Plant Immunity

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Contributor: Changjun Huang

In the plant immune system, according to the ‘gene-for-gene’ model, a resistance (R) gene product in the plant specifically surveils a corresponding effector protein functioning as an avirulence (Avr) gene product.

plant viruses | plant immunity | NB-LRR | avirulence gene | effector-triggered immunity (ETI) | viral effectors

1. Introduction

Plant viruses contain single-stranded or double-stranded RNA or DNA genomes and vary substantially in their genome structure and organization. Moreover, limited viral genome sizes and coding capacities have resulted in evolution of multifunctional proteins that are involved in different steps in the virus life cycle, including replication, movement, encapsidation and transmission. On the other hand, as obligate intracellular parasites, plant viruses absolutely depend on the host cell machinery to multiply, move throughout the plant and spread to susceptible hosts. During infection, viruses consume a substantial amount of host resources; subsequently, disease symptoms develop as a consequence of disruptions of the cellular machinery required for plant physiology and natural growth, and these disruptions eventually result in developmental abnormalities and other phenotypic manifestations. Viruses can be critical players in pathogenesis through direct or indirect interactions. However, in some plant species or varieties, virus-encoded proteins can sometimes act as determinants in plant defense responses and as host-controlled pawns to elicit extreme resistance (ER).

According to the zigzag model of plant–pathogen interactions, the plant innate immune system is broadly divided into two different layers: pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) [1]. PTI is activated by specific recognition between PAMPs, such as bacterial flagellin and fungal chitin, and the corresponding membrane-anchored pattern recognition receptors (PRRs) of plants, which serve as the first layer of defense against invading pathogens. Plant viruses were historically viewed as non-PAMP coding pathogens and plant antiviral immunity was previously excluded from classical PTI models. However, recent evidence shows that PTI also operates against viruses in plants: For example, novel paradigms in antiviral immunity include (I) identification of dsRNAs and viral nucleic acids as PAMPs [2][3]; (II) plant virus effects on cell wall remodeling that imply that virus infections can modulate damage-associated molecular patterns (DAMPs) pathways with molecular mechanisms similar to PTI [4][5][6][7]; (III) several PRRs, e.g., NIK1, BAK1, BIR1, BKK1 (BAK1-Like 1) and Serk1 that have been shown to have roles during antiviral PTI [8][9][10][11][12]; and (IV) virus

encoded proteins that interact with host factors involved in PTI pathways and interfere with PTI-mediated signaling to activate effector-triggered susceptibility (ETS) [13][14][15][16][17][18].

On the other hand, to counteract ETS, plants have evolved intracellular resistance (R) proteins that directly or indirectly recognize pathogen effectors or Avr factors to activate ETI and trigger the second layer of defense. ETI is often manifested as a hypersensitive response (HR), characterized by rapid cell death, production of reactive oxygen species (ROS) and salicylic acid (SA) induction and expression of defense-related genes [19][20][21]. Since the first viral Avr factor and antiviral *R* genes were identified in 1984 [22] and 1994 [23], increasingly diverse Avr factors and R proteins have been characterized in different virus–plant combinations. Most R proteins contain a nucleotide binding and leucine-rich repeat domain (NB-LRR) with an N terminal coiled coil domain (CC) or Toll/interleukin-1 receptors (TIR) domains. Increasing evidence also substantiates the notion that plants deploy typical ETI-based innate immune systems to control virus infections.

2. Coat Proteins (CP)

The CP, also known as the capsid protein, encapsidates and protects viral genomes from damage. Early expressed CPs function in disassembly of parental virions and have roles in assembly of progeny virions during the final infection steps. However, more and more evidence has shown that CPs of all plant viruses are multifunctional and have various roles during different replication stages, ranging from early to late events in the infection cycle. The diversity of these functions in different viral systems includes virus transmission by specific vectors, translation of viral RNA, regulation of intercellular and systemic movement of the virus, suppression of both post transcription gene silencing (PTGS) and transcription gene silencing (TGS), as well as determination of symptomatology and pathogenesis [24][25]. Owing to their obvious importance, CPs were the first example of pathogen-derived transgene resistance in plants [26]. In fact, CP encoded transgenic resistance provides an excellent solution to the global viral problems and provides an important venue for both basic and applied disease resistance breeding research and crop production [27].

Compared to CP-mediated genetic resistance engineered within the last 30 plus years, CP-induced natural resistance has evolved over millions of years. The role of CPs in the activation of *R* gene-mediated host defenses has been extensively characterized. The CPs of *Tobacco mosaic virus* (TMV), *Tomato mosaic virus* (ToMV), *Tobacco mild green mosaic virus* (TMGMV), *Bell pepper mottle virus* (BPeMV), *Paprika mild mottle virus* (PaMMV), *Obuda pepper virus* (ObPV), *Pepper mild mottle virus* (PMMoV), *Potato virus X* (PVX) and *Mungbean yellow mosaic virus* (MYMV) each serve as Avr factors that elicit resistance controlled by cognate dominant *R* genes (Table 1).

Table 1. Plant virus avirulence (Avr) factor and cognate NB-LRR resistance genes.

***Avr* Gene**	**Virus Species**	***R* Gene (Type)**	**Host Plant**	**Reference**
Coat Protein (CP)				

Avr Gene	Virus Species	*R* Gene (Type)	Host Plant	Reference
CP	*Potato virus X* (PVX)	*Rx1* (CC-NBS-LRR)	*Solanum tuberosum*	[28][29]
CP	PVX	*Rx2* (CC-NBS-LRR)	*S. tuberosum*	[30]
CP	PVX	*Nx* (locus)	*S. tuberosum*	[31]
CP	*Tobacco mosaic virus* (TMV)	*N′* (CC-NBS-LRR)	*Nicotiana sylvestris*	[32][33][34]
CP	TMV, *Tomato mosaic virus* (ToMV), *Tobacco mild green mosaic virus* (TMGMV), *Bell pepper mottle virus* (BPeMV), P*aprika mild mottle virus* (PaMMV), *Obuda pepper virus* (ObPV), *Pepper mild mottle virus* (PMMoV), *Mungbean yellow mosaic virus* (MYMV)	L^{1-4} (CC-NBS-LRR)	*Capsicum annuum*	[35]
CP	MYMV	*CYR1* (CC-NBS-LRR)	*Vigna mungo*	[36]
CP	*Cucumber mosaic virus* (CMV)	*RCY1* (CC-NB-LRR)	*Arabidopsis thaliana*	[37][38]
P38	*Turnip crinkle virus* (TCV)	*HRT* (CC-NB-LRR)	*A. thaliana*	[39][40]
Replication-Related Protein				
Rep/C1	*Tomato yellow leaf curl virus* (TYLCV)	*Ty2* (CC-NB-LRR)	*S. habrochaites*	[41]
p50	TMV	*N* (TIR- NB-LRR)	*N. glutinosa*	[23][42]
RNA-dependent RNA polymerase (NIb)	*Pepper mottle virus* (PepMoV), *Pepper severe mosaic virus* (PepSMV), and *Potato virus Y* (PVY)	*Pvr4* (CC-NBS-LRR)	*C. annuum*	[43][44]
2a	CMV	*RT4-4* (TIR-NB-LRR)	*Phaseolus vulgaris*	[45]
	CMV	Unknown	*Vigna unguiculata*	[46][47]
Helicase (CI)	*Turnip mosaic virus* (TuMV)	*TurB01* (locus) *TurB05* (locus)	*Brassica napus*	[48][49]

Avr Gene	Virus Species	*R* Gene (Type)	Host Plant	Reference
Movement Protein (MP)				
NSm	*Tomato spotted wilt virus* (TSWV), *Tomato chlorotic spot virus* (TCSV), *Groundnut ringspot virus* (GRSV), *Chrysanthemum stem necrosis virus* (CSNV) and *Impatiens necrotic spot virus* (INSV)	*Sw-5b* (SD-CC-NB-LRR)	*S. peruvianum*	[50][51][52][53]
NSm	TSWV	*RTSW* (locus)	*N. alata*	[54]
30-KDa MP	TMV, ToMV	*Tm-2* and *Tm-2$^{(2)}$* (CC-NB-LRR)	*S.peruvianum*	[55]
TGB1	*Barley stripe mosaic virus* (BSMV)	*Bsr1* (CC-NB-LRR)	*Brachypodium distachyon*	[56]
BV1	*Bean dwarf mosaic virus* (BDMV)	*PvVTT1* (TIR-NB-LRR)	*P. vulgaris*	[57][58][59]
P1	*Cauliflower mosaic virus* (CaMV)	CAR1 (locus)	*A.thaliana*	[60]
25-KDa MP	PVX	*Nb* (locus)	*S. tuberosum*	[61]
RNA Silencing Suppressor (RSS)				
NSs	TSWV	Tsw (CC-NBS-LRR)	*C. annuum*	[43][62]
P0	*Cucurbit aphid-borne yellows virus* (CABYV), *Turnip yellows virus* (TuYV) and *Potato leafroll virus* (PLRV)	*RPO1*(locus)	*N. glutinosa*	[63]
P0	*Cotton leafroll dwarf virus* (CLRDV)	*Cbd* (locus)	*Gossypium hirsutum*	[64]
Other Proteins				
P6	CaMV	Unknown	*Datura stramonium and N. edwardsonii*	[22][65]
P3 + HC-Pro	*Soybean mosaic virus* (SMV)	*Rsv1* (CC-NBS-LRR)	*Glycine max*	[66]
P3	TuMV	*TurB03* (locus) *TurB04* (locus)	*B. napus*	[60][67][68]

Avr Gene	Virus Species	*R* Gene (Type)	Host Plant	Reference
NIaPro or CP?	PVY *Potato Virus A* (PVA)	Ry_{sto} (TIR-NB-LRR)	*S. stoloniferum*	[69][70][71]

TMV CP was identified as an Avr responsible for eliciting host ER responses during interactions with the *Nicotiana sylvestris N′* gene. Two groups independently found this property by analyzing a series of recombinant viruses between resistance-inducing (RI) and resistance-breaking (RB) strains [72][32][33]. Subsequently systematic studies of CP amino acid substitutions have demonstrated that *N′*-mediated recognition requires maintenance of the CP three-dimensional structure, either directly, or through specific structural motifs [73][74]. The *N′* gene and its orthologues were recently cloned from *N. sylvestris* and other TMV resistant *Nicotiana* species and shown to encode CC-NB-LRR type proteins [34][75]. Interestingly, a more recent study of phylogeny of the CP of tombusviruses indicated that CP representatives of the family could be divided into four clades. All tested CP members in two separate clades triggered an HR in *Nicotiana* section *Alatae* species [76]. Moreover, a previous study had shown that several members of *Nicotiana* section *Alatae* carry functional *N′* orthologues [75] and implied that *N′* and *N′* orthologues might have been inherited from a common ancestor followed by evolution to confer tobamovirus and tombusvirus resistance to *Nicotiana* genus species. In pepper, a broadening spectrum of resistance to seven known pepper-infecting species of tobamoviruses (TMV, ToMV, TMGMV, BPeMV, PaMMV, ObPV and PMMoV) is conferred by the corresponding *localization (L)* alleles [35]. *L* gene alleles also encode CC-NB-LRR type resistance proteins with the ability to elicit resistance responses to different tobamoviral CP Avr effectors [77][78]. Since both *N′* and its *Nicotiana* orthologues and the *L* alleles from pepper mediate resistance against tobamoviruses by recognizing the CP [34][75], it seems that these genes have evolved from a common *Solanum* ancestor. However, a resistance gene evolution assay indicates that the *L* gene from pepper is not an *N′* orthologue, suggesting that tobamovirus resistances in pepper and *Nicotiana* originated independently [75]. Several *R* genes within the same locus recognize different CP proteins from overlapping virus species indicating that the conserved R proteins are able to recognize similar structures but with an adapted spectrum. These results also support the idea that interactions between *L* genes or *N′* orthologues and tobamovirus CPs serve as good systems for study the mechanisms and evolution of virus perception by plants.

Another representative study involves PVX CP-elicited ER mediated by the *Rx1* gene, which encodes a class of CC-NB-LRR R proteins in potato [28]. Under virus-free conditions, intramolecular interactions between the CC domain and NB or LRR domains retain *Rx1* in an auto-inhibited (off) state [79][80]. Upon PVX infection, Rx1 protein recognizes the PVX CP by leucine-rich repeat domain interactions that result in disruption of Rx1 intramolecular host interactions. However, PVX CP-induced ER by Rx1 does not involve natural cell death at the inoculation site, but instead suppresses virus replication per se, even in protoplast infections. In contrast, *RX1* does trigger an HR upon overexpression of the Avr PVX CP or under high PVX concentrations [29]. An additional study has demonstrated that nuclear-cytosolic shuttling of CP-activated Rx1 mediated by Ran GTPase-activating protein 2 (RanGAP2) is required for PVX defenses [81]. However, recent studies have shown that nuclear or cytosol restricted Rx1 variants cannot trigger ER or suppress the spread of virus infections, but can still induce an HR. Furthermore, perturbation of the nucleocytoplasmic distribution of *Rx1* leads to translational arrest of PVX CP

transcripts and compromises extreme resistance against PVX [82]. Thus, many mysteries still need to be addressed, e.g., how to explain the mutual regulation of the PVX CP and NLR activation and whether other important host factors are involved in ER and HR induction. Notably, another ER gene locus in potato, *Nx*, also confers resistance to the PVX CP. However, ER by the *Rx1* gene is induced via interactions with PVX CP conserved amino acids (aa) 121–127, whereas the *Nx* gene confers resistance to PVX through the recognition of PVX CP aa 62–78 [28][31][83].

In the *Arabidopsis thaliana* ecotype Di-17, *Turnip crinkle virus* (TCV) CP P38 functions as the Avr resistance determinant for the HRT CC-NB-LRR R protein [39][84]. By use of natural mutant isolates and interaction region screening, the TCV P38 *N* terminus has been shown to be involved in eliciting resistance responses [84][85]. Moreover, the TCV P38 *N* terminal nuclear localization domain is important for elicitation of host resistance responses and could be a key trigger for HRT-dependent resistance to TCV [86]. In another *A. thaliana* ecotype C24, *RCY1*, which encodes a CC-NB-LRR class R protein, was isolated and identified as the first *R* gene conferring resistance to *Cucumber mosaic virus* (CMV) [37]. The CMV genes involved in the *RCY1* Avr resistance response also mapped to the CP [38]. Interestingly, both the *RCY1* and *HRT R* genes belong to HRT/RPP8 gene family, and the *RCY1* locus in ecotype C24 were was found to be allelic to *HRT* in Dijon-17. These functionally divergence genes therefore seem to have evolved via recombination of ancestral genes [87]. More intriguingly, the CMV and TCV CPs, which lack sequence similarity, recognize the allelic *RCY1* and *HRT* genes [38][84]. Therefore, several possibilities have been presented; one possibility is that *RCY1* and *HRT* are elicited by completely different ligands. Another possibility is that the single CPs of CMV and TCV, or their possible complexes with other host components (e.g., guardee or decoy factor) may have highly similar CP protein folding domains [37].

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