicine and Health Sciences, I didn't know much about how to blend in with the new crowd or what you had to do to obtain the consumables, kits, reagents etc. for your research. Luckily, I had the assistance of many fellow postgraduate students who have been more than willing to share their knowledge and opinion with me. They are none other than Shamin, Yana, Shahriman, Kak Sarah, Kak Aini, Amira, Kiven and Kak Zuleha. Additionally, I have had the great pleasure of meeting some of the newer members of the lab, including Vanitha, Umar, Lily, Ahmad Badawi, Kak Nabilah, Wafa and Doreen, who have shown remarkable competencies in their respective works and have inspired me greatly along the way. As time goes by, my life became hectic with hours and hours of literature readings and writings (proposals, review papers, journal articles, thesis), data analysis and even more frustratingly, countless of failed experiments. It was with the help of some of the most amazing staff members of the department that has allowed me to progress this far into my research. A huge thank you to Puan Amrina, Kak Marsitah, Kak Ummu, Kak Aishah, Kak Atul and Uncle Anthony for their relentless support. My family has and forever will be my pillars of strength. With that I would like to thank my parents, Mr. Jana Money and Mdm. Selvi, my siblings, Pravin Prasad and Deepa Darshini and my sister-in-law, Privita Nair, for always believing in me no matter what. Credits also goes to Alexandra E. and Mariah C., both of whom have aided me in more ways than one over the course of the years. On that note, I would also like to thank my four-legged buddy, Bruno for his love and positive vibes. Lastly, to myself, for staying true to my dreams and never giving up under any circumstances. I've come a long way, but I feel like I'm just getting started.

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This is to confirm that:

- the research and the writing of this thesis were done under our supervision;
- supervisory responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2015-2016) are adhered to.

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LIST OF ABBREVIATIONS

AAP	Amino acid pair
ACC	Auto cross covariance
ANN	Artificial neural network
APC	Antigen presenting cell
AR	Allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ARP	Allergen representative peptide
BCR	B cell receptor
Beffs	Effector B cells
BHR	Bronchial hyperreactivity
BLAST	Basic Local Alignment Search Tool
Bregs	Regulatory B cells
BSA	Bovine serum albumin
CD	Cluster of differentiation
CIITA	Class II transactivator
CLIP	Class II-associated invariant chain peptide
Der p 1	Dermatophagoides pteronyssinus antigen 1
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot assay
ENT	Ear, nose and throat
FASTA	File format used to represent DNA/protein sequences
FBS	Foetal bovine serum
FSC	Forward scatter
GA2LEN	Global Allergy and Asthma European Network
GWAS	Genome-wide association study
HDM	House dust mites
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IEDB	Immune Epitope Database
IMGT	International ImMunoGeneTics project
IPD	Immune Polymorphism Database
ISAAC	International Study of Asthma and Allergies in Childhood
IUIS	International Union of Immunological Societies
LS	Löfgren's syndrome
MAST	Motif Alignment and Search Tool
MEME	Multiple Expectation Maximizations for Motif Elicitation
MERCI	Motif - EmeRging and with Classes - Identification
MHC	Major histocompatibility complex
NAR	Non-allergic rhinitis
NCBI	National Center for Biotechnology Information
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PHA-L	Phytohemagglutinin-L
PMNL	Polymorphonuclear leukocyte
QOL	Quality of life
RA	Rheumatoid arthritis
RNN	Recurrent neural network

RPMI	Roswell Park Memorial Institute
SDR	Specificity-determining residues
SLE	Systemic lupus erythematosus
SMM	Stabilized matrix method
SNP	Single nucleotide polymorphism
SPSS	Statistical Package for Social Sciences
SSC	Side scatter
SSP	Sequence-specific primer
SVM	Support vector machine
TBE	Tris-borate-EDTA
TCR	T cell receptor
Tregs	Regulatory T cells

CHAPTER 1

INTRODUCTION

Allergic rhinitis (AR) is a nasal inflammation disorder which results in symptoms such as nasal itchiness, sneezing, rhinorrhea and blockage (Wheatley & Togias, 2015). Usually, the allergy is triggered by reactions against environmental allergens such as house dust mites (HDM) and cat fur (Lim et al., 2015). In Malaysia, the prevalence of AR among children and teenagers were found to be increasing in many major cities (International Study of Asthma and Allergies in Childhood, ISAAC) (Ellwood et al., 2005). For adults, the occurrence rate was estimated to be 53.0% (Lim et al., 2015). Apart from the clinical burdens, AR also has major implications on the quality of life; causing sleep deprivation, absenteeism and impairment of productivity, especially for school children and working adults (Kulthanan et al., 2018; Mir et al., 2012). In 2018, the socioeconomic cost of AR within the Asia-Pacific region alone ranged from 30.7 to 105.4 billion USD (Kulthanan et al., 2018). These reports support the notion that AR is a vexing form of allergy with multiple adverse repercussions.

An individual's genetic makeup may greatly influence their susceptibility to allergen sensitization. The major histocompatibility (MHC) genes which give rise to highly polymorphic protein forms, expressed on antigen presenting cells, are important initiators of adaptive immune responses. Degraded antigen peptides bind selectively to MHC which are then presented to T cells for activation. These specific peptides are known as T cell epitopes. Polymorphism in human leukocyte antigens (HLA), the human equivalent of MHC, have been shown to be associated with the manifestation of AR. For example, *HLA-DQB1*06:01:01* and *HLA-DRB1*08:03:02* were deemed as risk alleles for HDM-sensitized AR in a Chinese Han population (Zhao et al., 2016) whereas the *HLA-DPB1*05:01* allele was linked to cedar pollen-induced AR among Japanese adolescents (Morii et al., 2018). Genome-wide association studies (GWAS) continue to demonstrate the involvement of HLA genes in the pathogenesis of AR (Andiappan et al., 2011; Gao et al., 2020; Laulajainen-Hongisto et al., 2020; Yatagai et al., 2013). These findings imply that inherited variation in the HLA genes may result in differences within the amino acid residues of the peptide-binding pocket, which may lead to lower or higher allergen-binding affinities (Waage et al., 2018). Furthermore, structural variations within the allergenic peptides may allow for preferential binding by specific HLA molecules (Morii et al., 2018).

The house dust mite (HDM) *Dermatophagoides pteronyssinus* is one of the most prevalent aeroallergens in Malaysia (Mariana et al., 2000) and a huge proportion of the population is highly sensitized to this species (Gendeh et al., 2000; Lim et al., 2015). To date, 30 types of allergens from *D. pteronyssinus* have been classified, with Der p 1 being one of the major allergenic proteins (Miller, 2019). The existence of various epitopes within HDM-derived allergens has been shown to induce potent immune responses in terms of the type of cytokines and antibodies secreted (Cai, Chen, et al., 2019; Greene et al., 1991; Hinz et al., 2015; Tsai et al., 2000; Wambre et al., 2014). It is possible that people with different HLA genetic backgrounds present different T cell epitopes from one allergen alone and result in the production of varying types of cytokines. Similarly,

distinct IgE and IgG inducing regions on these allergens (also known as B cell epitopes) may also cause variations in the antibody outcomes (De-Simone et al., 2014). Understanding the interactions between different HLA backgrounds and HDM-derived peptides for induction of specific cytokine and antibody profiles may provide useful clues on the molecular mechanism of allergen sensitization. However, the full spectrum of MHC-restricted T and linear B cell epitopes of Der p 1 have not been properly established thus far.

In silico methods for peptide prediction studies are both cheap and time-saving. NetMHCIIpan, TepiTool and PREDIVAC are freely available software used to determine T cell epitopes whereas ABCPred, BCPREDS and BepiPred are utilised to identify linear B cell epitopes (Sanchez-Trincado et al., 2017). Furthermore, the allergenicities of these peptides can be predicted using AllerTOP 2.0 (Dimitrov, Bangov, et al., 2014), AllergenFP 1.0 (Dimitrov, Naneva, et al., 2014) and AlgPred (Saha & Raghava, 2006). Not only that, prediction of pro- and anti-inflammatory cytokines based on T cell epitopes can be made using IL4Pred (Dhanda, Gupta, et al., 2013), IL-10Pred (Nagpal et al., 2017) and IFNepitope (Dhanda, Vir, et al., 2013). For analysis of specific antibody secretions by B cells, the online webtools Bcipep (Saha et al., 2005) and IgPred (Gupta et al., 2013) have been developed for public use.

It is widely accepted that in many atopic disorders, the balance between the effector and regulatory components of the immune system becomes highly dysregulated (Boguniewicz & Leung, 2011; Lipscomb & Wilder, 1999). For instance, the levels of peripheral effector T (Th2 & Th17) cells were found to be significantly higher among AR patients, however their circulating regulatory T (Treg) cell population remained substantially lower in numbers (Agrawal & Shao, 2010; Huang et al., 2014; Shaoqing et al., 2018; Sun et al., 2016). Similarly, the expression of pro-inflammatory cytokines in the serum of AR patients was higher compared to the healthy controls (Huang et al., 2014; Sun et al., 2016). The exact reason for these observations is unknown, but it is assumed that environmental exposure and genetic predisposition may play key roles (Calzada et al., 2018).

The pathogenesis of AR constitutes allergen sensitization and effector phases, both of which are governed by various cells of the immune system (Pawankar et al., 2011). Here, the functionality of B cells is of particular interest as they employ distinct roles during the allergen processing, recognition and reaction stages. As professional APCs, they can internalize the antigens via B cell receptor (BCR)-mediated endocytosis prior to presenting them with high efficiency for T cell activation. In return, the T cells aid in class switching of B cells for secretion of antigen-specific IgEs (Chen & Jensen, 2008). It was previously observed that the frequencies of IgA-expressing plasmablasts and memory B cells were considerably higher in AR patients but memory cells exhibiting IgM and IgG were significantly lower (Henriques et al., 2015). This imbalance in the effector B cell population suggests the involvement of certain factors that require further investigation.

Regulatory B (Breg) cells are a type of B cells that participate in immunosuppressive activities by preventing Th2-based hypersensitive reactions (van de Veen et al., 2016).

According to the study by Kamekura *et al*. (2015), the frequency of circulating $CD19^{+}CD24^{hi}CD27^{+}$ Bregs was significantly reduced among AR patients (Kamekura et al., 2015). Interestingly, another study showed that the percentages of the $CD19^{+}CD24^{hi}CD27^{+}$ Bregs were higher among the AR subjects (Luo et al., 2018). Both of these studies did not evaluate interleukin-10 (IL-10) production capacity of B cells which is also necessary for tolerance induction (van de Veen et al., 2016). Functional assessment of Breg populations is therefore necessary to correctly identify their true role in the pathomechanism of AR. During humoral immunity, B cell activation, proliferation and differentiation occur via signalling from epitope-HLA interactions with T cell receptors (Katikaneni & Jin, 2019). Nevertheless, the implications of specific HLA variants on the homeostasis of B cells have not been clearly demonstrated thus far, particularly in the case of mite induced-allergy. As mentioned earlier, B cells perform various functions as APCs, effectors (Beffs) and regulators (Bregs) during the response against allergens. However, *in vitro* models that replicate the inflamed nature of the immune system relative to the frequency of B cells are yet to be available. Thus, by selecting individuals with the candidate HLA backgrounds and culturing their B cells in a dust mite-challenged environment, the dysregulation of B cell homeostasis can be explored further.

Thus, it is hypothesized that Der p 1 epitopes restricted by certain HLA-DR serotypes can induce different types of cytokines which in turn may trigger class switching of B cells for secretion of specific antibodies. Furthermore, these HLA-DR backgrounds can also affect the frequencies of various B and T cell subpopulations in the presence of Der p 1 allergen. In general, the aim of this study is to first determine the relationship between Der p 1 epitopes, cytokines, antibodies and various HLA-DR serotypes using *in silico* approaches, followed by experimental cultures of healthy and allergic rhinitis PBMC samples (with selected HLA-DR genetic backgrounds) in a Der p 1-challenged environment in order to understand the role of HLA in the dysregulation of B and T cell homeostasis. The specific objectives of this study are:

1) To conduct *in silico* prediction and immunogenicity analysis (allergenicity, cytokine and antibody responses) of $CD4^{+}$ T and linear B cell epitopes of Der p 1 allergen from *Dermatophagoides pteronyssinus*.
2) To associate the predicted epitopes and its properties (cytokine propensities and antibody responses) with selected HLA-DR serotypes using *in silico* methodologies.
3) To evaluate the frequencies of B cells (transitional, naïve, mature, memory, plasma, regulatory and IL-10-secreting) and IL-10-secreting T cells in Der p 1-stimulated cultures of PBMCs from allergic rhinitis patients and controls with risk and protective *HLA-DRB1* alleles.

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