REVIEW

Advances in research on maize lethal necrosis, a devastating viral disease

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Abstract

Maize lethal necrosis (MLN) is a devastating disease of maize caused by synergistic infection with maize chlorotic mottle virus (MCMV) and at least one potyvirid (e.g., sugarcane mosaic virus, SCMV). MLN results in leaf necrosis, premature aging, and even whole plant death and can cause up to 100% losses in yield. MLN has emerged world-wide and resulted in serious loss in maize production. Over the past decade, extensive research has been conducted to understand the epidemic and pathogenic mechanisms of MLN. In this review, we summarize recent findings in understanding the biological functions of proteins from both viruses and discuss recent advances in molecular plant-virus interactions, particularly the co-evolutionary arms race between maize anti-viral defense and viral pathogenesis (counter-defense). Based on recent research progress, we discuss how to combine different strategies for enhancing the effectiveness of maize resistance to MCMV/SCMV, and the possible approaches for effective control of MLN.

Keywords: Maize chlorotic mottle virus (MCMV), Maize lethal necrosis (MLN), Sugarcane mosaic virus (SCMV)

Background

Synergism may commonly occur in mixed infections of plants with two or more viruses under field conditions. Unlike antagonism, which can exclude coinfection of the same cell by closely related viruses, synergistic interactions always enable coinfection of the same cell by unrelated viruses which belong to different families (Tatineni et al. 2019). In some cases, synergism or antagonism is determined by the order of virus infection. For instance, synergism usually occurs in *Carica papaya* infected first with *Papaya ringspot potyvirus* or simultaneously co-infected with *Papaya mosaic potexvirus* (Chávez-Calvillo et al. 2016). Generally, synergism often leads to more severe symptoms than that caused by either virus alone (Uyemoto et al. 1981; Scheets 1998; Xia et al. 2016; Tatineni et al. 2019). For instance, the co-infection of

potato virus X with some potyviruses [e.g., potato virus Y (PVY)] results in systemic necrosis in *Nicotiana benthamiana* (Aguilar et al. 2019).

Maize lethal necrosis (MLN) is a devastating disease, which is caused by synergistic infection of maize (*Zea mays* L.) with *Maize chlorotic mottle machlomovirus* and at least one of several cereal-infecting potyvirids, such as *Sugarcane mosaic potyvirus* (Niblett and Claflin 1978; Adams et al. 2013; Xia et al. 2016; Fentahun et al. 2017; Wang et al. 2017), *Johnsongrass mosaic potyvirus* (Stewart et al. 2017), *Maize dwarf mosaic potyvirus* (Goldberg and Brakke 1987) and *Wheat streak mosaic tritimovirus* (Scheets 1998). MLN results in leaf necrosis, premature aging, small cobs and even plant death (Fig. 1a), which can cause up to 100% yield losses with damaging impacts on food security (Wangai et al. 2012; Braidwood et al. 2018; Redinbaugh and Stewart 2018). Synergistic interactions between potyvirids and viruses from other families (nonpotyvirids) have been well documented. Intriguingly, in most cases, the beneficiary of synergistic interaction is nonpotyvirid(s) (Goldberg and Brakke 1987; Karyeija et al. 2000; Pacheco et al. 2012; Xia et al. 2016). Xia et al. (2016) revealed that the synergistic infection

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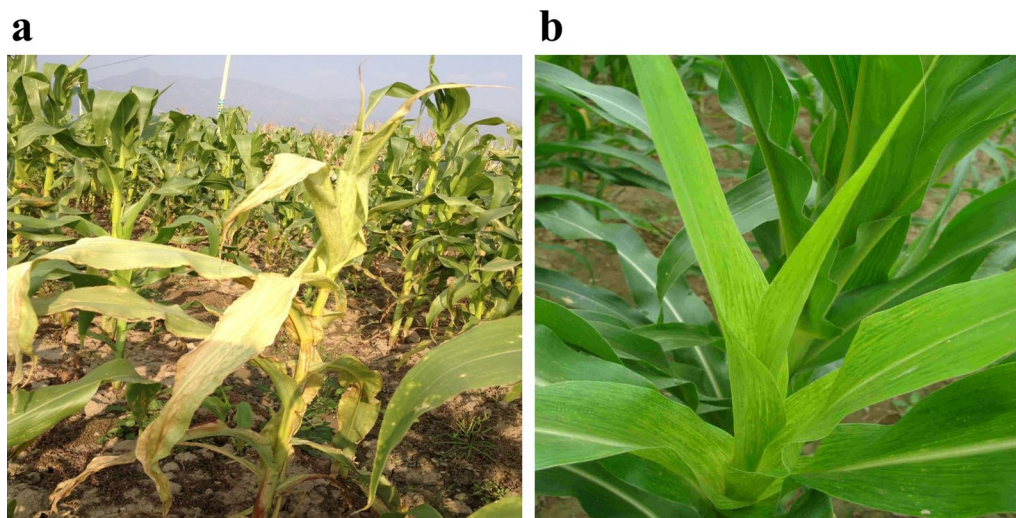Full list of author information is available at the end of the article

Fig. 1 Maize plants showing lethal necrosis and dwarf mosaic. **a** Maize plants with lethal necrosis (infected with sugarcane mosaic virus and maize chlorotic mottle virus) in a field in Yunnan Province. **b** A maize plant infected with sugarcane mosaic virus in Beijing

of maize chlorotic mottle virus (MCMV) and sugarcane mosaic virus (SCMV) resulted in a dramatic increase in the accumulation level of MCMV. However, no obvious difference in the expression of SCMV coat protein (CP) was detected between mix-infected and singly-infected leaves, although the SCMV RNA was slightly decreased in mix-infected maize plants (Xia et al. 2016). Similarly, it is reported that the coinfection of PVY and cucumber mosaic virus (CMV) led to increased accumulation of CMV but decreased accumulation of PVY during synergistic interaction (Mascia et al. 2010). In contrast to the synergistic interaction between MCMV and SCMV, wheat streak mosaic virus (WSMV) infection in doubly infected (MCMV + WSMV) plants was enhanced by the presence of MCMV compared with that in singly inoculated plants (Scheets 1998). Similar phenomenon was also observed when WSMV and triticum mosaic virus (TriMV, genus *Poacevirus*, family *Potyviridae*) coinfected wheat (i.e., WSMV and TriMV caused synergistic disease with elevated accumulation of both viruses) (Tatineni et al. 2010). In addition, wheat cultivar-specific disease synergism was observed during co-infection with WSMV and TriMV (Tatineni et al. 2019).

In addition to the synergistic infection between MCMV and potyvirids, some viruses from other families can also co-infect with MCMV and SCMV. Li et al. (2015) showed that one maize plant was co-infected with MCMV, SCMV and southern rice black-streaked dwarf virus (genus *Fijivirus*, family *Reoviridae*). Recently, maize yellow mosaic virus (MaYMV, genus *Polerovirus*, family *Solemoviridae*) was found in plants co-infected with both SCMV and MCMV (Scheets et al. 2020; Stewart and

Willie 2021). However, severe symptoms did not appear in MaYMV + MCMV or MaYMV + SCMV co-infected maize plants (Stewart and Willie 2021). Intriguingly, although MaYMV could strongly suppress the SCMV-induced titer increase of MCMV in triple infections, MLN symptoms still occurred (Stewart and Willie 2021).

In this review, we present an overview of MLN research and highlight recent important discoveries on MCMV and SCMV. In addition, based on the investigations in maize-virus interactions, we discuss how these discoveries could improve plant protection strategies in the future.

Pathogens associated with MLN
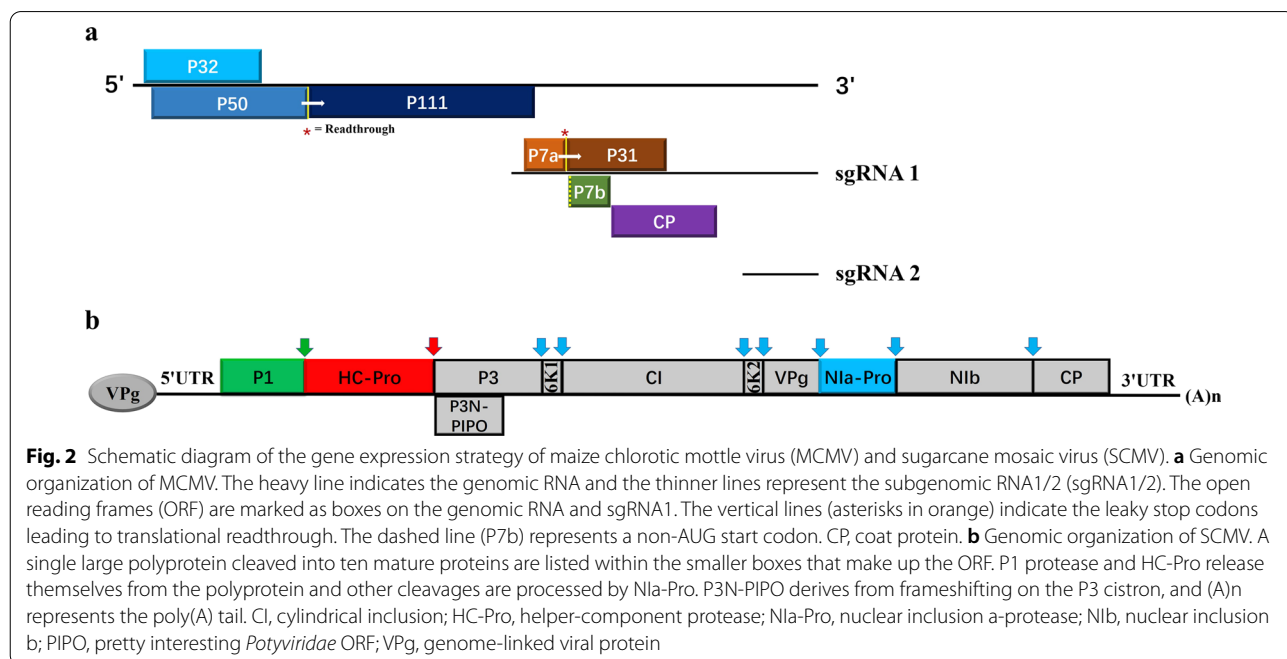### Maize chlorotic mottle virus
MCMV is the only member of the genus *Machlomovirus* in the family *Tombusviridae*. It is the major virus that drives MLN expansion. MCMV has a positive-sense, single-stranded RNA genome of 4437 nt in length that is neither capped nor polyadenylated (Nutter et al. 1989; Scheets et al. 1993; Scheets 2016). The host range of MCMV is restricted to graminaceous plants (Poaceae), and maize is one of its natural hosts (Huang et al. 2016; Scheets 2016). Other natural host plants include sugarcane (*Saccharum officinarum*) (Wang et al. 2014), finger millet (*Eleusine coracana*) (Kusia et al. 2015), sorghum (*Sorghum bicolor*) and coix seed (*Coix chinensis* Tod.) (Huang et al. 2016). Bockelman et al. (1982) reported that MCMV can be mechanically inoculated to some other cereal crops and weedy grasses in the laboratory, e.g., barley (*Hordeum vulgare* L.), common millet (*Panicum miliaceum* L.), foxtail millet (*Setaria italica*) and wheat

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(*Triticum aestivum* L.). The virion of MCMV is highly stable which can retain infectivity at 20 °C for more than one month, with thermal inactivation at 80–85 °C (Uyemoto et al. 1981). Isometric particles of approximately 30 nm in diameter were found in MCMV-infected leaf samples (mainly in the cytoplasm, peroxisomes and vacuoles) under transmission electron microscope (Xie et al. 2011; Wang et al. 2015; Jiao et al. 2021b). More recently, maize peroxisomes were observed to form aggregated bodies which served as the major viral replication site in MCMV-infected maize cells (Jiao et al. 2021a).

The MCMV genome contains five major open reading frames (ORF) which encode seven proteins with several expression strategies (Scheets et al. 1993; Scheets 2016; Fig. 2a). Three proteins are expressed from MCMV genomic RNA. The first ORF encodes a 32-kDa protein (P32) which is unique to MCMV and lack of its expression leads to *ca*. 2/3 decrease of virus accumulation in maize protoplasts and produces delayed, mild infections in maize plants compared with the wild-type virus (Scheets 2016). ORF2 partially overlaps with ORF1 and leaky scanning mechanism allows expression of P50 and its read-through protein P111 (readthrough of a UAG stop codon at the end of P50) which are the only viral proteins required for MCMV replication (Nutter et al. 1989; Scheets 2016). In addition, MCMV generates two 3'-coterminal subgenomic RNAs: subgenomic RNA1 (sgRNA1), spanning nucleotides 2971–4437 on the genomic RNA serves as the mRNA from which P7a, P7b (likely using an unusual CUG start codon),

P31 and CP are translated. Mutagenesis analyses (preventing the expression of P7a, P7b and CP, respectively) demonstrated that the three proteins are required for viral cell-to-cell movement in maize plants (Scheets 2016). Another unique protein P31 is expressed as a readthrough extension of P7a (readthrough of a UAG stop codon at the end of P7a). It is the major pathogenicity determinant of MCMV, and its expression by virus vectors induces necrosis in systemically infected leaves (Jiao et al. 2021b). The 337-nt noncoding sgRNA2 (spanning nucleotides 4101–4437 in the genome) accumulates in MCMV-infected maize protoplasts and plants (Scheets 2000). Previous investigations indicated that many plant viruses produce protein-coding and noncoding sgRNAs for efficient infection (Miller et al. 2016; Steckelberg et al. 2018). For instance, the subgenomic noncoding RNA of red clover necrotic mosaic virus contained a cap-independent translation element that could bind translation initiation factor eIF4G (Miller et al. 2016). Thus, it is worthy of investigating whether the sgRNA2 of MCMV can regulate viral infection.

MCMV was firstly identified in Peru in 1971 (Castillo and Hebert 1974), subsequently, it was found in many maize-cultivating countries/regions of all the continents except Australia and Antarctica (Regassa and Dechassa 2021). The infection of MCMV causes mottle, chlorosis, stunting and even necrosis in maize plants (Uyemoto et al. 1981; Redinbaugh and Stewart 2018; Jiao et al. 2021b). In addition, maize may be stunted with short, malformed, partially filled ears, and male inflorescences

Fig. 2 Schematic diagram of the gene expression strategy of maize chlorotic mottle virus (MCMV) and sugarcane mosaic virus (SCMV). **a** Genomic organization of MCMV. The heavy line indicates the genomic RNA and the thinner lines represent the subgenomic RNA1/2 (sgRNA1/2). The open reading frames (ORF) are marked as boxes on the genomic RNA and sgRNA1. The vertical lines (asterisks in orange) indicate the leaky stop codons leading to translational readthrough. The dashed line (P7b) represents a non-AUG start codon. CP, coat protein. **b** Genomic organization of SCMV. A single large polyprotein cleaved into ten mature proteins are listed within the smaller boxes that make up the ORF. P1 protease and HC-Pro release themselves from the polyprotein and other cleavages are processed by NIa-Pro. P3N-PIPO derives from frameshifting on the P3 cistron, and (A)n represents the poly(A) tail. CI, cylindrical inclusion; HC-Pro, helper-component protease; NIa-Pro, nuclear inclusion a-protease; NIb, nuclear inclusion b; PIPO, pretty interesting *Potyviridae* ORF; VPg, genome-linked viral protein

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may be shortened with sparse spikes (Uyemoto et al. 1981; Goldberg and Brakke 1987). The differential severity of disease caused by MCMV is based on the maize variety and plant growth stage when infected. In addition, the roles of environmental factors (e.g., temperature) in symptom development need to be further investigated. Some species of beetles and thrips are reported to be the vectors to transmit MCMV (Redinbaugh and Stewart 2018). Six beetle species were tested and found to transmit MCMV both at larval and adult stages with no latent time (Nault et al. 1978). Since the known vectors of beetles were not present but some species of thrips were abundant in Hawaii during MLN emergence, maize thrips (*Frankliniella williamsi* Hood) and western flower thrips (*F. occidentalis*) were tested and proven to transmit MCMV in a semi-persistent manner (Krczal et al. 1995; Zhao et al. 2014). Interestingly, MCMV has been reported to induce changes in host plant volatiles that attract vector thrips species (Mwando et al. 2018). Both sexes of maize thrips were significantly attracted to (E)-4,8-dimethyl-1,3,7-nonatriene, methyl salicylate and (E, E)-4,8,12-trimethyltrideca-1,3,7,11-tetraene which were strongly induced in MCMV-infected maize seedlings (Mwando et al. 2018).

MCMV can also be transmitted by maize seeds (Jensen et al. 1991; Regassa et al. 2021). Earlier experiments showed that the rates of MCMV transmission to progeny plants were 0–0.33% (Bockelman et al. 1982; Jensen et al. 1991; Sánchez et al. 1994). Similarly, MCMV was also detected in 0.33% (2 of 600) maize seeds (Zhang et al. 2011). Preliminary experiments indicated a high incidence (45–72%) of MCMV in seedlings which were planted in contaminated soil taken from MLN-occurred maize fields (Mahuku et al. 2015). However, further research needs to be performed to determine the infectivity of MCMV in the field and the duration of maize plant-free period required to prevent MCMV transmission through soil.

Potyviruses

Maize-infecting potyviruses (particularly SCMV) are distributed in maize-cultivating regions worldwide (Redinbaugh and Stewart 2018). Different maize-infecting potyviruses predominate in different countries/regions, and SCMV is the prevalent virus in China (Fan et al. 2003). Potyviruses possess a single-stranded, positive-sense RNA genome of approximately 10 kb in length. The viral genome contains only one ORF which can be translated to yield a single large polyprotein, then it is cleaved into ten mature proteins [P1 protease, helper component-protease (HC-Pro), P3, 6K1, cylindrical inclusion (CI) protein, 6K2, viral genome-linked protein (VPg), nuclear inclusion a-protease (NIa-Pro), nuclear inclusion b (NIb),

and CP] by three viral proteases (Urcuqui-Inchima et al. 2001; Fig. 2b). An additional protein, P3N-PIPO, generated via ribosomal frameshift or polymerase slippage, was discovered to influence virus cell-to-cell movement (Vijayapalani et al. 2012; Revers and García 2015; Rodamilans et al. 2015).

Since transgenic plant production is time-consuming and costly in most crop species, virus-based expression vectors have been widely used to deliver heterologous proteins in plants. Some maize-infecting potyviruses have been developed as tools for gene expression or silencing. For instance, the SCMV cDNA clone was modified through inserting exogenous fragments at the P1/HC-Pro junction to express foreign proteins in maize plants (Mei et al. 2019; Chung et al. 2021). Recently, MDMV was reported as a tool for simultaneous gene expression and multi-gene silencing in maize (Xie et al. 2021a, b).

Sugarcane mosaic virus

As some other maize-infecting potyviruses (e.g., MDMV), SCMV can also cause maize dwarf mosaic disease (Xiao et al. 1993; Kannan et al. 2018). Upon infection with SCMV, maize display symptoms like leaf mosaic and even plant dwarfism (Chen et al. 2017a, c; Fig. 1b). Single infection of SCMV sometimes leads to massive losses (10% to 50%) of maize yield in China (Zhu et al. 2014; Chen et al. 2017a, c). However, the mixed infection of SCMV and MCMV results in up to 100% losses of maize yield (Xia et al. 2016; Redinbaugh and Stewart 2018). Like many maize-infecting potyvirids, several aphid species are the major insect vectors for transmission (Redinbaugh and Stewart 2018; Yang et al. 2021).

Recently, ribosome profiling paralleled with RNA-seq was performed to reveal the translational responses in maize to SCMV infection (Xu et al. 2019). Detailed analyses indicated that only the genomic positive-stranded RNA of SCMV was involved in translation at the early stage of infection, and photosynthesis and metabolism were dramatically repressed at both transcriptional and translational levels (Xu et al. 2019). A recent study reported that endoplasmic reticulum, Golgi apparatus, mitochondria and peroxisomes were targeted by SCMV to form genomic RNA replication sites (Xie et al. 2021a, b).

RNA silencing plays a critical role against viral infection. To counteract this anti-viral response, plant viruses have evolved various viral suppressors of RNA silencing (VSRs) (Pumplin and Voinnet 2013). Potyviral HC-Pro is a kind of well-characterized VSR, and can target multiple steps of RNA silencing to block the defense response (Valli et al. 2018). Besides, as a multifunctional protein, potyviral HC-Pro is also involved in the aphid

transmission (Govier and Kassanis 1974), enhancement of viral particle production (Valli et al. 2014), symptom development (Maia et al. 1996), genome replication (Maia et al. 1996) and virus movement (Syller 2005).

Zhang et al. (2008) demonstrated that the HC-Pro encoded by SCMV down-regulated the accumulation of 3′ secondary siRNAs, but not 5′ secondary and primary siRNAs, and transient overexpression of HC-Pro can also down-regulate the accumulation of RDR6 mRNAs. Recently, it is reported that the arginine at position 184 of SCMV HC-Pro is the key amino acid for suppressing RNA silencing (Xu et al. 2020). The substitution of arginine with isoleucine in the FRNK motif at position 184 of HC-Pro not only drastically reduced the virulence and accumulation level of SCMV, but also impaired the synergism between SCMV and MCMV (Xu et al. 2020). In addition, a spontaneous mutation of glycine at position 440 to arginine in HC-Pro can damage its RNA silencing-suppression activity, rescue the virulence of SCMV and disturb the synergism of MCMV and SCMV (Xu et al. 2020). Unlike SCMV HC-Pro, the host RNA silencing pathway was dispensable for the synergism induced by PVX P25/plum pox virus HC-Pro (Aguilar et al. 2019). However, different from SCMV, the tritimovirus WSMV HC-Pro is not required for synergism (Stenger et al. 2007). One possible reason is that WSMV has a silencing suppressor different from some potyviruses (Young et al. 2012). For WSMV, P1 functions as the suppressor of RNA silencing and enhancer of disease symptoms (Young et al. 2012).

Virus detection/disease diagnostics

It is well known that the detection and identification of viruses is the first step in controlling viral diseases. Many methods, such as symptomatology, nucleic acids-based methods and serological methods, have been used for the practical diagnosis of MCMV and SCMV (Redinbaugh and Stewart 2018). In recent years, some new methods have been developed and used in the detection of MCMV and/or SCMV-infected plants/seeds. For instance, next-generation sequencing was used to identify and characterize MLN in Kenya (Adams et al. 2013). In addition, one-step reverse transcription-loop-mediated isothermal amplification (RT-LAMP) assay and recombinase polymerase amplification (RPA) methods have been developed for MCMV and SCMV detection (Keizerweerd et al. 2015; Chen et al. 2017b; Jiao et al. 2019; Gao et al. 2021).
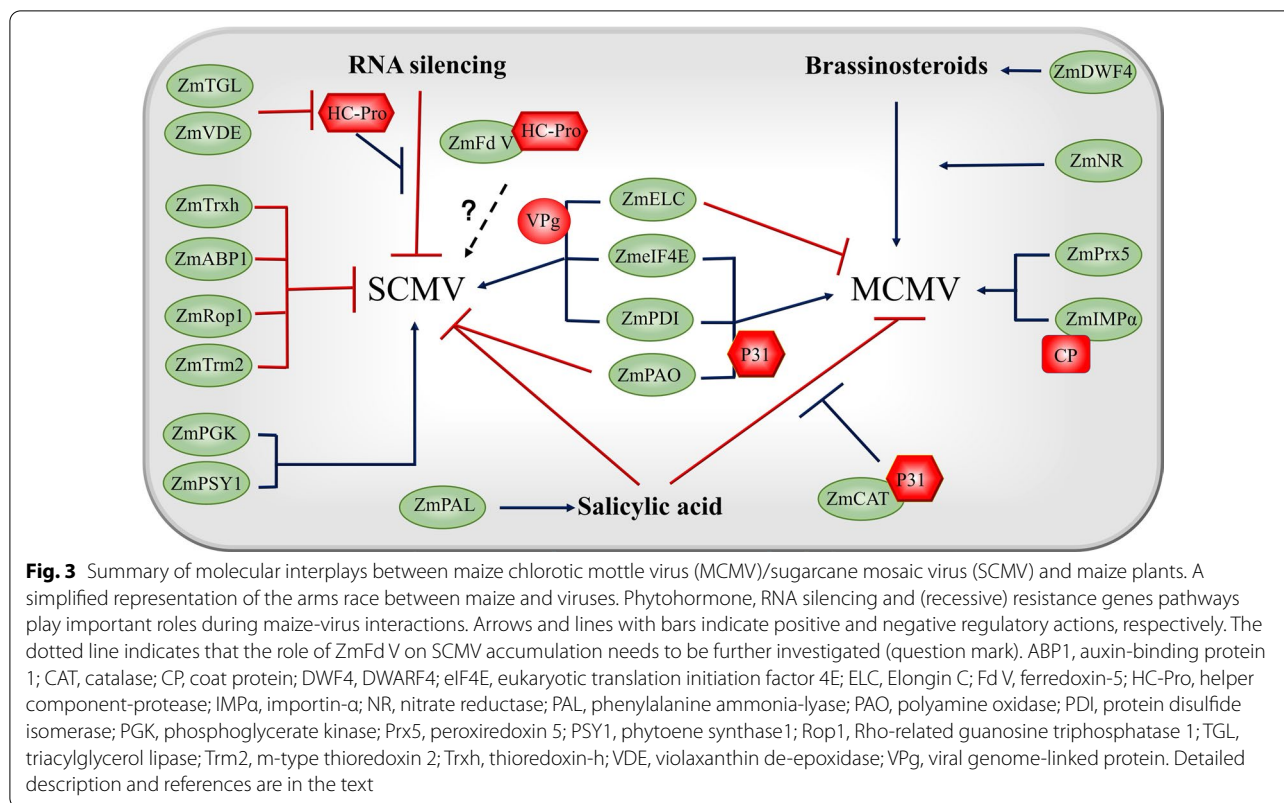
Molecular plant–virus (MCMV/SCMV) interactions

Plants have evolved an intricate immune system to ward off different invading pathogens (Jones and Dangl 2006). Facing viral invasion, plants also employ multiple defense pathways (including phytohormone, RNA silencing and recessive resistance gene-mediated pathways) to restrict viral infection (Boualem et al. 2016). Due to the limited encoding capacity of viral genomes, plant-infecting RNA viruses, including SCMV and MCMV, depend on host factors to complete their infection cycles (Fig. 3). To establish systemic infection, plant viruses must induce profound alterations in host physiology, disturb distinct endogenous processes and empower the capacity to suppress or evade host antiviral responses.

Phytohormones and viral infection

Plant hormones play a crucial role in plant resistance against virus infection (Jameson and Clarke 2002). It is well known that salicylic acid (SA) plays a critical role in plant development, as well as in defense against various of pathogens (Ji and Ding 2001; Rivas-San Vicente and Plasencia 2011; Yuan et al. 2017; Murphy et al. 2020). MCMV infection significantly increased SA accumulation and expression of SA-responsive pathogenesis-related (*PR*) protein genes (Jiao et al. 2021b) (Fig. 3). Similar results were also obtained in SCMV-infected maize plants (Yuan et al. 2019) (Fig. 3). In addition, exogenous SA treatment on maize seedlings enhanced resistance against MCMV/SCMV infection (Yuan et al. 2019; Jiao et al. 2021b; Xu et al. 2022). Yuan et al. (2019) also demonstrated that maize phenylalanine ammonia-lyase (*ZmPAL*) genes expression were significantly up-regulated during SCMV infection, and knockdown of *ZmPAL* expression by using a brome mosaic virus (BMV)-derived virus-induced gene silencing (VIGS) vector decreased SA accumulation and exacerbated SCMV infection. However, plant viruses have evolved effective strategies to disrupt or interfere with SA-mediated resistance (Qi et al. 2018). More recently, maize catalases were shown to interact with P31 protein which attenuated the expression of SA-responsive *PR* genes by inhibiting catalase activity during MCMV infection (Jiao et al. 2021b). Brassinosteroids (BRs), a class of steroid phytohormones, were reported to respond to MCMV infection (Cao et al. 2019). Transcriptome sequencing data analyses showed that BR-associated genes were significantly upregulated upon MCMV infection (Cao et al. 2019). Unlike the roles of SA, BRs render the susceptibility of maize seedlings to MCMV infection. Maize plants with knocking-down of *DWARF4* (*ZmDWF4*, a key gene of BR synthesis) and nitrate reductase gene [*ZmNR*, important in nitric oxide (NO) synthesis] by VIGS displayed resistance to MCMV, which indicated that BR pathway was involved in the susceptibility to MCMV accumulation in an NO-dependent manner (Cao et al. 2019) (Fig. 3). However, the regulatory mechanisms underlying the roles of BRs in plant antiviral immunity need to be further investigated.

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Fig. 3 Summary of molecular interplays between maize chlorotic mottle virus (MCMV)/sugarcane mosaic virus (SCMV) and maize plants. A simplified representation of the arms race between maize and viruses. Phytohormone, RNA silencing and (recessive) resistance genes pathways play important roles during maize-virus interactions. Arrows and lines with bars indicate positive and negative regulatory actions, respectively. The dotted line indicates that the role of ZmFd V on SCMV accumulation needs to be further investigated (question mark). ABP1, auxin-binding protein 1; CAT, catalase; CP, coat protein; DWF4, DWARF4; eIF4E, eukaryotic translation initiation factor 4E; ELC, Elongin C; Fd V, ferredoxin-5; HC-Pro, helper component-protease; IMPα, importin-α; NR, nitrate reductase; PAL, phenylalanine ammonia-lyase; PAO, polyamine oxidase; PDI, protein disulfide isomerase; PGK, phosphoglycerate kinase; Prx5, peroxiredoxin 5; PSY1, phytoene synthase1; Rop1, Rho-related guanosine triphosphatase 1; TGL, triacylglycerol lipase; Trm2, m-type thioredoxin 2; Trxh, thioredoxin-h; VDE, violaxanthin de-epoxidase; VPg, viral genome-linked protein. Detailed description and references are in the text

Antiviral RNA silencing and viral suppression strategies

RNA silencing is a conserved and sequence-specific mechanism in most eukaryotic organisms that regulates gene expression and counteracts viral infections, which involves the production of small-interfering RNAs (siRNAs) and microRNAs (miRNAs) (Voinnet 2009; Pumplin and Voinnet 2013; Rosa et al. 2018; Guo et al. 2019). Viral double-stranded RNAs (dsRNAs) produced during virus replication can trigger RNA silencing in plants by the cleavage of viral dsRNA into 21–24-nt-long small interfering RNAs (vsiRNAs) (Niehl et al. 2016). Recent studies have characterized four vsiRNAs which could efficiently inhibit the accumulation of SCMV RNA, among the vsiRNAs derived from SCMV by high-throughput sequencing (Xia et al. 2018a, b). The characterization of maize miRNAs in response to synergistic infection of MCMV and SCMV has also been investigated and miR159, miR393 and miR394 were suggested to be involved in the synergistic infection of MCMV and SCMV (Xia et al. 2019). Recently, maize miR167b was reported to positively modulate host resistance against MCMV infection (Liu et al. 2022). As a counter-defense, MCMV-encoded P31 protein repressed *Zma-miR167*-mediated resistance (Liu et al. 2022).

SCMV-encoded HC-Pro can inhibit the function of RNA silencing machinery (Chen et al. 2017c). How HC-Pro exerts its RNA silencing suppressor function has not been extensively investigated. Meanwhile, plants have evolved counter-counter defense strategies to balance RNA silencing suppression by VSRs. Violaxanthin de-epoxidase of maize (ZmVDE), a nuclear-encoded chloroplast protein, was shown to interact specifically with SCMV HC-Pro (Chen et al. 2017c) (Fig. 3). In addition, the RNA silencing suppressor activity of HC-Pro was attenuated by ZmVDE in a specific protein interaction-dependent manner, contributing to the decrease in SCMV accumulation (Chen et al. 2017c). Recently, another maize protein ZmTGL (triacylglycerol lipase) was also demonstrated to inhibit the RNA silencing suppression activity of HC-Pro, most likely through promoting the VSR degradation (Xu et al. 2022).

Resistance/recessive resistance genes for the control of MCMV/SCMV infection

It is well known that the most economically viable and environmentally sustainable approach for the control of viral diseases in crops is to deploy virus-resistant cultivars and hybrids, while the availability of resistance (or recessive resistance) genes is a prerequisite. Once these resistance genes and/or recessive resistance genes are

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identified, we can take advantage of the genetic diversity of maize, the availability of substantial genomic information and advanced breeding approaches [e.g., clustered regularly interspaced short palindromic repeats (CRISPR)-Cas for genome editing] to create new resistant or tolerant cultivars and germplasms (Xu et al. 2017).

To date, two major resistance quantitative trait loci (QTL), *Scmv1* and *Scmv2*, have been identified in diverse independent mapping populations to confer resistance to SCMV (Leng et al. 2017; Liu et al. 2017) (Fig. 3). *Scmv1*, a major gene required for strong early resistance to SCMV on chromosome 6, encodes an atypical thioredoxin-h (ZmTrxh) that is expressed at high levels in virus-resistant lines and significantly associated with SCMV resistance without eliciting an SA- or jasmonic acid (JA)-mediated defense responses (Tao et al. 2013; Liu et al. 2017). *Scmv2*, a second major resistance gene on chromosome 3 encoding auxin-binding protein 1 (ZmABP1), mainly functions at later infection stages (Xing et al. 2006; Leng et al. 2017). Although two dominant SCMV resistance loci have been identified in maize cultivars, more research is required to investigate the mechanisms by which these two genes confer SCMV resistance. Unlike SCMV, little is known about the genetic basis of MCMV tolerance/resistance in maize plants. Though many QTLs associated with resistance to MCMV/MLN have been identified across maize chromosomes in multiple mapping populations, no maize line with significant MCMV resistance has been reported (Redinbaugh and Stewart 2018; Awata et al. 2020).

Suppression subtractive hybridization which served as a powerful tool for obtaining gene expression profiles was used to investigate the gene expression profile in SCMV-infected maize seedlings (Shi et al. 2011; Cao et al. 2012). A maize m-type thioredoxin 2 (*ZmTrm2*) and *Rop1* (Rho-related guanosine triphosphatase 1 from plants) gene expressions were found to be highly up-regulated and played an inhibitory role during SCMV infection (Shi et al. 2011; Cao et al. 2012). Recently, Du et al. (2020) demonstrated (by integrative analysis of RNA-sequencing datasets) that SCMV infection could perturb the alternative splicing of maize phytoene synthase1 (*ZmPSY1*) to prevent ZmPSY1 protein from decrease and promote viral pathogenesis. Whether these proteins are involved in MCMV infection remains to be investigated.

Emerging evidences show that characterization of host factors functioning in viral infection is critical for the development of new strategies to control viral diseases. The elucidation of interactions between viral and host proteins is a prerequisite to reveal the molecular mechanisms that underlie the viral infection process and symptom development in plants. SCMV HC-Pro

was reported to interact specifically with maize ferredoxin-5 (ZmFd V) to perturb chloroplast structure and function by disturbing the post-translational import of Fd V into maize bundle-sheath cell chloroplasts (Cheng et al. 2008) (Fig. 3). In addition, Zhan et al. (2016) demonstrated that importin-α (ZmIMPα) was employed by MCMV CP to facilitate viral accumulation (Fig. 3).

In recent years, with significant advances in large-scale and quantitative proteomics technologies [e.g., isobaric tags for relative and absolute quantitation (iTRAQ)], comparative proteomic analyses have been performed on MCMV/SCMV-infected maize seedlings (Chen et al. 2017a; Dang et al. 2020). Maize phosphoglycerate kinase (ZmPGK) and polyamine oxidase (ZmPAO) were identified by iTRAQ analyses, then it is confirmed that ZmPGK supported SCMV accumulation and ZmPAO enhanced plant resistance to viral infection by using BMV-based VIGS system (Chen et al. 2017a). More recently, Liu et al. (2022) revealed that inhibition of enzymatic activity of ZmPAO1 suppressed MCMV infection. In addition, it has been reported that a peroxiredoxin family protein (ZmPrx5) could enhance host susceptibility to viral infection by using proteomic datasets in response to MCMV infection (Dang et al. 2020).

Some resistance/recessive resistance genes to both MCMV and SCMV have been identified. Eukaryotic translation initiation factor 4E (eIF4E) has been identified as a susceptibility factor in many potyviruses (including SCMV)-plant combinations (Zhu et al. 2014; Yang et al. 2021) (Fig. 3). More recently, eIF4E was also identified to be usurped by MCMV to bind viral 3' cap-independent translation element (Carino et al. 2020). Intriguingly, eIF4E [including its isoform eIF(iso)4E] has also been shown to control resistance to plant viruses in other families/genera, such as carmoviruses, bymoviruses, cucumoviruses, sobemoviruses and waikiviruses (Wang and Krishnaswamy 2012; Sanfaçon 2015). Therefore, eIF4E may be a potential target for engineering resistance to MLN. Similar to the results obtained during the roles of eIF4E in MCMV/SCMV infection, protein disulfide isomerase (PDI) was also reported to support both MCMV and SCMV accumulation (Chen et al. 2017a; Dang et al. 2020). However, the roles of host factors in MCMV and/or SCMV infection are not always the same. For instance, maize Elongin C (ZmELC) could interact with SCMV VPg (the viral genome-linked protein) to facilitate viral replication, while transient overexpression of *ZmELC* reduced the replication of MCMV and silencing *ZmELC* enhanced MCMV accumulation (Zhu et al. 2014).

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Conclusions

In this review, we summarize current knowledge on MLN and maize-MCMV/SCMV interactions (Fig. 3). Understanding the underlying mechanisms during the arms race between maize and viruses will be conducive to finding new sources of virus resistance. In the long run, it is optimal to control MLN through utilization of immune or resistant hybrids and cultivars. Therefore, further investigations of maize germplasm for strong resistance against MCMV infection are warranted. In addition, the molecular identification of maize proteins that are essential for MCMV/SCMV infection but dispensable for plant growth and development is of significant interest in the development of CRISPR/Cas–mediated resistance in maize. Despite some significant progress in recent years, many aspects of maize-virus relationship remain to be addressed. For instance, what is the mechanism of synergism during MCMV and SCMV infection? How do some maize interactor proteins function in MLN? Are there broad-spectrum resistance or immune factors against both MCMV and SCMV? Thus, further efforts are required to obtain deeper insight into MLN and achieve effective control of the disease.

Abbreviations
ABP1: Auxin-binding protein 1; BMV: Brome mosaic virus; BRs: Brassinosteroids; CI: Cylindrical inclusion; CP: Coat protein; CRISPR: Clustered regularly interspaced short palindromic repeats; dsRNA: Double-stranded RNA; DWF4: DWARF4; eIF4E: Eukaryotic translation initiation factor 4E; ELC: Elongin C; Fd V: Ferredoxin-5; HC-Pro: Helper component-protease; IMPα: Importin-α; JA: Jasmonic acid; JGMV: Johnsongrass mosaic virus; MCMV: Maize chlorotic mottle virus; MDMV: Maize dwarf mosaic virus; MLN: Maize lethal necrosis; NIa-Pro: Nuclear inclusion a-protease; NIb: Nuclear inclusion b; NO: Nitric oxide; NR: Nitrate reductase; PAL: Phenylalanine ammonia-lyase; PAO: Polyamine oxidase; PDI: Protein disulfide isomerase; PGK: Phosphoglycerate kinase; Prx5: Peroxiredoxin 5; PSY1: Phytoene synthase1; Rop1: Rho-related guanosine triphosphatase 1; Trm2: M-type thioredoxin 2; Trxh: Thioredoxin-h; SA: Salicylic acid; SCMV: Sugarcane mosaic virus; WSMV: Wheat streak mosaic virus; sgRNA: Subgenomic RNA; VDE: Violaxanthin de-epoxidase; VIGS: Virus-induced gene silencing; VPg: Viral genome-linked protein.

Author contributions
ZJ and ZF wrote the manuscript. ZJ and ZF designed the Figures. All authors read and approved the final manuscript.

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