IN SILICO MOLECULAR INTERACTIONS STUDY OF PATTERN-RECOGNITION RECEPTOR XA26 AND PLANT PATHOGEN-ASSOCIATED MOLECULAR PATTERNS

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Dedicated to my beloved husband Ridhwan,
To my children Sumayyah and Ammar,
And to my dearest parents Danian and Umi,
Whose love yet support me,
With prayers and patience

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ABSTRACT

Plants are sessile organisms that rely entirely on innate immune system for defense against pathogenic microbes or pest. First line defense of plant is known as pattern-triggered immunity (PTI). PTI is activated by pathogen-associated molecular patterns (PAMPs) of the host plant by pattern-recognition receptor (PRR) with the recruitment of co-receptor protein. Xa26 which is also known as PRR is one of the resistance gene in rice plant that protect against bacterial leaf blight disease, one of the most threatening disease that affect the yield of rice production. Although a few studies have been conducted on PRR Xa26, the detailed component involved in the interaction mechanism has not been elucidated. The purpose of this study was to explore protein interactions between PRR Xa26 with several PAMPs namely flg22 and RaxX21-sY. In this study, these two PAMPs were docked with PRR Xa26 in the presence of different co-receptor which are BAK1, OsSerk2 (PDB:4Q3G) and its mutant (PDB:4Q3I). PRR Xa26 protein model was constructed by homology modelling using Modeller HHpred followed by docking and molecular dynamics (MD) simulation of PRR Xa26 with the PAMPs using Zdock and GROMACS respectively. The modelling of PRR Xa26 by Modeller HHpred produced the best result with Verify 3D of 99.68%, ERRAT of 65.854% and 90.2% amino acid in allowed region of Ramachandran plot. Docking result showed that complex interaction of PRR Xa26, PAMP RaxX21-sY with co-receptor OsSerk2 (normal) bind at the concave portion of Xa26 leucine-rich repeat (LRR) which match with the flagellin sensitive 2 (FLS2) mediated PTI, the only crystallized structure in PTI till date. This is the best docking complex as it maintains protein conformational structure and provides stable binding interaction without any loss of bond after the simulation. MD simulation results showed significant reduction of hydrogen bonds for all the docked complex structures. For the Xa26_RaxX21-sY_OsSerk2 (normal) protein complex, the hydrogen bonds were reduced from 768 to 760. Whilst in mutated protein complex the numbers of hydrogen bond were reduced from 767 to 0. This significant reduction resulted in conformational changes of protein complex thus triggered the formation of salt bridge between Arg152 with the nearby residue Glu174 that caused binding disruption among the protein. This study provides significant information on the interaction between PRR Xa26 and multiple PAMPs to find the right PAMP for PTI mechanism of PRR Xa26.

ABSTRAK

Tumbuhan adalah organisma sesil yang bergantung sepenuhnya pada sistem keimunan inat untuk mempertahankan diri dari sebarang serangan mikroorganisma atau makhluk perosak. Lapisan pertahanan pertama bagi sistem keimunan inat ini adalah dikenali sebagai sebagai imuniti cetusan corak (PTI). PTI diaktifkan melalui mikroorganisma tanggapan relatif patogen (PAMPs) oleh reseptor pengesanan corak (PRRs) tumbuhan perumah dan merekrut protin ko-reseptor. Xa26 atau dikenali sebagai PRR adalah antara gen rintangan dalam pokok padi yang melindungi daripada penyakit hawar daun bakteria, yang mana salah satu antara ancaman mati yang menganggu produksi penghasilan pokok padi. Walaupun beberapa kajian yang telah dijalankan khusus ke atas PRR Xa26, komponen terperinci yang terlibat dalam interaksi mekanisme ini masih belum diketahui. Tujuan kajian ini adalah untuk mengkaji hubungan interaksi di antara PRR Xa26 dengan beberapa PAMPs iaitu flg22 dan RaxX21-sY. Dalam kajian ini, kedua-dua PAMPs tersebut akan bertindak balas dengan ko-reseptor yang berbeza iaitu BAK1, OsSerk2 (PDB:4Q3G) dan mutasinya (PDB:4Q3I). PRR Xa26 telah dibina melalui pemodelan homologi menggunakan Modeller HHpred diikuti proses mengedok dan simulasi dinamik menggunakan Z-dock dan GROMACS masing-masing. Pemodelan homologi menghasilkan nilai dan struktur yang terbaik menggunakan Modeller HHpred iaitu 99.68% Verify 3D, 65.84% ERRAT dan 90.2% nilai asid amino dalam kawasan yang dibenarkan oleh lakaran Ramachandran. Hasil keputusan dok menunjukkan bahawa interaksi kompleks antara PRR Xa26, PAMP RaxX21-sY dengan ko-reseptor normal OsSerk2 mengikat di kawasan palung pada struktur XA26 LRR menepati struktur PTI yang telah dikristalkan setakat ini. Struktur kompleks dok ini merupakan yang terbaik kerana ia mengekalkan struktur konformasi protin dan memberikan pengikat interaksi protin yang stabil tanpa kehilangan sebarang ikatan setelah selesai proses simulasi. Hasil simulasi MD menunjukkan semua struktur kompleks protin melalui pengurangan ikatan hidrogen. Bagi struktur kompleks protin Xa26_RaxX21-sY_OsSerk2 (normal), ikatan hidrogen berkurang daripada 768 ke 760. Manakala, struktur kompleks protin mutasi melalui pengurangan daripada 767 ke 0. Signifikan pengurangan ini terhasil daripada perubahan struktur kompleks protin yang mencetuskan pembentukan titian garam di antara Arg152 dengan sisa yang berdekatan Glu174 yang menyebabkan gangguan pengikatan protin. Kajian ini menyumbang maklumat penting mengenai kewujudan interaksi antara PRR Xa26 dan pelbagai jenis PAMPs dalam mencari PAMPs yang paling sesuai untuk mekanisme PRR Xa26.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

RMSD	-	Root Means Square Deviation
RMSF	-	Root Means Square Fluctuations
RaxX21-sY	-	RaxX21-sY protein with sulphation at tyrosine region
TM	-	Transmembrane Domain
YSU	-	Sulphotyrosine
BLB	-	Bacterial leaf blight
R gene	-	Resistance gene
LRR	-	Leucine-rich repeat
PAMPs	-	Pathogen-associated molecular patterns
PRR	-	Pathogen recognition receptor
PTI	-	Pattern-triggered immunity
ETI		Effector-triggered immunity
ER	-	Endoplasmic reticulum
Rg	-	Radius of gyration

LIST OF SYMBOLS

α	-	Alpha
β	-	Beta
Å	-	Angstrom
nm	-	Nano meter
ns	-	Nano second
%		Percent
β	-	Beta
ps	-	Pico second

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background research

Rice has been a staple food source for thousands of years among half of the human population. According to Jena and Khush (2009), almost 23% more rice need to be produced by 2035 to meet the expected demand of the growing world population. However, there is decrease in rice production (1.0% yr^{-1}) compared to the rate of population growth rate (1.5% yr^{-1}) (Prahalada *et al.*, 2017). The rice distribution often limited due to biotic and abiotic stress. In biotic stress, more than 70 diseases have been recorded caused by fungi, bacteria, viruses or nematodes (Zhang, M. *et al.*, 2004). Bacterial leaf blight (BLB) disease is one of the most threatening diseases causes by bacteria that affect the yield of rice production. The infection occurred in xylem tissues of rice causes wilting of seedlings, yellowing and drying of leaves (Figure 1.1). This will consequently reduce the photosynthetic area and thus reduced the photosynthesis system of plant leaves. The causal agent of BLB disease is *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), that affect almost 80% grain quality of rice annually (Kumar *et al.*, 2012). `Due to the high damage on rice field, there is lot of studies and researches were conducted to control this disease. According to (Sun, X. *et al.*, 2004), the most effective and environmental friendly strategy to control bacterial blight is through the breeding and deployment of major resistance (R) genes in rice plant. R genes are important for

plants to defend themselves from pathogen attacks. It was supported by laboratory result that heterologous Until now, 40 BLB R genes have been identified in cultivated rice and the wild relatives (Khan, M. A. *et al.*, 2014; Kim, S. M. *et al.*, 2015).

Among all the 40 genes isolated, PRR Xa26 has the highest sequence homology with rice BLB and is the only R gene that was confirmed to encode leucine-rich repeat (LRR) receptor kinase-like protein (Song *et al.,* 1995; Hulbert *et al*., 2001). This LRR receptor kinase-like protein consist of transmembrane motif which recognize special extracellular ligands via LRR domain and initiate the downstream signaling through the intracellular kinase domain (Zhang *et al.*, 2011). Besides, it was recorded that LRR domain of resistance proteins of plants directly interact with any avirulence gene involved in host-pathogen interaction (Sun *et al.,* 2003). PRR Xa26 is also cell surface localized pattern-recognition receptor (PRR). PRRs will recognize pathogen-associated molecular patterns (PAMPs) and activates pattern-triggered immunity (PTI) which is the first line defense in plant.

Figure 1.1: Rice plants showing symptom of BLB (right) with the resistance (left) (Khan, M. A., Naeem, and Iqbal, 2014)

Other than rice, different plant and animal species also carry this type of receptors which has the similar mechanism as PRR Xa26 (Ronald and Beutler, 2010). However, in plants, there are multiple molecular strategies employed by plants to detect any potential invaders for their survival. Various molecular immune signaling mechanisms triggered after PAMP perception were found in different type of plants (Figure 1.2). The first plant PAMP/PRR to be characterized was the perception of bacterial flagellin by the LRR-RK FLS2 recognized by higher plants (Gomez *et al.,* 2000). This is followed by elongation factor Tu (EF-Tu). In the bacterial flagellin, binding of PAMP flg22 to FLS2 leads to instantaneous recruitment of co-receptor BAK1, which required for the full activation of immune signaling. Whereas, binding of elf18 on EFR lead to spontaneous recruitment of co-receptor BAK1. Although most of plant PRRs are identified and illustrated clearly, PAMPs for specific PRR interaction of PRR Xa26 are still unknown. Besides, most of their mechanism is yet to be discovered. In the current study, an attempt to interact PRR Xa26 with other existed complexes from different plant species to study the difference or any similarity in term of interaction at atomic level was discovered.

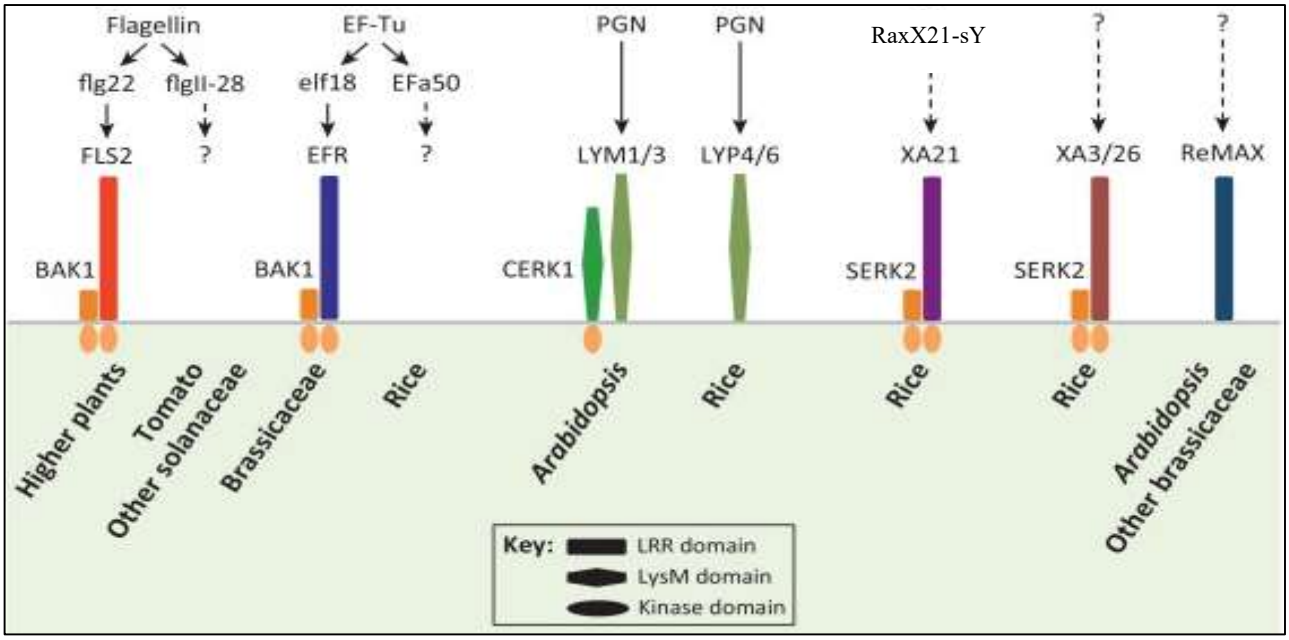

Figure 1.2: Different plant PRR with their recognized PAMPs (Zipfel, 2014)

1.2 Statement of problem

In rice plant, PRR Xa26 is a membrane bound PRR that synthesized in the endoplasmic reticulum (ER) where later transferred to the plasma membrane (Park *et al*., 2014). When the pathogen attacked the plasma membrane, PRR Xa26 will recognize the conserved microbial signature and eventually triggers a series of downstream events resulting in a robust resistance response. From this molecular signaling mechanism, the early events governing PRR Xa26 activation have not yet been fully elucidated except association of OsSerk2 with PRR Xa26 as co-receptor which positively regulated the PTI in rice plant. PTI is the first mode of innate immune system in plant which is triggered upon the perception of microbe or pathogen associated molecular pattern (M/PAMPs) through PRR.

The presence of few confirmed PAMP/PRR pairs has already clearly helped to demonstrate the importance of these early sentinel mechanisms for plant immunity. Indeed, the transferred of corresponding PRR across plant families can provide new recognition specificities that ultimately increase the disease resistance (Zipfel, 2014). For example, the transfer of the rice Xa21 into sweet orange (*Citrus x sinesis*), tomato and banana conferred enhanced resistance to *X.axonopodis* pv. *citri*, *Ralstonia solanacearum* and *Xanthomonas campestris* pv. *musacearum* respectively (Zipfel, 2014).

On the other hand, following same PTI mechanism as PRR Xa26, PRR FLS2 interacts with the PAMP flg22 and make FLS2-flg22 complex. PRR FLS2 is the only plant PAMPs that has been characterized and crystallized. Due to that, FLS2-flg22 complex is used as template and reference. In this study, PRR Xa26 is interacting with another PAMPs and co-receptor existed in different plant species such as flg22, PAMP RaxX21-sY, co-receptor BAK1 and OsSerk2. This study will be the first ever computational study on the molecular interaction between the plant PRRs and PAMPs of different family.

1.3 Significance of study

The findings of this study will contribute to the benefit of understanding the plant defense mechanism. It was found that there is presence of interaction between PRR and PAMPs from different plant species (Zipfel, 2014). PRR Xa26 protein is one of the R gene that involve in controlling BLB disease in rice plant. Therefore, *in silico* study of PRR Xa26 interaction with PAMPs by proper modelling and molecular dynamics simulation will contribute significantly in understanding the plant defense mechanism. Besides, this study also helps to uncover the type of relationship presence among PRR Xa26 with different PAMPs such as flg22, PAMP RaxX21-sY, and co-receptor BAK1 and OsSerk2 through docking method.

1.4 Objectives of study

The overall aim of this study is to understand the mode of interaction of the PRR Xa26 with different PAMPs. As such, the objectives are outlined as follows;

1. To model the plant PRR Xa26 immune receptor and validate the model.
2. To construct the docking complex of plant PRR Xa26 immune receptor and bacterial PAMPs including flg22, RaxX21-sY together with co-receptor, OsSerk2 and co-receptor BAK1, thus stabilized the model through the molecular dynamic simulation.
3. To analyze the role of co-receptor OsSerk2 and its interaction with plant PRR Xa26 and effect of mutation on co-receptor OsSerk2 towards binding of PRR Xa26 and PAMPs.
4. To compare the interaction of complex PRR Xa26_flg22_ co-receptor BAK1 with the crystallized structure of FLS2_flg22_ co-receptor BAK1 obtained from protein data bank, PDB id, 4MN8

1.5 Scope and limitation of study

This current study is exclusively conducted by computational in nature. First, the PRR Xa26 was modeled using different tools (AIDA, FFAS-3D, Geno 3D, I-Tasser, Muster, Phyre2 (Intensive), Phyre2 (Normal), PSIPRED, Raptor-X, Modeller (HHpred), SPARKS-X, Swissmodel). After that, the docking of PRR Xa26, PAMPs and co-receptor, OsSerk2 was performed using online tool, Zdock. Then, the molecular dynamics simulation was conducted to analyze the types of interaction occur between PRR Xa26 and it PAMPs through GROMACS. Root means square deviation (RMSD), root means square fluctuation (RMSF), radius of gyration (Rg) were measured using this open source software. According to these measurement and others measurement provided in methodology part, the results were discussed and assessed.

The major limitation in this study was expensive software was needed to model the full multi domain PRR Xa26. Thus, free open source software was used for protein modelling. Since there is unknown mechanism of PRR Xa26 plant immune system, FLS2-flg22 complex was used as template in protein modeling of PRR Xa26.

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