Abstract: Pepper mottle virus (PepMoV) is a destructive pathogen that infects various solanaceous plants, including pepper, bell pepper, potato, and tomato. In this review, we summarize what is known about the molecular characteristics of PepMoV and its interactions with host plants. Comparisons of symptom variations caused by PepMoV isolates in plant hosts indicates a possible relationship between symptom development and genetic variation. Researchers have investigated the PepMoV–plant pathosystem to identify effective and durable genes that confer resistance to the pathogen. As a result, several recessive *pvr* or dominant *Pvr* resistance genes that confer resistance to PepMoV in pepper have been characterized. On the other hand, the molecular mechanisms underlying the interaction between these resistance genes and PepMoV-encoded genes remain largely unknown. Our understanding of the molecular interactions between PepMoV and host plants should be increased by reverse genetic approaches and comprehensive transcriptomic analyses of both the virus and the host genes.

Keywords: pepper mottle virus; *Potyvirus*; pepper resistance gene; virus–host interaction

1. Introduction

*Pepper mottle virus* (PepMoV), which is in the genus *Potyvirus* and the family *Potyviridae* [1], has been isolated from economically important solanaceous plants including pepper (*Capsicum* sp.), potato, and tomato in North America, India, and Asia [2–9]. PepMoV is transmitted by several species of aphids but can also spread via mechanical inoculation, grafting, and infected seeds [10,11]. PepMoV causes various symptoms in host plants, including severe or mild mottling mosaic, necrosis, vein clearing or necrosis, and leaf curling or yellowing [12,13]. When pepper plants are co-infected with PepMoV and cucumber mosaic virus, synergistic disease development is the result [14,15].

PepMoV has a single-stranded positive-sense RNA genome that is about 10 kb in length [13,16,17]. The PepMoV RNA is expressed as a large polyprotein, which is catalyzed and cleaved into smaller mature proteins in the host [17,18]. Variation in symptoms, pathogenicity, and molecular properties among PepMoV isolates in Korea suggested that certain virus-encoded proteins determine host specificity or pathogenicity [4,19]. Recent studies of compatible/incompatible responses between PepMoV and host plants revealed dynamic interactions between PepMoV-encoded viral proteins and host proteins [20–22]. The development of full-length infectious clones of PepMoV has enabled researchers to investigate the interaction between PepMoV and hosts as well as to explore the feasibility of using PepMoV as a viral vector for the stable expression of heterologous genes in plants [23,24]. Here, we review what is know about PepMoV with a focus on recent major findings concerning the interactions between PepMoV and its plant hosts.
2. Diversity and Pathogenicity

PepMoV was reported first in Arizona and Florida in the early 1970's and is considered as a species in the *Potyvirus* genus (lineage 5; [25,26]). Compared to potato virus Y (PVY), which is one of the major potyviruses infecting pepper, PepMoV forms relatively long and thin pinwheel inclusions in infected leaves and also differs in the symptoms it induces, its serological characteristics, the molecular weights of its proteins, and its nucleic acid contents [12,27,28].

To date, PepMoV has been reported from many regions in North America, East Asia, and India, and full genome sequences of 23 isolates are available and sequences of 45 isolates are partially released at the NCBI database. A phylogenetic analysis based on the deduced amino acid sequences indicated that all 13 Korean isolates of PepMoV formed one cluster that was distinct from American isolates [4]. A recent report indicated that full genome sequences of an isolate of PepMoV from Hunan China (PepMoV HN) are closely related to 18 PepMoV isolates from Korea that reported in previous studies [4,29,30]. However, when the authors of the latter study analyzed coat protein (CP) genes of nine PepMoV isolates from pepper in Southern China, they detected two distinct groups and subgroups.

Based on its genetic variation and on its symptom severity and pathogenicity on different host plants, researchers divided 13 Korean isolates of PepMoV into two groups [4,13]. Having acquired data on the highest ratio of synonymous (dS) to non-synonymous (dN) base substitutions for the P1 and 6K2 genes of PepMoV and on amino acid (aa) variation encoded by the 6K2 gene, Kim et al. suggested that the P1 and 6K2 genes might be involved in PepMoV host specificity and pathogenicity [4]. As discussed later in this review, Kim et al. also described a system that could be used to identify viral-encoded proteins affecting pathogenicity and host specificity.

3. Genome Organization

Like all potyviruses, PepMoV forms a flexuous rod-shaped virion that consists of about 2000 copies of CP subunits with an Mr of 30.8 kDa [31]. The virion contains a positive-sense single-stranded viral genomic RNA with a genome-linked protein (VPg) at its 5'-terminal end and a poly(A) tail at its 3'-terminal end [17,31]. The PepMoV genome is translated into a large polyprotein that is catalyzed by three potyvirus proteases (P1, HC-Pro, and NIa) and catalyzed into 10 mature viral proteins (P1, HC-Pro, P3, 6K1, CI, 6K2, VPg, NIa, Nlb, and CP) [16,17]. The existence of a short open reading frame, termed P3N-PiPO, embedded within the P3-encoding region of the polyprotein is a universally conserved feature and has conserved coding capacity throughout the genus [32–34] (Figure 1A).

Both of the approaches described in the previous paragraph have been used to construct full-length cDNA clones of PepMoV. A Korean isolate of PepMoV (PepMoV-Vb1) was cloned downstream of a bacteriophage SP6 promoter and was tagged with green fluorescent protein (GFP), which was inserted between the coding regions for Nlb and CP in the plasmid [29]. In vitro RNA transcripts from this clone were infectious and stably expressed GFP in tobacco and pepper plants [29]. Although infectious clones are useful and fundamental tools in studying virus–host interactions, some challenges remain in constructing and stably delivering infectious clones into host plant using *E. coli*-based plasmids. For example, toxicity to *E. coli* has been reported for plasmids containing full-length clones of several viruses including citrus tristeza virus, tobacco etch virus (TEV), and influenza A virus; such toxicity makes it difficult or even impossible to use the clone for molecular manipulation [35–37]. During their modification and construction, full-length clones in *E. coli* have also been reported to be unstable for plant RNA viruses including potyviruses [36,38–41] and tobraviruses [42,43]. To reduce or minimize undesired toxic effects or instability in *E. coli*, insertion of introns into the viral genome has been extensively used [38,40]. For example, insertion of the potato ST-LS1 intron 2 sequence into the Nla coding region of PepMoV increased the stability of the infectious clone [23]. Relative to traditional pPepMoV infectious clones, the modified infectious clone inserted plant intron into pPepMoV could restore infectivity and maintain plasmid stability. *Agrobac-
terium-mediated inoculation of this modification clone showed faster symptom induction compared to non-modified clones when the same amount of *Agrobacterium* cell suspension was inoculated in plants [23]. In addition, the resulting symptom intensity was similar to that following sap inoculation [23].

**Figure 1.** Genome organization and schematic representation of replication of pepper mottle virus (PepMoV). (A) The genomic maps of PepMoV. The genome is translated into a large polyprotein that is catalyzed by three potyviral proteases (P1, HC-Pro, and Nia) and cleaved into 10 mature viral proteins (marked in different colors). The next depicted represents a short open reading frame, termed P3N-PIPO, embedded within the P3-encoding region of the polyprotein. (B) Schematic representation of replication in a plant cell. The cycle begins (left upper corner) when the viral particle or RNA enters the cell from infected cells or initially inoculated by its vector. The genomic RNA undergoes decapsidation, translation, and proteolytic processing to generate mature proteins. The replication complex uses the positive genomic RNA to generate a complementary negative genomic RNA, which functions as a template for the synthesis of numerous genomic RNAs. After replication, the progeny RNAs can be encapsidated and acquired by vectors to be transmitted again, or they can move to adjacent cells through plasmodesmata.

**4. Replication and Movement: Functions of Viral Proteins**

In research on the role of virus-encoded proteins during the virus infection process, use of the infectious full-length cDNA clones has provided reliable information on viral RNA replication and movement [44,45]. Almost all of the potyviral proteins are involved in viral replication [31] (Figure 1B). For example, the potyviral proteins HC-Pro, CI, VPg, Nib, and CP have multiple functions during viral infection, and CI, CP, HC-Pro, VPg, and P3N-PIPO have been implicated in viral intercellular movement [44]. The protein functions of PepMoV are largely unknown. However, the possible roles of PepMoV-encoded proteins could be expected from the reported functions of the other closely related potyviruses.
The P1 protein of potyviruses is a chymotrypsin-like serine proteinase that cleaves itself at C-terminus [31,46]. P1 is the most divergent and variable protein among potyvirus-encoded proteins [46,47]. The TEV P1 protein has been shown to function in trans to stimulate genome amplification [48]. The function of clover yellow vein virus P1 has been reported for its involvement in elf4E-mediated recessive resistance [49]. The potato virus V (PVV) P1 does not have direct association with RNA silencing suppression, but self-cleavage activity of P1 affects RNA silencing suppression indirectly by modulating function of HC-Pro [50].

The HC-Pro is a cysteine protease and well-established multitasking protein that is involved in many potyviral infection processes such as aphid-mediated transmission, RNA silencing suppression, genome replication, symptom expression, and long-distance movement [51,52]. HC-Pro could interact with several other potyviral proteins and many host factors [47]. Two conserved motifs, i.e., the N-terminal ‘KITC’ and the C-terminal ‘PTK’ motifs, have been identified in HC-Pro [53]. Site-directed mutation replacing lysine to glutamic acid (K59E) within the KITC motif using several PVY isolates abolishes the interaction of HC-Pro with aphid stylets and aphid transmissibility of PVY [53]. It is reported that the PVY HC-Pro interacts with three Arabidopsis 20S proteasome subunits (PAA, PBB, and PBE), which is related to the antiviral response [54]. In addition, HC-Pro from three potyviruses, including potato virus A (PVA), PVY, and TEV could interact with the eukaryotic translation initiation factors (eIF4E) and eIF(iso)4E of Nicotiana tabacum and eIF(iso)4E and elf4E of potato suggesting possible new role(s) in potyvirus infection cycle [55].

The protein P3 is also one of the well-characterized multifunctional potyviral proteins. Dual roles of TEV P3 in virus movement and replication have been reported [56,57]. A polymerase slippage mechanism on P3 cistron leads to the production of P3N-PIPO [32], which localizes at PD and involves in the viral cell-to-cell movement in conjunction with CI protein [58]. P3 plays crucial roles as virulence and symptom determinants [59].

The 6K1 of plum pox virus (PPV) is required for viral replication and is a necessary viral element of the viral replication complexes (VRC) at the early infection stage [60].

The multifunctional CI protein, as part of the VRC, participates in viral genome replication. In addition to replication, it also functions in viral cell-to-cell and long-distance systemic movement, probably by interacting with the recently reported viral P3N-PIPO protein [44,58,61]. There is genetic evidence suggested that CI protein of TEV interacts directly with plasmodesmata and CP-containing ribonucleoprotein complexes to facilitate intracellular movement [62]. The lettuce mosaic virus CI has been shown to interact with the viral VPg and with lettuce elf4E [63] and involved in the elf4E-mediated resistance-breaking [64,65].

The potyviral 6K2 protein has been found to be involved in long-distance movement and symptom development [66–68]. In addition, potyviral 6K2 exhibits critical components of the VRC with Nlb, HC-Pro, P3, CI, and NLa [69]. The potyviral 6K2 induces proliferation of ER membrane for construction of VRCs at ER exit sites in cellular coatamer protein I- and II-dependent manner [67,70]. The TEV 6-kDa protein is membrane associated and has been shown to be necessary for virus replication [71]. It contains transmembrane (TM) domain at N-terminal region and putatively luminal domain at C-terminal region [72,73]. The TM domain of potyviral 6K2 protein is typically required for targeting and anchoring to the ER membrane [72]. The N-terminal region of TEV 6K2 includes a D(X)E motif which is crucial for ER exit of the 6K2-induced replication vesicles [73].

Potyvirus VPg contains two nuclear localization signals (NLSs) and nucleotide triphosphate binding motifs [74]. VPg is required for several viral processes, including translational initiation of viral RNA and replication [74]. Potyviral VPg can form an intrinsically disordered state of the protein and this structural flexibility provides accessible interaction complexes with different virus or host proteins to enable its diverse functions [47,74]. Including PVA VPg, it requires host elf4E to promote viral RNA replication as well as the viral translation products [75]. In contrast, interaction between VPg and host elf4E
and eIF(iso)4E might be involved in translation inhibition in host cellular mRNAs [75,76]. VPgs in PVY, TEV, and turnip mosaic virus (TuMV) can inhibit cellular cap-dependent translational initiation in vitro through binding with eIF4E or eIF(iso)4E [77–79]. The interaction between VPg and eIF4E is also related to recessive resistance response against several potyviruses [80,81]. TuMV 6K2–VPg–Nla complex, membrane-associated precursor form, is found within vesicular structures derived from the ER where replication might occur [82]. TuMV VPg also has RNA silencing suppressor activity by inducing degradation of suppressor of gene silencing 3 (SGS3), which is involved in RNA silencing pathway [83].

Potyvirus Nla-Pro is a cysteine protease and generally functions proteolytically in the processing of the potyviral polyprotein [47]. Nla-Pro accesses differential cleavage efficiency, and it affects host range and viability of potyviruses [84]. Previous studies have described how PVY and PepMoV Nla were able to elicit Ry-mediated HR in Solanum stoloniferum by sharing the same recognition/cleavage site for Nla [85]. Expression of Nla-Pro interferes ethylene signaling pathway and enhances aphid fecundity in TuMV-infected Arabidopsis [86]. Nla-Pro relocalization from cytoplasm and nucleus to the vacuole of the cell during TuMV and PVY infections when in the presence of the aphid vector has reported [87]. This relocalization confers the ability to promote vector performance to potyvirus Nla-Pro [87]. Recent study suggested that PepMoV Nla was involved in pathogenicity and suppression of host antiviral defense response [88].

Nlb of potyviruses acts as an RNA-dependent RNA polymerase (RdRp) or RNA replicase, and is therefore required for potyviral genome replication [69]. Beyond its major role as an RdRp during viral infection, Nlb also has additional functions such as a recruiter that interacts with many pro-viral host factors participated in the assembly and activation of the VRC, a suppressor of host defense response, a target of host antiviral defense, and an elicitor that activates effector-triggered immunity (ETI) [69]. One of the characterized functions of PepMoV Nlb was associated with Pvr4- or Pvr9-mediated hypersensitive response (HR) [20,21].

The potyviral CP has also been reported to participate in the regulation of viral RNA replication [31,89]. Potyvirus CP is indispensable for viral intra- and intercellular movement [90,91]. Including PVA CP, the CP-vRNA interaction regulates virion assembly/disassembly and coordinates switch between viral RNA translation and replication [47,92]. Both terminal regions of the PVY CP have a crucial role in PVY infectivity. However, only the N-terminal region of CP is essential for virus-like particle (VLP) formation [89]. Recent findings for TuMV CP also suggest functions of the N-terminal region of CP in virion maturation and/or termination of virion formation. However, several studies demonstrated that the involvement of the N-terminal of potyviral CP in cell-to-cell movement and systemic infection varies from virus-to-virus [95]. N-terminal domains of TuMV and zucchini yellow mosaic virus CPs were dispensable for viral cell-to-cell and long-distance movements. However, the same regions in TEV and PVY are necessary for establishing cell-to-cell movement and systemic infection [89,93–95]. In contrast, C-terminal regions of TuMV, PVY, and TEV CPs were shown to be associated with viral cell-to-cell and long-distance movement [90,92,94]. The aromatic residue tryptophan at core domain (W122) of CP in tobacco vein banding mosaic virus, which is highly conserved residue among potyviruses, plays a role in maintaining stability of CP during viral replication and this involvement in viral cell-to-cell movement was also observed with the same residue of watermelon mosaic virus and PVY [96]. An additional role as the pathogenicity determinant for CP has been reported in PVY [97]. The highly conserved DAG motif in the N-terminal domain of CP is responsible for aphid transmission by mediating the interaction between CP and HC-Pro [98,99].

So far, extensive research has mainly focused on the defense response-related PepMoV-encoded proteins and their corresponding host genes. Although the functions of HC-Pro remain to be established in PepMoV, the protein is likely to be involved in replication and systemic movement. Likewise, PepMoV Nlb might have roles in symptom development and virus multiplication, which is supported by our recent study (unpublished data).
5. Resistance Genes against PepMoV

Plants have evolved multi-layered systems to defend against viral invasion, including RNA silencing, regulation of RNA stability, ubiquitination-mediated protein degradation, autophagy, HR, R gene-mediated resistance responses, and systemic acquired resistance [47,100,101]. Several studies have described incompatible interactions between PepMoV and pepper plants; the host symptoms associated with those resistance responses have been used to identify efficient resistance (R) genes for application in plant breeding [20,102]. Characterized host genes are listed in Table 1.

Table 1. Reported resistance genes against PepMoV.

| Resistance Genes | Resistance Type | Target Virus | Source | References |
|------------------|----------------|--------------|--------|------------|
| pvr1             | Recessive      | PepMoV, TEV and PVY | Capsicum chinense PI159236 and PI152225 | [22,103] |
| pvr3             | Recessive      | PepMoV and TEV | C. annuum 'Avelar' | [104] |
| Per4             | Dominant       | PepMoV and PVY | C. annuum 'CM334' | [105] |
| Per7             | Dominant       | PepMoV        | C. chinense PI159236 | [103] |
| Per9             | Dominant       | PepMoV        | C. annuum 'CM334' | [21] |

* PepMoV, pepper mottle virus; TEV, tobacco etch virus; PVY, potato virus Y.

5.1. Recessive Resistance Genes

In incompatible interactions between a plant virus and host, resistance responses can be mediated by recessive or dominant host genes (Figure 2) [21,80,81,106]. Recessive resistance genes are produced by the loss or mutation of a host factor that has an important function in disease development [15,100,107]. Recessive resistance genes are thought to be more durable and to provide more broad-spectrum resistance than dominant R genes [108]. Recessive resistance genes are more common than dominant resistance genes, especially against potyvirus infections, and usually function at the single-cell level and thereby limit cell-to-cell movement [81].

In Capsicum spp., pvr1 and pvr3 have been characterized as two unlinked recessive loci that confer distinct kinds of resistance to PepMoV [104]. The pvr1 gene, which was identified in C. chinense PI159236 and PI152225, confers relatively broad resistance to PepMoV, TEV, and PVY [22,81]. In contrast, the pvr3 gene, which was identified in C. annuum 'Avelar', confers a different type of resistance to PepMoV than to TEV and PVY [104]. The mechanisms of resistance responses in Capsicum spp. against PepMoV differ depending on whether the response is pvr1- or pvr3-mediated [15,104]. C. chinense PI 152225 and PI 159236, which contain pvr1, do not support replication of PepMoV at the cellular level, whereas C. annuum 'Avelar', which contains pvr3 allows for PepMoV accumulation in inoculated leaves and its movement into the vascular system but not its spread into upper leaves [15,104,109]. However, this restriction of systemic movement was collapsed when PepMoV was co-infected with cucumber mosaic virus [15,109]. Other recessive genes, i.e., pvr2 and pvr6, that are located on the pepper chromosomes 4 and 3, respectively, confer digenic recessive resistance to another pepper potyvirus, pepper veinal mottle virus [110]. However, the effect of pvr2 and pvr6 in response to the infection of PepMoV remains to be determined.

The eukaryotic translation initiation factors (eIF4Es) have been identified and cloned from diverse hosts as resistance genes that are natural, recessive, and inherited (Figure 2A) [80,111]. The pvr1 locus encodes an eIF4E homolog, and pvr6 is expected to encode eIF(iso)4E [81]. Recessive resistance against several potyviruses in plant hosts is conditioned by mutations in eIF4E and its isoforms [80,106,112]. Using transgenic tomato progeny with ectopic expression of the pvr1, researchers documented dominant resistance to several potyviruses, including PepMoV and TEV [113]. Moreover, resistance induced by mutation of eIF4E1 in tomato, obtained by TILLING platform or by Clustered Regularly Interspaced Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9)-mediated targeted mutagenesis, was enhanced against PepMoV but not against TEV [22,114]. These
studies indicated that pvr1 or eIF4E greatly affects the resistance/susceptibility to plant viruses, especially to PepMoV, although the specific mechanism is unclear. In general, previous studies have suggested that eIF4E is also required for cell-to-cell movement and viral RNA replication during potyvirus infections [80,81,115]. The interaction between eIF4E and potyviruses will be discussed later in this review.

![Figure 2](image_url)

**Figure 2.** A scheme of host genes that may mediate recessive and dominant resistance and an explanation of the R protein-mediated signaling pathway. (A) Recessive resistance results from a host factor, the loss or mutation of which causes an incompatible interaction between a viral protein and a host protein. (B) Dominant resistance results from a compatible interaction between a viral effector and plant R proteins. Pvr9-mediated hypersensitive response requires several proteins, like NDR1 and the SGT1-HSP90 complex. Pvr9-mediated HR might also involve the SA pathway. NBS, nucleotide-binding site; LRR, leucine-rich repeat; CC, coiled-coil motif; HR, hypersensitive response; SA, salicylic acid.

### 5.2. Dominant R Genes

Dominant R genes, corresponding to pathogen effector-encoding or avirulence (Avr) genes, confer an active resistance resulting in the development of an HR that limits pathogen spread [97,116] or that provides extreme resistance (ER) to a broad range of potyviruses [97,117,118]. The major class of R genes encode proteins consisting of a nucleotide-binding site (NBS), a leucine-rich repeat (LRR) region at the C-terminal, and Toll/Interleukin-1 receptor homology or a coiled-coil (CC) domain at the N-terminal end (Figure 2B) [116].

Dominant resistance genes such as Pvr4, Pvr7, and Pvr9 confer HR against potyviruses in pepper [21,103,105]. The Pvr7 gene from C. chinense PI159236 and the Pvr4 gene from C. annuum ‘CM334’ confer ER to PVY and PepMoV. Pvr7 was tentatively re-designated as Pvr4 in recent study [119].

Pvr4 encodes a coiled-coil nucleotide-binding leucine-rich repeats (CNLs)-type protein, and ectopic expression of Pvr4 in N. benthamiana confers resistance against PepMoV [120]. Kim et al. found that pvr4 in the susceptible allele from C. annuum ‘ECW’ had higher similarity with the coiled-coil nucleotide-binding domain than with the LRR domain, which might be involved in specific recognition of Avr factors [121,122]. Researchers have demonstrated that the Nlb of several potyviruses including PepMoV serves as an avirulence factor for Pvr4 in pepper [20]. The Nlb of PepMoV, pepper severe mosaic virus, and PVY induced an HR, but the Nlb of TEV could not induce HR-like cell death in
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Kim et al. suggested that the differences in resistant responses among four potyviruses might be related to the low sequence identity of NIb with TEV compared with that of other potyviruses [20].

Another R gene, **Pvr9**, is orthologous to *Rpi-blb2* of *Solanum bulbocastanum* and was isolated via screening of Agrobacterium-based transient expression of candidate R genes that were able to induce an HR upon PepMoV infection in *N. benthamiana* [102]. **Pvr9** is expected to be located on pepper chromosome 6, and encodes 1298 amino acids that contain CNL-type protein domains [21]. PepMoV infection in pepper resulted in a minor increase in **Pvr9** gene expression in the resistant cultivar *C. annuum* ‘CM334’ but in a slightly reduced expression of the susceptible allele in the susceptible cultivars *C. annuum* ‘FloralGem’ [21]. Tran et al. also demonstrated that PepMoV NIb elicits the **Pvr9**-mediated HR, which is similar to the **Pvr4**-mediated HR [20,21].

### 6. Characterization of Interacting Virus and Host Factors

#### 6.1. Host Responses upon PepMoV Infection

Previous research has demonstrated that virus infection of plants affects host gene expression and metabolism, which results in altered host development and growth defects [123]. The changes in host gene/protein expression depend on whether the interaction is compatible or incompatible but also varies with plant species [123]. In early interactions between potato and PVY, for example, comparative transcriptomic analysis showed that transcriptional changes in compatible and incompatible reactions in one host shared more overall similarities in the response to PVY inoculation than compatible reactions between two different hosts [124]. The latter study also showed that a different cascade of molecular changes was triggered by two different PVY strains [124]. Although these previous studies documented changes in global gene/protein expression and in pathways in diverse host species following infection by different viruses, little is known about host responses to PepMoV infection under different conditions at a genome-wide level.

To identify pathways related to the **Pvr9**-mediated HR against PepMoV infection, researchers silenced selected genes using tobacco rattle virus-based virus-induced gene silencing and thereby assessed their functions [125]. The results showed that **Pvr9**-mediated HR requires the host genes **HSP90**, **SGT1**, **NDR1**, and **NPR1** genes but not the **EDS1** gene [125]. This indicated that **Pvr9**-mediated HR might involve the salicylic acid (SA) pathway but not the jasmonic acid (JA), ethylene (ET), reactive oxygen species (ROS), or nitric oxide (NO) pathways (Figure 1) [125]. Further research is needed to clarify the role of the SA pathway in **Pvr9**-mediated HR and the contribution of the HSP90-SGT1 complex to plant immunity against PepMoV.

Recent research showed that potato virus X vector-mediated expression of PepMoV NLa, which is highly conserved among potyviruses, resulted in severe mosaic symptoms and triggered a HR [88]. In the latter study, Gong et al. observed significantly increased expression levels of host genes including the ER-localized binding protein (Bip) and heat shock protein 90-2 (HSP90-2) in NLa-expressed plant, whereas the expression of the basic leucine zipper protein 60 (bZIP60) was not changed by NLa expression [88]. Given that Bip and HSP90-2 are required for the stabilization of many proteins in response to endoplasmic reticulum (ER) stress, the authors suggested that NLa might induce ER stress [88].

#### 6.2. PepMoV–Host Interaction: Avirulence and Virulence Genes

Although the exact mechanism by which eIF4E mutations control resistance remains to be elucidated, protein–protein interaction(s) between viral elicitor(s) and the host receptor(s) might contribute to the resistance responses. In this regard, it is noteworthy that the potyviral protein VPg, which is required for viral infection, interacts with eIF4E to induce infection; mutations in eIF4E. However, prevent VPg binding and thus inhibit viral infection, resulting in a resistance response [80,115]. At the same time, amino acid substitutions in VPg that restore its binding to the mutated eIF4E can break down the resistance [18,47].
Continuous co-evolution between viral effectors and their host counterparts has apparently resulted in the diversification of both genes.

Mutation of eIF4E affects the infectivity of PepMoV in tomato [22], but there is no biological evidence for a correlation among mutated eIF4E and viral proteins of PepMoV. In the case of PVA, VPg and HC-Pro interact with each other and with eIF4E and eIF(iso)4E proteins [18,55]. A recent study revealed that HC-Pro and VPg can both interact through the eIF4E-binding motif YXXXYLΦ, which is similar to the motif in eIF4G [18]. In the latter study, Ala-Poikela et al. analyzed and compared the central region of VPg that contains a putative 4E-binding motif among 40 potyviruses [18]; they found a putative eIF4E-binding motif in the VPg of PepMoV (YADIVDV), but that motif is slightly different from that of PVA (YTDIRLI), which is similar to the eIF4E-binding motif in the VPg of PVY (YADIRDl) [8].

Several potyvirus proteins have also been identified as elicitors of resistance or determinants of avirulence, and these correspond to dominant resistance proteins in plants [126]. As previously noted, the Nlb of PepMoV serves as an avirulence factor for Pvr4 in pepper plants [20]. However, an interaction between Pvr9 and its elicitor or so-called avirulence factor Nlb of PepMoV was not detected in the model plant N. benthamiana [21]. The authors of the latter study suggested that the interaction depended on a third unknown factor that was present in N. benthamiana but not in pepper.

An HR was also triggered when Pvr9 was co-expressed with Nlbs from PepMoV, PVY, PVA, and turnip mosaic virus, but not with Nlbs from zucchini yellow mosaic virus or soybean mosaic virus [21]. Although evidence was lacking for the direct binding between Pvr9 and Nlb in yeast or in plants, the mutational analyses suggested their possible relationship between Pvr9 and Nlb [21]. The amino acid substitutions E492G, V701E, F1117S, and R1160K in Pvr9 failed to trigger an Nlb-elicited HR in plants, while internal regions of Nlb (the residues 186–235 and 370–445) are essential for Nlb elicitor activity [21].

6.3. PepMoV–Host Interaction: Viral RNA Silencing Suppressors

In many potyviruses, VPg and especially HC-Pro help block or interfere with RNA silencing [47]. A recent study showed that treatment with dsRNA targeting HC-Pro or Nlb inhibited PepMoV accumulation in N. benthamiana [127]. However, it was not clear whether this inhibitory effect was caused by reducing expression of these target genes.

As noted earlier, the use of a potato virus X-based Nla expressing vector indicated that PepMoV Nla might be responsible for symptom development in N. benthamiana [88]. In addition, Gong et al. found that PepMoV Nla functions as a potent suppressor of host transcriptional gene silencing by negatively affecting the DNA methylation pathway in plant hosts [88]. These results suggested that PepMoV Nla might inhibit global DNA methylation by regulating expression of essential genes involved in RNA-directed DNA methylation including NbAGO4, NbMET1, NbDRM2, and NbCMT3 [88].

7. Genome-Wide Approaches for Identifying Additional Host Factors

In the last decade, many researchers studied plant–virus interactions by focusing on genome-wide expression patterns of host and virus genes [128]. The genome-wide analyses, especially of transcriptomic data, have allowed researchers to predict some of the major biological processes that are affected by virus infection and to detect genes that are differentially expressed under specific conditions or during different stages of virus–plant interactions [128]. In C. annuum ‘Zunla-1’ pepper plants, for example, transcript profiles of CMV-Fny infected leaves showed different expression patterns at different time points [129]. Kim et al. reported the comprehensive transcriptomic profiling obtained from C. annuum at different time points after infection by Phytophthora infestans, PepMoV, or tobacco mosaic virus [130]. Further detailed analysis based on global transcriptomic data will be useful for identifying host factors involved in infection or resistance to infection and for elucidating host molecular networks that respond to virus infection.
8. Concluding Remarks and Future Prospects

PePmMoV is one of the most important pathogens of solanaceous vegetables worldwide. Although the roles of each encoded PePMoV gene can be inferred by comparison with analogous genes in other potyviruses, the role(s) or function(s) of each PePMoV protein remain poorly characterized. Use of a PePMoV infectious clone will help researchers to identify the determinants of PePMoV pathogenicity/virulence and to understand the replication and movement of the virus in infected host plants.

Author Contributions: Conceptualization, K.-H.K.; writing—original draft preparation, M.F. and J.Y.; writing—review and editing, J.Y. and K.-H.K. All authors have read and agreed to the published version of the manuscript, and all have contributed especially to specific paragraphs.

Funding: This research was supported in part by grants from the Korea Institute of Planning and Evaluation for Technology in Food, Agriculture and Forestry (320037-05-1-HD020), funded by Ministry of Agriculture, Food and Rural Affairs and the Agenda Program (No. PJ01488703), the Rural Development Administration (RDA), Republic of Korea. MF was supported by a research fellowship from the Brain Korea 21 Plus Project.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in the article.

Conflicts of Interest: The authors declare no conflict of interest.

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