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# Structure and Function of Disease Resistance Proteins in Plants

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## Abstract

Resistance proteins are the most effective weapons of plants against pathogen invasion since they can recognize the corresponding pathogen effectors or associated proteins to activate plant immune response. Up to date, greater than seventy resistance proteins have been identified from different plant species. Most resistance proteins contain conserved domains such as the nucleotide-binding sites, the leucine-rich repeat, the coiled-coil domain and others. These domains play significant roles in resistance proteins interaction with effector proteins from pathogens and inactivating signals involved in innate immunity. This review highlights illuminating the structure and function of the isolated plant resistance proteins in different plant-pathogen interaction systems.

## Keywords

Plant Disease, Resistance Proteins, Defense Response

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## 1. Introduction

Plants are attacked by disease causing pathogens (e.g. viruses, bacteria and fungi), nematodes and insects. Most of the times, plants recognize pathogens and pests and counter their attacks either through active, passive or both defense mechanisms [10].

The active defense responses of plants can be based either on basal defense or on adaptive immune system [10]. Basal defense can be activated during recognition of conserved pathogen-associated molecular patterns (PAMPs) or microbe associated molecular patterns (MAMPs) such as chitin, flagellin, peptides and lipid polysaccharides by pattern recognition receptors (PRRs) [3]. Recognition of this PAMPs or MAMPs by PRRs triggers basal defense responses through the process called PAMP-triggered immunity (PTI) [5]. However, pathogens develop counter strategies to overcome PTI through modifying or changing PAMPs or MAMPs. Then, plants develop means to recognize these effectors and trigger a faster and stronger secondary defense response known as effector-triggered immunity (ETI). ETI is mediated by R proteins and accompanied by localized cell death around the site of infection [5; 17].

Depending on the presence or absence of the kinase domain in the receptors, PRRs can be receptor-like proteins (RLPs) or receptor-like kinases (RLKs). The extracellular class of resistance proteins contains the Receptor-Like Proteins (RLPs) and Receptor-Like Kinase (RLKs) having extracellular Leucine-rich repeat (eLRR) domain attached to transmembrane (TM) domain. RLKs have kinase domain, whereas RLPs do not [13]. These two receptors are found attached to the cell membrane and recognize pathogen effectors to provide resistance [2]. For example, the tomato *Cf* resistance proteins are among members of RLPs that provide resistance against the leaf mould fungi, *Cladosporium fulvum*.

The resistance protein based defense mechanism is highly specific and it depends on the recognition of virulence factors of the pathogen called “effectors” [10]. Resistance proteins are responsible for inducing plant defense in response to

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pathogen-derived effectors through direct or indirect recognition [5]. For example, the *Arabidopsis thaliana* NOD–like receptor (NLR) proteins RPS4 and RRS1 are both required to identify the cognate bacterial effector AvrRps4 from *Pseudomonas syringae* and PopP2 from *Ralstonia solanacearum* and also the fungal pathogen *Colletotrichum higginsianum* [39].

Passive defenses are preformed/preexisting structural properties of plant tissue against pathogen invasion. For example, waxy cuticle, lignification, callose deposition, rough leaf surface, presence of trichomes and stomatal closure are among the structural defenses against pathogens attack. In addition, cytoskeletal networks of the plant such as actin filaments and microtubules provide a physical barrier against penetration of *Arabidopsis thaliana* plants by fungal appressorium [9] who found that, treatment of *Arabidopsis thaliana* hypocotyls with a bacterial microbe-associated molecular pattern elf26 increased the actin filament abundance depending on presence of the cognate PRR, as mutants treated with elf26 in the absence of part of the PRR did not show an increase in actin filament abundance. As a result, changes in the actin cytoskeleton serve as a microbe perception signal to activate PTI. Understanding R proteins structure, functions and their position in the plant defense system is essential. Even though the mechanisms to stop pathogen infection still remains unclear, recent studies on R protein receptors and their interaction with pathogen effectors become available. Therefore, the objective of this review paper focuses on providing an overview of plant R protein families: their structure and functions in the plant innate immune system.

## 2. Structural Domains of Resistance Proteins

Many resistance (R) proteins have been identified in several plant species, for example in *Arabidopsis thaliana* and *Medicago trunculata*. Most of the identified resistance proteins belong to the NB-ARC-LRR R proteins [16]. These R proteins exhibit modular structural domains that interact with each other and with other proteins to activate defense responses [22]. Disease resistance can be achieved after pathogen effectors are recognized through signal transductions [22, 2].

Many reviews suggest that, resistance proteins are grouped into four major classes according to their structural motifs. R-proteins can be broadly grouped into two intracellular and two extracellular protein families [34]. TIR-NB-LRRs (TNLs) are one of the classes of intracellular proteins having fused the N-terminal Toll/Interleukin-1 receptor (TIR) domain, central nuclear binding NB-ARC domain and a C-terminal Leucine-rich repeats (LRRs) domain. The central NB-ARC domain has the NB, ARC1 and ARC2 sub-domains. The second classes of intracellular proteins are called CC-NB-LRRs (CNLs); proteins that have coiled-coil (CC) domain instead of the TIR domain in their N-terminus [5]. Based on the presence of additional domains in their amino-terminus, CNL proteins can be further divided. For example, the BED ZNF DNA-binding domain in the rice Xa1 [35] and the SD (solanaceous domain) that only found in the Solanaceae [25]. are among the CNLs sub-groups. CNL proteins can be found both in monocots and in dicots whereas; TNLs have never been identified in monocots [14]. TNLs and CNLs not only differ by the presence or absence of the TIR domain, but also differ in the NB domain sequence [19]. TNLs having diverse structures were detected in dicots like *Arabidopsis thaliana*. The *Arabidopsis thaliana* TNLs differs in their structure from the usual TIR-NB-LRRs domain organization [20]. For example, the *A. thaliana* R protein that gives resistance to *Ralstonia solanacearum* (RRS1) contains WRKY DNA-binding domain in the C-terminus in addition to TNLs [7]. Moreover, R proteins having two LRRs domains and domains without the CC domain were found in *Populus trichocarpa, Oryza sativa,* and *A. thaliana* [20, 14]. For example, proteins having two nucleotide binding domains (CC-NB-NB-LRRs) were found in rice that is a monocot crop [21]. On the other hand, proteins missing the coiled-coil (CC) domain were found in Arabidopsis, poplar and rice genomes [20; 14]. Proteins showing some resemblance to CNL proteins with missing LRRs domain or entirely having either the CC or NB domain alone were also identified in poplar and Arabidopsis genomes [21].

### 2.1. The NB-ARC Domain

The nucleotide binding (NB) domain is shared between human Apoptotic Protease-Activating Factor 1 (Apaf-1), some plant resistance proteins and Caenorhabditus elegans Dead protein 4 (CED-4); in short called the (NB-ARC domain). The NB-ARC domain is the nucleotide binding adapter [27] that contains the NB, ARC1 and ARC2 sub-domains [36] to form either helix bundle or a winged helix fold structure [37]. The NB sub-domain makes the NB pocket containing a five strand parallel ß-sheet enclosed by seven α-helices. The ARC1 sub domain forms a four-helix bundle and the ARC2 forms a winged-helix fold [37]. These three sub domains are conserved in many R proteins due to the presence of several conserved motifs in the NB-ARC domain [31]. Biochemical studies on the “N” in the NB-ARC domain confirmed that, it interacts with nucleotides due to the presence of several conserved residues [31]. This proposes a similar structure and probably a similar molecular system essential for their function.

### 2.2. The NB-LRR Domain

Majority of resistance proteins have the LRR domain that contains 2-42 repeats each having a β-sheet [5]. Each repeat in the plant LRR domains is made from 20-29 residues together with 11 conserved residues having the pattern LxxLxLxxN/CxL encircling a ß-sheet structure and adjacent loop regions [11]. The differences in the number of repeats in this domain suggest the presence of different structural classes among NB-LRR proteins in plants. The intracellular LRR domain is found fused to a transmembrane (TM) domain in both PAMP receptors and RLKs [23]. The extracellular LRR (eLRR) domain is also found fused to a TM domain in the RLPs, such as the tomato *Cladosporium fulvum* resistance proteins [26]. However, the LRR domain is found intracellularly fused to the nucleotide binding (NB) domain in many R proteins. The core NB fold in currently identified R proteins is part of the NB-ARC domain due to its presence in the Apaf-1 and CED-4 proteins [31]. The plant NB-LRR proteins are divided into two classes based on their N-terminal domains. These are the TIR-NB-LRR class that contains an N-terminal domain with similarity to TIR domain and the non-TIR class that contains the CC domain [19]. The NB-LRR core of R proteins is often found with variable N-terminal (contains positively charged residues) and sometimes C-terminal (contains aromatic amino acids probably involved in hydrophobic interactions) domains in plants. For example, the LRR domain seems to interact with the N-terminus in Bs2 and N NB-LRR proteins [22; 36]. These intra-molecular interactions are probably important for the regulation of NB-LRR protein activity and thus recognition of pathogen effectors to induce ETI.

### 2.3. The Coiled-Coil Domain

The coiled-coil (CC) domain consist of two long anti-parallel a-helices connected by a short loop, thus making the crystal structure of helix-loop-helix super coil that maintains homodimerization and protein-protein interaction [17]. For example, the crystal structure of the CC domain for the barley mildew A (Mla10) resistance protein shows a rod-shaped homodimer [17]. The CC domain consists of seven residue repeats known as heptads [24]. The heptad has seven positions that are known as a–b–c–d–e–f–g. The positions a and d are occupied by hydrophobic residues that interacts with other helix to make the inter-helical hydrophobic core whereas, e and g are occupied by hydrophilic residues forming inter-helical hydrophilic interactions. These properties of residues make helices to have both hydrophilic and hydrophobic parts [24; 17].

### 2.4. Toll/Interleukin-1 Receptor (TIR)

The structure of plant Toll/Interleukin-1 receptor (TIR) domain has not been determined yet. However, the crystal structure of the TIR domain shows a fold that consists of five parallel-stranded ß-sheets (ßA-ßE) surrounded by five a-helices (aA-aE) and connected by loops. This loop in between a2 and ß2 has quite a lot of highly conserved residues that are involved in innate immune receptor signaling [12]. Recently, the TIR crystal structure of the flax rust resistance protein L6 was determined that consists of two monomers. This structure revealed that, the TIR domain is involved in pathogen detection and signal transduction [2].

## 3. Function of Resistance Proteins

### 3.1. The NB-ARC Domain

The NB-ARC domain is believed to function as a molecular switch that controls R protein's activation depending on the nucleotide (ATP or ADP) that is bound to the NB-ARC domain [31; 1]. According to a report by [29], the ATP- and ADP-bound states were observed having different stabilities, which indicates having different protein structures. In addition, the NB sub-domain was found as a catalytic core that catalyzes the hydrolysis of ATP to ADP [32]. For example, the tomato R proteins Mi-1.2, giving resistance against the root-knot nematode Meloidogyne incognita and I-2 conferring resistance against Fusarium oxysporum, were thought to bind and hydrolyze ATP [32] which is considered as a breakthrough to better understand the activation of R proteins. According to a report by [32], nucleotide binding is vital for R protein activation because R protein inactivation was shown in the NB-ARC domain due to mutations in its P-loop (Phosphate binding loop). The ARC1 sub-domain is also useful for intra-molecular interactions between different protein domains [25] and the ARC2 sub-domain is used for LRR-mediated pathogen recognition that leads to R protein activation [32].

### 3.2. The NB-LRR Domain

Recent observations shown that, the NB domain is fused to the C-terminal LRR domain in many R proteins [25]. In addition, the LRR domain was also shown to interact with the N-terminal part of Rx, Bs2 and N NB-LRR proteins [22; 36]. These interactions with both termini might be important to induce ETI via regulating activities of the NB-LRR protein. The NB-LRR domains of R proteins are involved in the recognition of pathogen effectors either by binding directly to the effector proteins or indirectly through coevolving with pathogen effectors [6]. For example, the LRR domain has been shown to interact directly for the potato resistance protein Rx1, the tobacco resistance protein N and the Arabidopsis resistance protein RPS5 [22; 36; 1].

These studies showed that interaction between the N-terminus and the LRR domain are important for R protein function [37]. The potato resistance protein Rx1 confers resistance against Potato virus X (PVX) through direct recognition of the PVX coat protein and subsequently stops virus replication [30].

The immune receptors of most R proteins can also recognize pathogen effectors indirectly. For example, the enzymatic activity of the *Pseudomonas syringae* effector protein AvrPphB can be sensed indirectly by the Arabidopsis CC-NB-LRR protein, RPS5 [28]. Recent research results indicate that, the N-terminus of some NB-LRR proteins also binds to virulence targets of host proteins in order to guard them against attack by pathogen effectors. For example, the AvrPphB effector protein kinase PBS1, binds to the RPS5 Arabidopsis NB-LRR protein to confer resistance against *Pseudomonas syringae* [1]. Co-immunoprecipitating the NB domain with the LRR domain by inter-domain and intra-molecular interactions between domains helps to keep the RPS5 protein in a functionally inactive state [1; 37]. During infection, the bacterial effector AvrPphB cleaves PBS1 that leads to conformational changes in RPS5. The LRR domain was also shown to be an inhibitory domain of RPS5 to keep RPS5 in the off state through physically interacting with the NB domain during infection [25]. For example, both Mi-1 and I-2 immune receptors of tomato bind and hydrolyze ATP at their NB domain [32] and cleavage of PBS1 causes a conformation change that then enables PBS1 to bind to the LRR domain of RPS5 enables PBS1 to bind to the LRR domain of RPS5 [28; 36]. However, effector proteins can change, modify, phosphorylate or cleave these virulence targets. For example, the Arabidopsis virulence target protein RIN4 keeps the NB-LRR immune receptor RPS2 inactive until it is cleaved by the *Pseudomonas syringae* effector, AvrRpt2 [28]. Consequently, the R proteins activate defense responses via modifying their virulence target proteins. The modification of the virulence targets is believed to trigger the guarding NB-LRR protein to activate ETI.

### 3.3. The Coiled-Coil Domain

Many resistance proteins are shown to interact with the Coiled-Coil (CC) domain. Due to this, the CC domain is known to be a site for protein-protein interaction and R-Avr specific recognition through binding with the virulence target proteins [33; 1]. For example, the CC domain of *A. thaliana* RPS5 protein interacts with PBS1, which is the target of AvrPhB, the effector of the pathogen *Pseudomonas syringae* [1]. The Rx1 CC domain interacts with a protein known as Ran GTPase Activating Protein 2 (RanGAP2) [33]. The RanGAP2 protein interacts with the CC domain of the GPA2 and Rx1 R proteins, which gives resistance against the potato cyst nematode, *Globodera pallid* [15]. In addition, the *Arabidopsis thaliana* R protein RIN4 interacts with RPM1 and these R proteins are targeted by the *Pseudomonas syringae* effectors AvrB and AvrRpm1 [1].

### 3.4. The TIR Domain

The Toll–interleukin-1 receptor/resistance protein (TIR) domain is found to recognize Avr proteins and activate defense responses. For example, interaction has been shown between the TMV p50 helicase protein and the tobacco N protein TIR domain. Subsequently, HR was activated despite the fact that, the TIR domain is essential for resistance against TMV [18; 4]. The TIR domain also regulates gene expression and immune signaling by mediating TIR/TIR interaction between intracellular TIR domain–containing adaptors and Toll-like receptors [38; 39]. For example, the A. thaliana immune receptors RRS1 and RPS4 are needed to activate defense responses against pathogens [39] both having TIR domain at their N-terminus [38]. According to a report by [39], RPS4/RRS1 effector recognition complex can be formed during heterodimerization of the TIR domain through activation of effector-independent defense by the RPS4 TIR domain and inhibition of defense by the RRS1 TIR domain [39].

## 4. Conclusion

Plant diseases are the most important limiting factors of plant growth and development. For this reason, R protein-based resistance is the main area of interest to protect plants against various pathogens. As a result, a series of researches has been conducted to better understand the structure and function of R proteins as well as their interaction with pathogens. But, very little is known about the process of pathogen recognition and signal transduction even though many resistance proteins and its signal transduction pathways are identified in several plant species like for example in Arabidopsis thaliana. The physical interaction of many R protein domains with *Avr* proteins or interaction between other host proteins also remains unclear. For example, little is known how the CC and TIR domain proteins confer *R-Avr* proteins specific recognition. However, mechanisms how these protein domains physically interact with other host proteins or the *Avr* proteins remain unclear. In addition, many R proteins are found clustered in the plant genome, but little is known about their resistance specificity. Therefore, future researches should focus on identifying new R proteins that can sense the activities of virulence targets and their interactions with other protein domains and/or with their corresponding pathogen effectors, using genomic tools is essential.

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