Review

Plant Immunity against Tobamoviruses

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Plant Immunity against Tobamoviruses

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Abstract: Tobamoviruses are a group of plant viruses posing a significant threat to agricultural crops worldwide. In this review, we focus on plant immunity against tobamoviruses, including pattern-triggered immunity (PTI), effector-triggered immunity (ETI), RNA-targeting pathway, hormones and reactive oxygen species (ROS). Further, we highlight genetic resources for resistance against tobamoviruses in plant breeding and discuss future directions on plant protection against tobamoviruses.

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Introduction

Tobamoviruses are a group of plant viruses belonging to the *Tobamovirus* genus, which is part of the *Virgaviridae* family. *Tobamovirus* genus includes 37 members [1]. The tobamovirus genome is a single-stranded, positive-sense RNA of about 6.4 kb encapsidated in rod-shaped virus particles, which encodes four viral proteins, including two subunits of the viral RNA-dependent RNA polymerase-a small one of 122-130 kDa and a large one of 178-183 kDa produced by a stop codon readthrough of small one ORF, movement protein (MP), and coat protein (CP) [2]. In addition, tobacco mosaic virus (TMV) contains two additional ORFs which potentially encode 54 kDa and 4.8 kDa protein, respectively [3,4]. Tobamoviruses infect a wide range of plant species and cause significant damage to a wide range of economically important crops, such as tomatoes, peppers, cucumbers, and tobacco.

In this review, we discuss plant immunity responses to tobamoviruses, including PTI, ETI, RNA-targeting pathway, hormones, and ROS. Further, we highlight genetic resources for resistance against tobamoviruses in plant breeding and provide future directions on plant protection against tobamoviruses.

1. Plant Defense against Tobamoviruses

Based on the studies on plant interactions with bacterial and fungal pathogens, plants are thought to employ a two-layer immune system consisting of PTI and ETI. PTI is triggered by pathogen-associated molecular patterns (PAMPs) via cell surface-localized pattern-recognition receptors (PRRs), whereas ETI is activated by pathogen effector proteins via predominantly intracellularly localized receptors called nucleotide-binding, leucine-rich repeat immune receptors (NLRs) [5]. The concept of PTI and ETI could also be applicable to plant-virus interactions.

PTI is triggered by PRRs to detect the conserved microbial cues known as PAMPs. Classic PRRs are localized to plasma membrane (PM) and play a crucial role in plant immunity against extracellular fungi and bacterial pathogens [6]. Because viruses are intracellular parasites, it seems unlike that there is a classic cell-surface-localized PRR-mediated PTI against intracellular viruses. However, antiviral PTI has been proposed because some viral proteins suppress PTI responses activated by non-viral PAMPs, and some receptor-like kinases are involved in basal antiviral defense

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[7]. For example, Brassinosteroid-associated kinase 1 (BAK1), the core regulator of PTI, contributes to plant defense against several RNA viruses including two tobamoviruses tobacco mosaic virus (TMV) and oilseed rape mosaic virus [8]. Viral double-stranded RNAs (dsRNAs) are proposed to be the potential PAMPs inducing antiviral defense response. Indeed, plant treatment with the purified viral dsRNA from virus-infected plants and the dsRNA analog polyinosinic:polycytidylic acid triggers typical PTI responses and antiviral defense, which depend on the PTI co-receptor SOMATIC EMBRYOGENESIS RECEPTOR-LIKE KINASE 1 [8]. Small RNAs (sRNAs) stimulate the production of callose near plasmodesmata (PD), consequently restricting the spread of viruses between plant cells. This defense response relies on various PTI signaling elements and several PD-localized proteins [9]. The expression of TMV MP suppresses dsRNA-induced callose deposition, facilitating intercellular TMV movement [10]. Interestingly, soybean mosaic virus-encoded cylindrical inclusion protein is reported to partially localize to the cell wall and can interact with cell wall-localized NLR Rsc4-3 [11], suggesting that some viral components are able to localize to apoplast and these viral components may contribute to the classical PTI against viruses. In addition, Ca^{2+} flux triggered by injuries to plant cells is thought as the common molecular pattern of different viral infections and primes antiviral RNAi defense [12]. These findings suggest that there could be both classic and non-classic PTI against plant viruses including tobamoviruses.

Plant NLRs play an important role in plant antiviral ETI by detecting viral effectors. These NLRs can recognize viral effectors and trigger antiviral ETI, usually including hypersensitive response (HR), a type of programmed cell death at pathogen infection sites [13]. Currently, most plant genetic resources for plant breeding are mainly controlled by the naturally identified dominant resistance genes including NLR genes and recessive resistance genes (Table 1).

Table 1. Plant genetic resources for resistance against tobamoviruses.

Gene name	Alleles	Plant of origin	Viral target	Protein type
N	NA	*Nicotiana glutinosa* [14,15]	p50 (Avr)[25–27]	TNL [18]
N′	NA	*Nicotiana sylvestris* [42]	CP (Avr) [42]	CNL [42]
Tm-2	*Tm-2* and *Tm-2²* [52]	*Solanum peruvianum* [43,53]	MP (Avr)[55,57,124]	CNL [52]
L	L^1, L^{1a}, L^2, L^3, and L^4 [63,65]	*Capsicum chinense* [62]	CP (Avr) [63]	CNL [63]
Tm-1	Several [101]	*Solanum habrochaites* S. Knapp & D.M. Spooner [43,44]	Replicase [45,47,49]	Unidentified
TOM1; TOM3	NA	*Arabidopsis* [71,72]	Replicase [50,67,78]	Seven-pass transmembrane [69]
TOM2A	NA	*Arabidopsis* [68]	NA	Four-pass transmembrane [68]
ARL8	NA	*Arabidopsis* [78]	Replicase [50,67,78]	N-terminal amphipathic helix [78]
WPRb	NA	*Citrullus lanatus* [79]	MP [79]	CC [79]

Abbreviations: NA, not available.

2. Plant Genetic Resources for Resistance against Tobamoviruses

2.1. Tobacco N Gene

The *N* gene is the first *R* gene identified in *Nicotiana glutinosa* [14,15]. *N* gene confers *resistance* to all known tobamoviruses except TMV-Ob [16,17]. It is a toll-interleukin-1 receptor homology/nucleotide binding/leucine rich repeat (TIR-NB-LRR, TNL) class of resistance gene [18]. The structure-function analysis shows that all three domains of N protein, including TIR, NB and LRR, are necessary for its function [19]. *N* gene encodes two transcripts by alternative splicing, N_S and N_L, both of which are essential for full resistance to TMV [20]. TMV induces HR lesion in *N*-containing plants. In *N*-containing plants, the burst of reactive oxygen intermediates occurs rapidly

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upon TMV infection [21]. Similarly, nitric oxide accumulates at the beginning of HR during TMV infection [22].

N protein recognizing the 50 kDa helicase domain (p50) within the 126 kDa replicase of tobamoviruses through its TIR domain, triggering HR and immune response in cytoplasm [23–26]. Simultaneously, N protein also operates resistance to TMV within cell nucleus [24,27]. Extensive research has revealed the roles of host regulators in *N*-mediated resistance primarily through their interaction with N protein. Transcription factor SQUAMOSA PROMOTER BINDING PROTEIN-LIKE 6 (SPL6) associates with N protein within distinct nuclear compartments, and is essential for *N*-mediated resistance against TMV. In particular, the N-SPL6 interaction is present in the nucleus and could be detected only when the p50 is present. It suggests that the association of N with SPL6 only exists after an active defense response [27]. Similar to other TNLs, N function is EDS1-dependent [28,29]. N requirement gene 1 (NRG1) serves as a helper NLR and is required for *N*-mediated resistance [30]. Rar1 is required for N function. The tobacco Rar1 interacts with SGT1, a novel subunit of the SCF-type (Skp1/Cullin/F box protein) E3 ubiquitin ligase complex involved in protein degradation. SGT1 and Rar1 associate with Hsp90, which interacts with N protein [31]. Moreover, Hsp90 suppression compromises *N*-mediated resistance to TMV [32]. Similarly, Hsp40-like Dna-J domain movement protein-interacting proteins (MIP1s) interact with SGT1 and are required for *N*-mediated resistance [33]. N receptor-interacting protein (NRIP1), a functional rhodanese sulfurtransferase, is identified to directly interact with both N TIR domain and TMV p50, which is necessary for complete resistance to TMV. NRIP1, normally localized in chloroplasts, is recruited to the cytoplasm and nucleus by p50 effector. Consequently, NRIP1 interacts with N only in the presence of p50 [34]. UBR7, a putative E3 ubiquitin ligase, directly interacts with N protein via its TIR domain and negatively regulates the level of N protein. Down-regulation of UBR7 increases the protein level of N and enhances TMV resistance. Moreover, TMV p50 disrupts the N-UBR7 interaction and relieves negative regulation on N [35]. In addition, MEKK1-like mitogen-activated protein kinase kinase kinase NPK1, MEK1 MAPKK, NTF6 MAPK, and WRKY/MYB transcription factors are essential for *N*-mediated resistance [36,37]. Transcription factor alfin-like 7 (AL7) interacts with N and inhibits the transcription of genes involved in ROS-scavenging to positively regulate *N*-mediated resistance to TMV [38]. Mitogen-activated protein kinases (MAPKs), salicylic acid-induced protein kinase (SIPK), and wound-induced protein kinase (WIPK) interact with and phosphorylate AL7, which inhibits AL7-N interaction and enhances its DNA binding activity, thus promotes ROS accumulation and enables immune response to TMV [38].

2.2. Tobacco N′ Gene

The *N′* gene from *Nicotiana sylvestris* encodes a CC domain-containing NLR (CNL) immune receptor that confers resistance against tobamoviruses accompanying the HR by recognizing viral CP [39–42]. *N′* is an ortholog of the pepper *L* genes with a different recognition spectrum. *N′* can confer resistance against tomato mosaic virus (ToMV), paprika mild mottle virus, pepper mild mottle virus (PMMoV), and even PMMoV pathotype $P_{1,2,3,4}$ [42] and tomato brown rugose fruit virus (ToBRFV) [17].

2.3. Tomato Tm-1 Gene

The *Tm-1* gene is introgressed into cultivated tomato species *Solanum lycopersicum* from the wild tomato species *Solanum habrochaites* S. Knapp & D.M. Spooner [43,44]. However, *Tm-1*-mediated ToMV resistance could be easily overcome by ToMV resistance breaking isolates [45]. In addition, *Tm-1* suppresses the visible viral mosaic symptoms but detectable virus multiplication occurs. Inhibition of TMV multiplication is *Tm-1* gene dose-dependent, whereas suppression of visible symptoms is not [46,47].

The *Tm-1* gene encodes a protein that binds to ToMV replicase and inhibits the RNA-dependent RNA replication of ToMV [48], suggesting that Tm-1 functions as a viral inhibitor. Moreover, structure analysis indicates that Tm-1 shows no sequence homology to functionally characterized

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proteins [48,49]. These results indicate that *Tm-1* differs from those of previously identified resistance genes in plants.

Tm-1 binds ToMV replication proteins to inhibit key events in replication complex formation on membranes that precede negative-strand RNA synthesis. Three host proteins, Tobamovirus multiplication 1 (TOM1), TOM2A, and ADP-ribosylation factor-like 8 (ARL8), are required for ToMV RNA replication, and suggested to be components of the ToMV replication complex [50]. Upon ToMV infection, Tm-1 inhibits the formation of viral RNA replication complex on membranes by inhibiting the association of TOM1, TOM2A and ARL8 with ToMV 130K replicase [51].

2.4. Tomato Tm-2/Tm-2² Gene

Tm-2 and *Tm-2²* are two alleles of the same gene in tomato and encodes a CNL [52]. It is introgressed into cultivated tomato from wild species *Solanum peruvianum*, which confer resistance to tobamoviruses, including TMV and ToMV, by recognizing viral MP [43,53–55]. *Tm-2²* also displays resistance to tomato mottle mosaic virus (ToMMV) by recognizing the MP, and the resistance is regulated by the allele combinations and the temperature [56]. The homozygous tomato harboring *Tm-2²* and heterozygous tomato containing *Tm-2²* and *Tm-2*, but not heterozygous tomato containing *Tm-2²* and tm-2, exhibit resistance to ToMMV. *Tm-2²*-mediated resistance is comprised at 35°C, but not at 30°C or lower temperature [56]. Previous studies show that the C-terminal 30-amino acid deletion of viral MP blocks *Tm-2²*-mediated resistance [55]. However, we show that N-terminus of MP is sufficient for inducing *Tm-2²*-mediated HR [57]. These combined data suggest that Tm-2² recognizes N-terminal but not C-terminal sequence of viral MP for *Tm-2²* recognition, and C-terminal domain of MP could affect exposure of protein structures that are recognized by Tm-2². Tm-2² is previously thought to function on PD due to the predominated localization of its Avr protein MP. However, Tm-2² function is independent of the PD localization of viral MP. Further, Tm-2² is found to be localized to and function on the PM although it lacks any PM-localization motif [57]. Tm-2² CC domain is the signaling domain and its self-association triggers defense response including HR. In presence of viral MPs, Tm-2² self-associates and is activated, which require nucleotide-binding domain-mediated self-association of CC domain in (d)ATP-dependent manner [58]. Tm-2² stability is regulated by SGT1 and Hsp90 [59] and MIP1s [33]. MIP1s function as co-chaperones and are required for both TMV infection and plant immunity including *Tm-2²*-mediated resistance by associating with SGT1 and Tm-2² [33]. Further, rubisco small subunit is required for both *Tm-2²*-mediated extreme resistance and tobamovirus movement by interacting with viral MPs [60]. In addition, *Tm-2²*-mediated resistance response is dependent on its expression level: High level of expression triggers extreme resistance without visible cell death; intermediate level of expression triggers complete resistance with HR lesions at virus infection sites; and low level of expression only confers a partial resistance with systemic viral infection and systemic necrosis throughout the plant [61].

2.5. Pepper L Gene

The *L* gene confers resistance against tobamovirus and encodes a CNL, which introgressed into *Capsicum annuum* from wild pepper species [62]. Upon virus infection, L protein recognizes viral CP, leading to HR [63]. There are four different alleles of *L* (*L¹*, *L²*, *L³*, and *L⁴*). All *L* alleles confers resistance to P_0 viruses including ToMV, yellow pepper mild mottle virus and chilli pepper mild mottle virus, and *L¹* only confers resistance to P_0 viruses, *L²* confers resistance to all P_0 and P_1 viruses including PMMoV J strain. *L³* defends against P_0, P_1 and $P_{1,2}$ viruses including PMMoV strains which can overcome *L²*. *L⁴* defends against P_0, P_1, $P_{1,2}$, and $P_{1,2,3}$ PMMoV pathotypes which can overcome *L³* [62–64]. However, some PMMoV strains can systemically infect all identified *L* alleles of pepper plants. Another allele, *L¹ᵃ*, is thermosensitive and does not confer resistance against tobamoviruses at elevated temperatures [65].

 doi:10.20944/preprints202403.0215.v1

2.6. Tobamovirus Multiplication (TOM) and ALR8

Host susceptibility proteins help virus infection at different stages of the virus life cycle. Among them, TOBAMOVIRUS MULTIPLICATION (TOM) proteins play a critical role in tobamovirus infection by interacting with viral replicases to help the formation of the viral replication complex [66]. *TOM* genes are critical for infection by tobamoviruses in various plant species [67]. TOM1 and TOM2A encode seven-pass and four-pass transmembrane proteins, respectively [68,69]. *TOM1* is first cloned from *Arabidopsis* with 3 homologues *TOM1*, *TOM3*, and *TOM1-like gene* (*THH1*) [69,70]. In *Arabidopsis*, *tom1* single mutant partially impairs tobamovirus multiplication, and double *tom1* and *tom3* mutant completely inhibits tobamovirus multiplication [71,72]. In double *tom1*/*tom3* mutant lines overexpressing *THH1*, the level of tobamovirus CP is similar to that of wild-type plants, suggesting that THH1 could weakly contributes to tobamovirus multiplication due to its lower level of expression than that of TOM1 and TOM3 [70].

TOM1 homologs are also found in tobacco and tomato [73,74]. Knockdown of *TOM1* homologs dramatically inhibits TMV/ToMV multiplication without introducing any obvious growth defects [73–75]. In addition, tobacco *TOM1* mutant lines are resistant to TMV [76]. In particular, the quadruple knockout of *SlTOM1* homologs, which is generated by genome editing, confers resistance to ToBRFV in tomato [77]. Meanwhile, double knockout of *SlTOM1a* and *SlTOM3* confers resistance to ToBRFV, but not to ToMV and TMV [66].

TOM1 and TOM2A promote tobamovirus multiplication. Upon TMV infection, TOM1 interacts with TMV 126-kDa replicase to promote the assembly of viral replication complex formation on host membranes. TOM2A also facilitates the formation of the viral replication complex by interacting with TOM1 [67].

Arabidopsis ADP-ribosylation factor-like 8 (ARL8) is a small GTP-binding protein and interacts with TOM1. ARL8 also interacts with ToMV 180K replicase and is required for tobamovirus multiplication. Upon tobamoviruses infection, ARL8 and TOM1 are components of the replication complex and play crucial roles in replication activation process including replicase' RNA synthesizing and capping [50,78].

2.7. WPRb

WPRb is a recessive resistance gene associated with cucumber green mottle mosaic virus (CGMMV) resistance in watermelon and encodes a weak chloroplast movement under blue light 1 and plastid movement impaired 2-related coiled-coil protein. Genome editing of *WPRb* in *N. benthamiana* also confers great tolerance to CGMMV. WPRb targets to the PD and interacts with CGMMV MP to facilitate viral cell-to-cell movement by affecting PD permeability [79].

3. RNA-Targeting Mechanisms

RNA silencing plays a key role in antiviral defense against all types of viruses [80,81]. RNA silencing is a sequence-specific process found in both plants and animals, which involves the generation of sRNAs [82,83]. In plants, RNA silencing is orchestrated by 21- to 24-nucleotide sRNA categorized as short interfering RNAs (siRNA) and microRNAs (miRNA). These sRNAs are generated as duplexes with 2-nt 3′ overhangs from longer dsRNA precursors or hairpin-like secondary structures, respectively, through the action of Dicer-like (DCL) enzymes [84]. RNA silencing has been used to engineer complete resistance against tobamoviruses [85]. In the case of tobamoviruses, the small replicase subunit (122-130 kDa) could function as the viral suppressors of RNA silencing (VSR). In particular, TMV 126 kDa protein is identified as the VSR by disrupting HEN1-mediated methylation of small RNAs to shield viral transcripts from host RNA silencing pathway [86,87]. In addition, the 122-kDa replicase subunit (p122) of crucifer-infecting TMV (crTMV) is a potent VSR and compromises both small interfering RNA- and microRNA-mediated pathways [88]. p122 is also reported to enhance the levels of *microRNA 168* to inhibit the expression of Argonaute 1 (AGO1) [89]. In addition, during oilseed rape mosaic tobamovirus (ORMV) infection, ORMV p125 replicase is required for the inhibition of HEN1 activity to suppress RNA silencing [84].

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On the other hand, TMV MP contributes to antiviral silencing during infection by enhancing the spread of RNA silencing signal and this ability of TMV MP may contribute to the control of virus propagation in the infected host. TMV 126 kDa replicase and MP with the contrast role in RNA silencing may balance viral propagation at different infection stages [90].

Beyond RNA silencing, other RNA-targeting mechanisms have also been shown to be involved in antiviral defense including RNA decay [91]. RNA decay is an essential RNA quality control and gene regulatory mechanism in eukaryotes. It is initiated in the cytoplasm by mRNA deadenylation, followed by exosome complex-mediated exonucleolytic decay in the 3′-5′direction or by decapping complex and exoribonuclease (XRN)-mediated decay in the 5′-3′direction [92]. A study suggests that TMV proteins (MP and CP) enhance transcriptional levels of RNA decay genes and induce RNA decay to impair antiviral RNA silencing for better virus infection [93]. However, silencing of *5′-3′ exoribonucleases NbXrn4* facilitates TMV systemic infection in *N. benthamiana* [94], suggesting that RNA decay may also play a role in antiviral defense against tobamovirus.

4. Phytohormones Interactions with Tobamoviruses

Plant hormones salicylic acid (SA), methyl salicylate (MeSA), jasmonic acid (JA), methyl jasmonate (MeJA), ethylene, and Auxin/indole-3 acetic acid (Aux/IAA) play important roles in plant-virus interactions. Among them, SA plays a critical role in plant defense against a broad spectrum of pathogens including multiple viruses. SA interfers with different steps of the viral cycle. In tobacco leaves, SA treatment decreases TMV RNA accumulation by disrupting TMV replication in mesophyll cells [95,96]. SA also inhibits TMV cell-to-cell movement [96]. Plum pox virus (PPV), which is impaired to move to the systemic tobacco leaves, is able to move to upper non-inoculated leaves of tobacco plants expressing bacterial salicylate hydroxylase (NahG) that degrades SA [97]. In addition, SA could also function its antiviral mechanism by activating RNA silencing. SA induces the expression of host RNA-dependent RNA polymerase1, which contributes to antiviral RNA silencing, thereby promotes the degradation of viral RNA to limit the infection by tobamovirus [98–100]. *N*-mediated TMV resistance is compromised in transgenic *NahG* tobacco plants and *NPR1*-silenced plants [36,101], suggesting that SA is essential for *N*-mediated antiviral immunity.

TMV infection induces HR accompanied by the production of phytohormones, including SA and JA. Exogenously MeJA application to plants reduces local TMV resistance and permitted systemic TMV movement [102], suggesting a positive role of MeJA in antiviral defense against TMV. The role of COI1 in *N*-mediated TMV resistance is controversial. Silencing of *COI1*, the JA receptor gene, comprises *N*-mediated TMV resistance in transgenic *N. benthamiana* [36], suggesting that JA positively regulates *N*-mediated TMV resistance. However, silencing of *COI1* reduces viral accumulation in *N. tabacum* Samsun *NN*, which possesses *N* gene [102]. The contrast data may be due to differences in the experimental plant systems used, *N. tabacum* Samsun *NN* and *N. benthamiana*. Indeed, *N. tabacum* Samsun *NN* is reported to have a novel *N* gene-associated, temperature-independent resistance [103].

TMV infection triggers plant release of several airborne compounds including (E)-2-octenal. (E)-2-octenal primes the JA/ET signaling pathway including upregulation of *NbMYC2, NbERF1*, and *NbPDF1.2* and then upregulates the pathogenesis-related genes, such as *NbPR1a, NbPR1b, NbPR2*, and *NbNPR1, to* activate antiviral defense against TMV in adjacent *N. benthamiana* plants [104].

Both MeSA and MeJA contribute to systemic resistance against TMV, possibly acting as the initiating signals for systemic resistance. Silencing of SA or JA biosynthetic and signaling genes in *N. benthamiana* plants increases susceptibility to TMV [105]. Silencing of either *SABP2* or *NAC2* compromises antiviral defense, suggesting that SA, but not MeSA, directly activates antiviral defense [106].

Ethylene plays a role antiviral defense against tobamoviruses. It increases watermelon resistance to CGMMV infection by inducing the expression of the *AGO5* gene [107]. In addition, ethylene pathway participates in transcription factor MYB4L-mediated resistance against TMV, and ethylene-induced MYB4L is involved in TMV resistance in *N. benthamiana* [108]. In addition, silencing of *CTR1*,

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an ethylene receptor, accelerates *N*-mediated HR [36], suggesting that ethylene signaling negatively regulates *N*-mediated HR induced by TMV.

Auxin is a crucial plant hormone and participates in various processes. Aux/IAA proteins are vital components within this regulatory framework, with a primary function of translating auxin levels into gene expression [109]. The interaction between tobamoviruses and Aux/IAA is first reported to involve the helicase domain of TMV replicase and IAA26. The expression of TMV replicase disrupts nuclear localization of IAA26, inhibiting its putative function as a transcriptional regulator of auxin-responsive genes for better viral symptoms and systemic movement [110–112]. TMV can reprograms auxin/IAA protein transcriptional responses and then enhances virus phloem loading [113].

6. Reactive Oxygen Species in Tobamovirus Infection

Upon pathogen infection, plants rapidly produce ROS to induce local or systemic signaling through the activation of cell surface-localized RBOH proteins. ROS signaling mediates systemic resistance against plant viruses and is often considered as a positive regulator of plant antiviral defense [114,115]. Intact TMV virion and isolated TMV CPs trigger a rapid oxidative burst when added to the apoplast of tobacco epidermal cells. TMV CP stimulates host NAD(P)H oxidase-like activity [116]. Meanwhile, TMV infection increases the expression of ROS-scavenging related genes including superoxide dismutases (CSD2), ascorbate peroxidase (APX1) and GDP-mannose pyrophosphorylase 1 (GMP1). Furthermore, silencing of *GMP1* enhances ROS level and reduces TMV accumulation [117,118]. Thus, ROS-scavenging pathway can also modulate the plant resistance against tobamoviruses.

7. Future Directions

In the last decades, a number of studies prove that transgenic approach, especially by enhancing RNA silencing against viral RNA sequences, can provide effective plant protein against viruses [119]. Due to public concerns and strict regulatory barriers, this approach has been restricted to be used in the field. However, it still holds great potential for generating the efficient antiviral plants.

Genome editing is another breakthrough for generating efficient virus resistance. Editing of tobamovirus susceptibility genes based on CRISPR/Cas9 systems can be used to generate crops with resistance against tobamoviruses. Numerous host susceptibility genes such as *TOM1/3, TOM2, ARL8,* and *WPRb,* have been identified, and their knockouts or mutants do not have any obvious effect on plant growth or morphology. More recently, Kunitz peptidase inhibitor-like protein (KPILP) is identified as a novel proviral factor during TMV or the closely related crTMV infection [120]. Editing of these genes may achieve tobamovirus resistance in different crops [121].

Engineering NLRs with new recognition targets is another approach that can be applied for protection against viruses [121]. The engineered NLRs can be generated for recognizing new pathogens by several technologies, including protein engineering, random or site-directed mutagenesis, and structure-based predictions. These strategies may be used to develop new crop resistance against tobamoviruses.

The exogenous application of dsRNA to induce RNA silencing have been perceived as an alternative to transgene and can be used for plant protection against viral disease. It has been shown to provide some protection against TMV [122] and can be modified to fight other tobamoviruses. However, the efficiency of this approach is affected by several factors, including concentration/dose and length/size of dsRNAs, application method, delivery technique, plant organ-specific activities, and stability under open-field conditions [123]. Technical advances in these fields will overcome these restrictions for agricultural application. In addition, cross-protection is another efficient strategy without genetic modification, which is able to fight against severe virus strains. Reverse genetics can be adopted to generate attenuated mutants that have potential in cross-protection against tobamoviruses [119].

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