Functional role of Geminivirus encoded proteins in the host: Past and Present

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Abstract

During plant-pathogen interaction, plant exhibits a strong defense system utilizing diverse groups of proteins to suppress the infection and subsequent establishment of the pathogen. However, in response, pathogens trigger an anti-silencing mechanism to overcome the host defense machinery. Among plant viruses, geminiviruses are the second largest virus family with a worldwide distribution and continue to be production constraints to food, feed, and fiber crops. These viruses are spread by a diverse group of insects, predominantly by whiteflies, and are characterized by a single-stranded DNA (ssDNA) genome coding for four to eight proteins that facilitate viral infection. The most effective means to managing these viruses is through an integrated disease management strategy that includes virus-resistant cultivars, vector management, and cultural practices. Dynamic changes in this virus family enable the species to manipulate their genome organization to respond to external changes in the environment. Therefore, the evolutionary nature of geminiviruses leads to new and novel approaches for developing virus-resistant cultivars and it is essential to study molecular ecology and evolution of geminiviruses. This review summarizes the multifunctionality of each geminivirus-encoded protein. These protein-based interactions trigger the abrupt changes in the host methyl cycle and signaling pathways that turn over protein normal production and impair the plant antiviral defense system. Studying these geminivirus interactions localized at cytoplasm-nucleus could reveal a more clear picture of host-pathogen relation. Data collected from this antagonistic relationship among geminivirus, vector, and its host, will provide extensive knowledge on their virulence mode and diversity with climate change

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ABSTRACT

During plant-pathogen interaction, plant exhibits a strong defense system utilizing diverse groups of proteins to suppress the infection and subsequent establishment of the pathogen. However, in response, pathogens trigger an anti-silencing mechanism to overcome the host defense machinery. Among plant viruses, geminiviruses are the second largest virus family with a worldwide distribution and continue to be production constraints to food, feed, and fiber crops. These viruses are spread by a diverse group of insects, predominantly by whiteflies, and are characterized by a single-stranded DNA (ssDNA) genome coding for four to eight proteins that facilitate viral infection. The most effective means to managing these viruses is through an integrated disease management strategy that includes virus-resistant cultivars, vector management, and cultural practices. Dynamic changes in this virus family enable the species to manipulate their genome organization to respond to external changes in the environment. Therefore, the evolutionary nature of geminiviruses leads to new and novel approaches for developing virus-resistant cultivars and it is essential to study molecular ecology and evolution of geminiviruses. This review summarizes the multifunctionality of each geminivirus-encoded protein. These protein-based interactions trigger the abrupt changes in the host methyl cycle and signaling pathways that turn over protein normal production and impair the plant antiviral defense system. Studying these geminivirus interactions localized at cytoplasm-nucleus could reveal a more clear picture of host-pathogen relation. Data collected from this antagonistic relationship among geminivirus, vector, and its host, will provide extensive knowledge on their virulence mode and diversity with climate change.

Keywords: Geminiviruses, virus-host interaction, plant signaling, viral suppressors, resistance

INTRODUCTION

Geminivirus is the second largest family in plant viruses that constitute either single genomic component (DNA A; monopartite) or two i.e., DNA A and B (bipartite) molecules. The size ranges from ~2.7-3.0 kb which is processed into dsDNA after using replication machinery inside the host nucleus. The geminiviruses encode only 5-7 proteins to interact with a host for its replication, transcription and movement across different plant species (Hanley-Bowdoin et al., 2013) through their insect vector (Gutierrez, 1999; Mansoor et al., 2003). Based on genome organization, host types and insect vector, International Committee on Taxonomy of Viruses (ICTV) has classified *Geminiviridae* family into nine genera earlier. Then five more genera were added and total fourteen genera namely, Becurtovirus, Begomovirus, Capulavirus, Citodlavirus, Curtovirus, Eragrovirus, Grablovirus, Maldovirus, Mastrevirus, Mulcrilevirus, Opunvirus, Topilevirus, Topocuvirus and Turncurtovirus are reported (Adams et al., 2013; Roumagnacet al., 2015; Varsani et al., 2017; Zerbini et al., 2017). Among all, Capulavirus and Grablovirus are characterized based on their infection through an insect vector aphid and alfalfa treehopper (Bahder et al., 2016). However, members belonging to the *Mastrevirus* and *Begomovirus* are widely studied at genome level producing different symptoms such as leaf streaking and mild curling, retarded growth in monocots where dicots shows severe curling and crumpling on leaf surface, yellowish spots with swelling in leaf vein (Rogers et al., 1986; Sunter et al., 1987; Boulton, 2002; Inoue-Nagata et al., 2016).

Begomoviruses have been reported from both old world (OW) and new world (NW) that harbors more than 445 virus species transmitted through an insect vector Bemisia tabaci (Nawaz-ul-Rehman & Fauquet, 2009; Zerbiniet al., 2017) Studying wide range of geminivirus affected crops associated with B. tabaci infection had become a serious pest to cause begomovirus infection in beans, cassava, cotton, cucurbits, eggplant, lettuce, pepper, okra, tomato, squash as well as broad range of weeds (Figure 1) from genera Ageratum, Asystasia, Clerodendrum, Emilia and Malvastrum (Leke et al., 2015; Zerbini et al., 2017). All these known

geminiviruses were reported by the end of nineteenth century and early era of twentieth century like cassava mosaic disease was reported in 1894 in Africa, maize streak virus in 1901 in South Africa, tobacco leaf curl disease in 1912 in Indonesia and cotton leaf curl disease in 1931 in Egyptian Sudan and Angola (Legg & Fauquet, 2004; Saeed & Samad, 2017). This 50-90% crop loss was reported based on high diversity, genetic recombination and limited knowledge on its interacting mode of action in alternative hosts. In recent years, this disease has become a severe threat to global food security in different part of Africa, Latin America and southwest America, Australia, Asia and Southern Europe (García-Andrés *et al.*, 2007; Martin *et al.*, 2010; King *et al.*, 2011).

Broadly begomoviruses can be divided into monopartite (DNA-A) and bipartite viruses (DNA-A & DNA-B) that encodes 5-8 ORFs possessing overlapping viral transcript under a strong promoter located within the intergenic region (Briddon et al., 2001). The main role of DNA-A is involved in virus replication that encodes four genes on C-sense strand including replication associated protein (C1-Rep), a transcription activator protein (C2-TrAP), a replication enhancer protein (C3-REn), a C4 protein and C5 gene (Guerrero et al., 2020, Wang & Lozano-Durán, 2023) (Brown & Bird, 1992). Additionally, coat protein and pre-coat (CP and V2) are present on V-sense strand. Later, another small hypothetical protein V3 was found in the golgi apparatus that acts as a RNA silencing suppressor ((Wang et al., 2019). The other component DNA-B functions for symptoms production and virus movement (Rogers et al., 1986; Sunter et al., 1987) and encodes movement protein (MP) from BV1 ORF and nuclear shuttle protein (NSP) from β C1 ORF on V-sense strand. The hairpin stem-loop structure consists of conserve nine nucleotides sequence (TAATATTAC) which is involved in the initiation of rolling circle amplification (RCA) (Hanley-Bowdoin et al., 1999). The OW genus is usually associated with satellite molecules referred to as alphasatellite, betasatellite and deltasatellite, and are dependent on helper virus for their replication, virus packaging (encapsidation), intracellular movement and transmission (Fauquet et al., 2005; Lozano et al., 2016). These satellites molecules encodes only one gene on V-sense and complementary strand respectively with the size of ~1.4 kb, with adenine rich region and conserve nine nucleotides forming a hairpin stem-loop structure (Briddon et al., 2004).

The bipartite virus constitutes both DNA particles in the size of 2.6-2.8 kb that are different from each other except the region of almost 200 nucleotides (common region; CR) present within the IR (Briddon & Markham, 2001). The OW viruses are different in genome organization from NW viruses due to the absence of V2 gene in NW viruses (Melgarejo *et al.*, 2013) and are classified into various strains, possessing almost 288 species (*www.ictvonline.org*).

Exploring the role of genes present in DNA-A, Rep is a highly conserved protein localizes mainly in the nucleus for viral replication and infection in multiple hosts (Elmer *et al.*, 1988), that performs a function as origin recognition protein (Fontes *et al.*, 1994) to catalyze virus replication initiation and termination step (Laufs*et al.*, 1995). Three dimensional structure of Rep shows it possess conserved catalytic domain which is highly conserved among prokaryotes and eukaryotes (Campos-Olivas *et al.*, 2002a). Likewise, most of begomo-, curto-, and topoco-viruses encodes TrAP with the same size, transcribing from promoter present within Rep gene (Dong*et al.*, 2003; Shivaprasad *et al.*, 2005) which is required for systemic infection in case of *Tomato leaf curl virus* (ToLCV) (Dry *et al.*, 1993). Whereas, bipartite begomovirus such as *Tomato golden mosaic virus* (TGMV)-TrAP transactivates CP and MP genes in viral genome (Sunter & Bisaro, 1991).

Bipartite begomoviruses including Sri Lankan cassava mosaic virus (SLCMV) and African cassava mosaic virus (ACMV) encodes C4 protein that binds with non-coding RNAs like miRNAs and siRNAs which results in a suppression of PTGS (Chellappan et al. , 2004). Subcellular localization study on C4 of East African cassava mosaic Cameroon virus (EACMCV) indicates that myristoylation motif in C4 functions mainly in virus pathogenicity and suppression of PTGS (Fondong et al. , 2007). It has the capability to bind with single stranded miRNA or siRNA to cause morphological changes in A. thaliana by inhibiting post transcriptional regulation of gene expression (Chellappan et al. , 2004; Vanitharani et al. , 2004). However, mutagenesis study on tomato yellow leaf curl virus encoded C4 protein has shown its role in stem and petioles elongation for disease symptoms (Rigden et al. , 1994; Amin et al. , 2011). Another viral suppressor V2 present on

virion sense, functions with CP for virus movement (Rojas et al., 2001). The expression analysis on CP and V2 using confocal microscopy shows CP present at the nucleus and V2 at cell periphery binds with each other for cell to cell movement (Poornima Priyadarshini et al., 2011). This CP-V2 complex produced large size aggregates in the cytoplasm and nucleus using microtubules and actin filaments to infection in tomato yellow leaf curl virus (TYLCV) (Moshe et al., 2015). Thus, V2 from tomato yellow leaf curl China virus (TYLCCNV) shows a loop formation through binding with siRNA molecules in its own sequence, indicating V2 itself interaction in cytoplasm. This self interaction of V2 act as a suppressor of RNA silencing (Zhang et al., 2012). On the other hand, CP is involved in long distance virus transmission from whitefly (Briddon et al., 1990; Harrison et al., 2002) that accumulates viral DNA in different compartments of the infected cells (Fedorkin et al., 2001). Geminiviruses have been reported to bind with several transcription factors such as NAC, WRKYs, MYC2, Myb, bZIP and TIFY4B (PEAPOD2) to monitor virus infection during host pathogen interaction. PEAPOD2 (PPD2), a transcription factor from A. thaliana binds specifically with CP promoter of TGMV and Cabbage leaf curl virus (CaLCuV). This interaction established a connection between CP and TrAP (PPD2-CP-C2) in the nucleus to enhance promoter activity for efficient virus replication and transcription (Lacatus & Sunter, 2009). It can also recognize its virus vector based on its specificity. For instance, ACMV encoded CP functions with whitefly for virus transmission. Wherein case of beet curly top virus (BCTV), it has changed the virus transmission vector as leafhopper and resulting in ACMV-BCTV:CP chimera infection in the host plant (Briddon et al., 1990).

BOX-1 Geminivirus proteins and its structure organization



Genome analysis shows betasatellite are circular ssDNA molecules of approximately 1350 nucleotides that contain conserved structures including, the adenine rich region (AR), satellite conserved region (SCR) and β C1 gene (Tan *et al.*, 1995; Saunders *et al.*, 2000). The β C1 acts as true satellite molecules and a known pathogenicity determinant that induce disease symptoms and is involved in counteracting host transcriptional gene silencing (TGS) and post-transcriptional gene silencing (PTGS) pathway (Li & Ding, 2006; Hayward *et al.*, 2009). Moreover, β C1 also augments accumulation of high levels of the helper begomoviruses (Saeed *et al.*, 2007) and regulates microRNA levels involved in the host developmental processes (Amin *et al.*, 2011). Unlike betasatellites, role of alphasatellites in begomoviruses is still in ambiguity. Due to their relevance with different viruses such as CLCuMV (Pakistan and India), TYLCV (China), AYVV (Africa and South East Asia), it has been assumed that alphasatellites are highly conserved and plays its role in RNA interference (RNAi) to weakens host defense mechanism and suppresses PTGS pathway (Nawaz-ul-Rehman *et al.*, 2010). Previous data has the evident that alphasatellite and betasatellite are found in association with monopartite begomoviruse (Lozano *et al.*, 2016) whereas deltasatellites are maintained by monopartite and bipartite begomoviruses and are considered as true satellite molecules (Fiallo-Olivé *et al.*, 2016).

Among all these crops, cassava cultivation is highly affected across Southeast Asia and Africa. The estimated

loss from ACMV-recombinants begomoviruses is about 15-28 million tons that damage up to 24% of total cassava production. This annual economic loss falls between \$1.7 and \$2.7 billion USD and showing an increase per vear (Patil & Fauquet, 2009; Tiendrebeogo et al., 2012; Chikoti et al., 2019). Another fiber producing cotton is also heavily affected by cotton leaf curl disease (CLCuD) leading to low yield and poor seed quality, resulting into a serious effects on economic growth of cotton (Gossypium hirsutum L.)(Amrao et al., 2010). On the other hand, epidemic spread of bean golden mosaic virus (BGMV) characterized by golden yellowing leaves, crumpling and blistering of the plant remains a major challenge especially in soybean, mungbean and blackgrams (Coco et al., 2013; Singh et al., 2019). Due to genetic recombination and local evolution, more than 60 species of *B.tabaci* of tomato infecting begomoviruses have been reported worldwide (Inoue-Nagata et al., 2016). Considering vegetative crop, tomato leaf curl virus has caused more than 90% fruit yield in tropical and subtropical regions including more than 20 countries of the world (Kil et al., 2016; Vaghi Medina et al., 2018; Fiallo-Olivé et al., 2019). However, it was observed that begomovirus infection in potato was caused by a *tomato yellow vein streak virus* (ToYVSV) through whitefly infected on tomato plants. This begomovirus infected in tubers of vegetative crop has become a major constraint in potato production (Souza-Dias et al., 2008; Butler et al., 2016). Due to its emerging threat to multiple hosts, geminiviruses have become a global problem in agricultural trade (Saeed & Samad, 2017). Currently, genome editing has emerged as an effective tool for desirable mutagenesis to weaken the interaction against this virus family (Zaidi et al., 2016). However, phylogenetic profiles, *in-silico* gene expression approaches and transcriptome analysis is far better option to understand geminivirus disease complex and its targeted partners in various hosts (Miozzi et al., 2014; Naqvi et al., 2019). Based on previous Protein-protein interaction (PPI) data and bioinformatics study, this geminivirus network (Figure 2) with its associated hosts proteins reveals number of possible interactions. Although geminivirus self-interaction studies could not reveal what are the host factor involved in spreading of this virus (Ramesh et al., 2017) and there is a need to investigate geminivirus interaction with its host proteins to understand this disease complex and different players involved in it which will lead the way to devise effective strategies for control of this disease (Li et al., 2017a; Wang et al. , 2018).

The trigonal relationship: Geminivirus-Insect-Plant

Geminiviruses are transmitted through different phloem feeding insects, including *Bemicia tabaci* (whitefly) and aphids, and various species of treehoppers and a leafhopper (Lozano-Duran *et al.*, 2011a; Roumagnac *et al.*, 2015; Bernardo *et al.*, 2016; Susi*et al.*, 2017). Begomoviruses initiates viral infection through whitefly that has the capability to transmits more than 300 viruses (Gilbertson *et al.*, 2015), which can cause severe damage in more than 600 plant species (Polston *et al.*, 2014).

Several new species of B. tabaci has also been reported which elucidates better understanding of all biotypes to differentiate its races and their evolutionary pattern (Mugerwa *et al.*, 2018). Upon feeding, virion particles of geminivirus is ingested into the esophagus, entering to the hemolymph which transport virion particles further to the salivary glands of the *B. tabaci* (McGRATH & Harrison, 1995; Douglas, 1998; Pan *et al.*, 2017). Virus particles protects itself from degradation through binding with GroEL protein in haemolymph node (Miao *et al.*, 2016) and is later spit up with salivary secretion to the phloem cells where it ejaculates ssDNA through virions in the plant cell (Torres-delosSantos *et al.*, 2022) (Gray *et al.*, 2014; Luo *et al.*, 2019).

BOX-2 Bemisia tabaci complex and its species

Previous data shows 36 *B. tabaci* species have been identified using sequence comparison of mitochondrial cytochrome c oxidase subunit I (mtCOI) (Alemandri *et al.*, 2015). These species are classified across the globe based on their resistance to parasites, insecticide and tolerance to the temperature and later as OW and NW (Frohlich *et al.*, 1999; Kontsedalov *et al.*, 2008; Himler *et al.*, 2011). These species includes B or B2 (Middle East-Asia Minor 1-MEAM 1, Asia II 2), Q, J and L biotypes (Sub-Saharan Africa 1-7/SSA1-7, Mediterranean-MED, Indian Ocean-IO) while A, C, D, F, N, R, Jatropha and Sida biotypes belongs to the NW and New World 2 group (Berry *et al.*, 2004; Gueguen *et al.*, 2010; De Barro *et al.*, 2011; Esterhuizen *et al.*, 2013). The biotypes from OW are usually reported from Indian subcontinent and equatorial Africa

(Frohlich et al., 1999) and NW species are identified from Sub-Saharan Africa SSA1-6 (Legg et al., 2014; Ghosh et al., 2015), America (Marubayashi et al., 2013; Barbosa et al., 2014) and Asia (Asia I-IV, China 1-3, Japan) (Firdaus et al., 2013; Jiuet al., 2017). These biotypes have been found prominently in virus transmission in cotton, tomato, cassava, cucumber, eggplant, potato and beans (Legg & Fauquet, 2004; De Barro et al., 2011). This interaction harbors several endosymbiotic bacteria (Gil et al., 2004) including primary endosymbionts (*Portiera aleyrodidarum*) and secondary endosymbionts (*Arsenophonus, Cardinium, Fritschea, Hamiltonella, Rickettsia* and *Wolbachia*) (Chiel et al., 2007; Bing et al., 2013). The primary endosymbionts provided essential nutrients and amino acids for insect life cycle (Baumann, 2005; Bing et al., 2013) where secondary amino acids plays its part in amino acids composition during metabolism (Gottlieb et al., 2010).

Virus movement from Insect-to-plant through Coat protein (CP)

The mutual relationship of *B. tabaci* with different hosts indicates virus CP and *B. tabaci* genes possess a strong binding for virus transmission. GroEL (63 kDa) is one of the well-studied protein from insect midgut and hemolymph nodes (Morin et al., 2000). The CP of TYLCV has been found in interaction with GroEL produced by secondary endosymbiont Hamiltonella defense (Morin et al., 1999; Gottlieb et al., 2010). Later, in vitro and in vivo study was performed on GroEL from Portiera and Arsenophonus with CP of *cotton leaf curl Rajastan virus* (CLCuRV). This data suggested that GroEL from Arsenophonus binds with CP of CLCuRV for virus transmission in cotton (Rana et al., 2012). This interaction of GroEL with NLS region of CP protects the virus from degradation in numerous virus vectors (Yaakov et al., 2011). Upon different temperature variants, it was found that B. tabaci produced heat shock protein (HSP) for its survival and reproduction (Cuiet al., 2008). Experimental validation from *in-vivo* and *in-vitro* study shows heat shock protein 70 (hsp70) from B. tabaci interacts with CP encoded by Squash leaf curl virus(SLCV) and TYLCV (Götz et al., 2012). The hsp70 from tomato has also been found in interaction with CP of TYLCV in the cytoplasm and nucleus, required for intracellular movement of the virus. Another report from yeast two hybrid and pull down analysis shows small heat shock proteins such as shsp16 interacts with CP of TYLCSV that plays its role in virus transmission (Götz et al., 2012). Further, it was studied that silencing of cyclophilin B (CypB) gene, peptidoglycan recognition protein impairs the insect normal growth, its structure development and transmission ability of begomoviruses (Kanakala & Ghanim, 2016; Wang et al., 2016). This cyclophilin protein has been found in interaction with TYLCV, colocalized mainly in the midgut, eggs and salivary glands. Moreover, this CypB protein binds with hsp70 in B. tabaci midgut that mediates the viral transmission of TYLCV (Kanakala et al., 2019). Recent study on hsp40, hsp70 and hsp90 from MED species demonstrate that hsp90 increases survival rate of B. tabaci nymph and adults under high temperature stress (Jianget al., 2017) and CP binds with hsp70 and hsp90 proteins to initiate interaction with plant chaperon protein network for a stable transmission of the virus from cell to cell and across the membrane (Gorovits & Czosnek, 2017)(Farooq et al., 2022).

For cellular movement of monopartite begomoviruses, CP possess nuclear localization signal (NLS) and leucine-rich nuclear export signal (NES) to transport viral DNA between cytoplasm, the nucleus (typically nucleolus) and cell periphery for cell-to-cell export (Unseld *et al.*, 2001; Sharma & Ikegami, 2009). For this systemic spread, virus particle uncoated itself in the cytoplasm as a ssDNA where it moves into the nucleus through DNA-bound CP. This shuttling of CP-DNA complex from cytoplasm into the nucleus and vice versa was observed in *Bhendi yellow vein virus* (BYVV). The BYVV encoded betasatellite protein β C1 protein and CP binds with karyopherin a1 (Kapa1) for cytoplasm-nucleo cytoplasmic trafficking. For cell-to-cell movement, V2 and C4 binds with CP-DNA complex to shuttle it to the plasmodesmata at the plasma membrane through endoplasmic reticulum. In case of bipartite begomoviruses such as *squash leaf curl virus* (SLCuV) and mungbean yellow mosaic India virus (MYMIV), CP possess NLS at N-terminal that enforces viral ssDNA particle to move across nucleus and cytoplasm through interaction with Importin α (Imp α) (Qin *et al.*, 1998; Guerra-Peraza *et al.*, 2005).

Currently, several candidate whitefly proteins have been identified which interact with CLCuMuV-AV1, including a vacual protein sorting-associated protein (Vps) twenty associated 1 (Vta1). Apparently,

CLCuMuV-AV1 showed a strong interaction with Vta1 of Asia II 1 whiteflies. Furthermore, acquisition and transmission of CLCuMuV was enhanced by RNAi-mediated knock-down of Vta1 gene in Asia II 1 whiteflies (Chi *et al.*, 2021, Farooq et al., 2022). Another study showed that BTB/POZ (BR-C, ttk and bab)/(Poxvirus and zinc finger) domain is also involve in protein-protein interaction (Farooq et al., 2022).

In plants, ssDNA virus utilize DNA polymerase machinery to produce dsDNA molecule, that transcribe itself with the host RNA polymerase II to start virus replication in the nucleus (Fedorkin *et al.*, 2001). Apart from CP, B. tabaci possess a hairy and enhancer of split homolog-1 (HES1) protein that has the capability to bind with intergenic region (IR) that promotes DNA transcription and accumulation of tomato yellow leaf curl China virus (TYLCCNV) during transmission phase (Corrales-Gutierrez *et al.*, 2020).

Plant nucleus and Rep-REn complex

The Rep has been found in interaction with several host proteins to facilitate viral replisome complex for DNA replication and repair system, proper cell division and signal transduction (Campos-Olivas et al. 2002). Another viral protein REn modulates Rep binding with the host protein in the nucleus, to regulate DNA repair and recombination leading to the controlled cell cycle machinery (Chodon et al., 2022) (Hanley-Bowdoin et al., 2004). Initially, Rep binds with a highly conserved plant protein proliferating cell nuclear antigen (PCNA), that overexpresses transcription level of geminivirus in infected cells (Nagar et al., 1995). A large subunit, replication factor C complex modulates PCNA binding with Rep to hold ssDNA for rolling circle-replication (Luque et al., 2002; Bagewadi et al., 2004). Generally in plants, PCNA sumoylation is accumulated with SUMO E2 conjugation enzyme (SCE1) that regulates PCNA activity by controlling post translational modifications. Rep interferes with PCNA sumoylation in infected cells and disturbs the SUMO activity. Sumoylation is like ubiquitination process, depending on SUMO-activation enzyme (E1), which is mediated by SUMO-conjugating enzyme (E2-SCE1) and transferred finally to the SUMO ligase enzyme (E3) for ligation. PCNA interaction with Rep protein interferes with all these sumovlated proteins in the nucleus that results in a multiplication of viral DNA (Gareau & Lima, 2010; Cappadocia & Lima, 2018). REn homo-oligomerizes in the nucleus to enhance the binding of Rep with PCNA in RCR process (Castillo et al., 2003; Settlage et al., 2005).

For DNA repair and DNA recombination, MYMIV encodes Rep that utilizes its DNA-dependent ATPase activity after binding with host RAD54 protein. It binds with RAD54 for Rep nicking activity by mediating helicase activity in recombination-dependent replication process (Kaliappan*et al.*, 2012). This MYMIV-Rep has also been reported to bind with minichormosome maintenance 2 (MCM2), a DNA replication factor in plants which is involved in eukaryotes genome pre-replication process. Rep tightly engaged this MCM2 protein to utilize this conserved eukaryotic protein machinery for virus replication (Kaliappan *et al.*, 2012). Thus, interaction of Rep with PCNA and RAD54 makes viral replication activity successful in infected cells (Castillo *et al.*, 2003; Richter *et al.*, 2015). Using plant methylation machinery, Rep displace the ring type histone H3 from viral DNA which promotes virus replication (Kong & Hanley-Bowdoin, 2002). *Chilli leaf curl virus* (ChiLCV) encoded Rep binds with histone H2B monoubiquitination machinery that results in a successful transcription of the viral gene. Rep-H2B interaction promotes the expression of H2K4me3 on viral chromatin with the help of UBC2 and HUB1 (Kushwaha*et al.*, 2017).

During cell division, retinoblastoma related protein (RBR) is essentially required to maintain stem cells and cell differentiation in plants. RBR protein reprograms cell cycle using E2F transcription factor, which eventually suppress the function of replication associated genes in the host. *Mastrevirus*, *Curtovirus* and *Begomovirus* Rep binds with this RBR-E2F complex and disrupts late G1 phase and S phase in cell cycle (Kong *et al.*, 2000; Desvoyes *et al.*, 2006). The Rep-REn complex also binds with retinoblastoma-related protein (pRBR) in TYLCV and *tomato golden mosaic virus* (TGMV) for positive cell division of geminivirus in infected cells (Hanley-Bowdoin *et al.*, 2004; Settlage *et al.*, 2005). Geminivirus Rep-interacting kinase (GRIK), a Ser/Thr kinase, mainly connects plants cell cycle to Ubc9, an important component in sumoylation process (Ilyina & Koonin, 1992; Shen *et al.*, 2009). This GRIK proteins functions with geminivirus Rep-interacting motor protein (GRIMP), a kinase protein that has a role in spindle formation in cell cycle (Kong & Hanley-Bowdoin, 2002). Thus, TGMV encoded Rep interaction with GRIK and GRIMP prevents

its entry into mitotic phase and delays sucrose non-fermenting kinase 1 (SnRK1) phosphorylation in cell signaling mechanism (Shen & Hanley-Bowdoin, 2006; Glab *et al.*, 2017). This provides a source of energy to geminivirus during plant metabolism. Mainly, SnRK1 protein has been found in various physiological processes including regulation of energy metabolism and stress signaling during biotic and abiotic stresses by phosphorylating both pathogen and host proteins (Hulsmans *et al.*, 2016; Wurzinger *et al.*, 2018). Recently, it was found that SnRK1 phosphorylates Rep protein of *tomato mottle virus* and *tomato yellow leaf curl virus* (TYLCV) through serine-97 residue. It results into a reduced DNA binding and interferes with DNA replication and plays a key role against geminivirus infection (Shen *et al.*, 2018).

In past, REn has also shown its independent interaction with several host proteins for virus replication. REn encoded by *tomato yellow leaf curl Sardinia virus* (TYLCSV) binds with lactoylglutathione lyase (GLO1) enzyme and Coatomer delta subunit (deltaCOP) in glyoxalase pathway to enhance virus replication (Hulsmans *et al.*, 2016; Sankaranarayanan *et al.*, 2017). In case of ToLCV, REn has been found in interaction with *Solanum lycopersicum* encoded NAC1 (SINAC1) domain in the nucleus. NAC domain is a transcription factor which is involved in plant development such as shoot meristem (Sablowski & Meyerowitz, 1998; Zhang *et al.*, 2018) and regulates auxin level in lateral rooting system (Xie *et al.*, 2000; Chen *et al.*, 2016). Moreover, SINA3, a member of Seven In Absentia family and a ubiquitin E3 ligase enzyme promotes NAC1 degradation through polyubiquitination process (Miao *et al.*, 2016). REn protein overexpresses SINA3, which upregulates viral DNA accumulation in the nucleus of the infected leaf cells and results into enhanced virus replication in several plants (Selth *et al.*, 2005; Huang *et al.*, 2013; Miao *et al.*, 2016).

Cross talk between plant signaling mechanism and TrAP

Overexpression of TrAP delays plant development cycle and disturbs hormone signaling causing cell death in host cells (Rajeswaran *et al.*, 2007). Related to the host-pathogen interaction study, TrAP has a central role in jasmonic acid, salicylic acid, auxin and cytokinin responsive pathways (Park *et al.*, 2004; Chen *et al.*, 2010; Yang *et al.*, 2011). During jasmonic acid (JA) mediated signaling, TrAP deregulates a cascade of protein network to suppress defense and secondary metabolism under biotic and abiotic stresses (Buchmann*et al.*, 2009; Rosas-Díaz *et al.*, 2016). COP9-signalosome (CSN) complex regulates ubiquitine/26 proteosome pathway for light inducive responses and hormonal balance in a cellular machinery (Wei*et al.*, 2008). TrAP binds with one of the catalytic subunits CSN5 that removes the ubq-like protein RUB from Cullin subunit and cause abnormalities in E3 ligase. This E3 ligase belongs to the SCF (SKP1, CUL1/CDC53, F-box proteins) family in ubiquitination process that inhibits jasmonate signaling (Lozano-Duran *et al.*, 2011b; Nezames & Deng, 2012). A ubiquitin E3 ligase encoded by an imprinted gene Variant in Methylation (VIM) regulates the expression of DNA methyltransferases CMT3 and MET1 in plants. TrAP-REn complex encoded by BSCTV downregulates the expression of VIM5 gene that suppresses the proper establishment of transcription and post translational stage after degrading MET and CMT3. Thus, inducing the early activation of viral suppressor protein TrAP and REn maintains the function of Rep during infection (Chen *et al.*, 2020).

During DNA methylation, TrAP binds and overexpresses adenosine kinase (ADK) in infected cells (Wang et al., 2003). ADK plays an important role in adenosine salvage pathway and maintains intracellular AMP level (Moffatt et al., 2002; Kwade et al., 2005). Binding of TrAP with ADK also inhibits the role of S-adenosyle methionine decarboxylase 1 (SAMDC1) in plant methyl cycle (Zhang et al., 2011). SAMDC (S-Adenosyl-methionine decarboxylase) is a known proenzyme which is involved in various plant metabolic and developmental processes (Shibata et al., 2003). TrAP binds directly with PEST sequence of SAMDC1 that degrades its production to suppress methylation cycle (Zhang et al., 2011). It results into increasing level of cytokinin which enhance the susceptibility to geminivirus infection (Wang et al., 2005; Baliji et al., 2010). Overall, interaction of ADK, GRIK-SNF1 with Rep and TrAP provides a suitable environment for geminivirus replication and its transcription (Ascencio-Ibánez et al., 2008; Hanley-Bowdoin et al., 2013).

TrAP overexpresses histone protein kryptonite (KYP), causing epigenetic modification in histone methylation and turn off the host defense machinery (Castillo-Gonzalez *et al.*, 2015; Sun *et al.*, 2015). Kryptonite protein is required for DNA methylation that maintains TGS in plants. To overcome this methylation machinery, TrAP disturbs plant metabolism through interaction with calmodulin and calmodulin-like proteins. This protein family regulates intracellular Ca+2 concentration and maintains protein network involved in calcium dependent channels or pumps (Zeng *et al.*, 2015). TGMV encoded TrAP increases the level of rgsCaM in infected plants of *A. thaliana* and *N. bethamiana* to destabilize plants TGS and PTGS pathway (Chung *et al.*, 2014). Altogether, TrAP hijacks proper function of argonuate family and dicer-like proteins that effects the production of siRNA in RNAi pathway (Yang *et al.*, 2013). However, all these host proteins that interacts and overexpressed by TrAP mainly functions in hormone signaling (Ascencio-Ibánez *et al.*, 2008; Dogra *et al.*, 2009), reprogrammed cell death (Trinks *et al.*, 2005), silencing (Raja *et al.*, 2008; Li *et al.*, 2017a) and defense related mechanism (Hanley-Bowdoin *et al.*, 2013; Ramesh*et al.*, 2017). Geminivirus proteins illustrated in Figure 3 shows their role in nucleus and cytoplasm.

Inter/intra cellular movement of virus and C4/C5 role

Among all proteins, C4 is one of the proteins which is studied at a limited level to date. This smallest protein of about 10 kb present in a compelementary strand along with C1/rep was involved in symptom induction during the infection (Zhang *et al.*, 2018). It is encoded by *Begomoviruses*, *Curtoviruses*, *Maldovirus*, *Opunvirus*, *Topocovirus*, and *Turncurtovirus*. Whereas, *Becurtovirus*, *Mastrevirus* and *Mulcrilevirus* C4 is homologous and possess similar features to the C3 of *Capulavirus*, *Grablovirus* and *Topilevirus*(Corrales-Gutierrez *et al.*, 2020). Previous studies showed that C4 belonging to the monopartite geminiviruses possess a role in disease symptoms (Stanley & Latham, 1992; Gopal *et al.*, 2007) while C4 gene encoded by bipartite viruses does not play role in symptom production during geminivirus infection (Hoogstraten *et al.*, 1996; Bull *et al.*, 2007). However, the positive selection and intrinsic disordered nature of C4 provides multifunctional characteristics to this protein to cause symptoms in mono- and bipartitite viruses (Mills-Lujan *et al.*, 2015).

The C4 protein was localized throughout different cell compartments including plasma membrane (PM), plasmodesmata (PD) and chloroplast for cell-to-cell virus movement. PM/PD localization is dependent on myristoylation motif at N-terminus which is essential for full TYLCV infectivity. The phosphorylation and myristoylation of C4 enables it to bind ss and dsDNA to export it into the cell periphery during intra cellular movement. This intracellular feature of C4 was localized through East African cassava mosaic Malawai virus (EACMMV) and BCTV infection (Fondong *et al.*, 2007; Teng *et al.*, 2010). For intercellular movement, C4 binds with V2 protein incorporated with CP to transport viral DNA of TYLCV (Rojas *et al.*, 2001). This C4-mediated virus movement is promoted through interaction with exportin α XPOI, a nuclear cargo protein that functions as a nuclear exporter for virus movement across the cell for TYLCCNV (Mei *et al.*, 2018b).

Interference at transcriptional level effects host defense mechanism and its development during pathogen attack. Restricting RNA silencing mechanism via RNA mediated DNA methylation enhances viral infection throughout cell to cell in the plants (Corrales-Gutierrez et al., 2020). It was postulated that C4 interferes RISC complex to suppress gene silencing by regulating dsRNA molecules (short and long RNA) and siRNA in the host (Amin et al., 2011). Recently, C4 oftomato leaf curl New Dehli virus (ToLCNDV) showed interaction and colocalization with AGO4 in the nucleus, suppressing RNA silencing network to regulate cytosine methylation of the viral genome (Vinuthaet al., 2018). S-acylation is a kind of lipid modification which regulates normal leaf and root development by regulating the expression of RHO proteins (Vinutha et al., 2018) as well as calcineurin B-like protein members during signal transduction (Vinutha et al. 2018). It was noted that S-acetylated form of C4 from Beet severe curly top virus (BSCTV) bind with CLAVATA 1 (CLV1) to suppress WUSCHEL (WUS) expression that leads to the abnormal meristem and shoot development in A. thaliana and N. benthamiana (Li et al., 2018). The same C4 binds with Pep1 Receptor 2 (PEPR2) to trigger its release from plasma membrane and cause its virulence function. Moreover, CLCuMV encoded C4 interacts with S-adenosyl methionine synthetase (SAMS) enzyme. This C4-SAMS binding inhibit its enzymatic activity, providing methyl group to DNA or RNA in methylation cycle which leads to the improper functioning of plants silencing pathway (Ismayil et al., 2018).

The C4 interacts with several host proteins present in brassinosteroid (BR) regulated signal transduction mechanism. Shaggy related protein kinase family (SKs) and receptor like kinases (leucine rich repeat

receptor-like kinase-RLK/LRR) controls leaf development and growth under different physiological condition in BR-signaling (Chevalier & Walker, 2005). Several RLKs are involved to spread viral infection across different cell compartments via interaction with C4, localized in plasma membrane and chloroplast (Rosas-Diaz et al., 2018). It binds with two RLKs such as Flagellin sensing 2 (FLS2) and brassinosteroid insensitive 1 (BRI1) in CLTV1 based signaling mechanism to impair RLKs clade in plasma membrane transduced signaling for abnormal plant development (Garnelo Gómez et al., 2019). Thus, receptor like kinases and shaggy related kinases regulates signal transduction from cell exterior to the cell interior and responds to the environmental changes (Piroux et al., 2007). The enhancement of viral infection is further studied with shaggy related kinases. Phosphorylation of C4 belonging to curtoviruses through shaggy related kinase Brassinosteroid insensitive 2 (BIN2) and Glycogen synthase kinase 3 (GSK3) showed leaf abnormalities in A. thaliana (Lozano-Duran et al., 2011b; Youn & Kim, 2015). This C4 phosphorylation was further determined in BCTV that induced hyperplasia and altered leaf development through interaction with SK21 and SK23 (Mills-Lujan et al., 2015). This C4 suppressing activity with SKs results into a negative role on transcription factors like BES1/BZR1 that downregulates a cascade of genes network involved in pollen development and male fertility (Biet al., 2017). This C4-SKs interaction also impairs phosphorylation dependent degradation process of the cyclin-CDK complex through its substrate Cyclin D1.1. Thus, high accumulation of CycD1.1 induces abnormal cell division caused by tomato leaf curl Yunnan virus (TLCYnV)-C4 and showed severe developmental abnormalities in N. benthamiana leaves. This TLCYnV-encoded C4 binds with SKn that increases the virualnee effect of TYLCCNV to cause diverse symptoms in the plants (Mei et al., 2018).

Recent data also showed that C4 belonging to the Ageratum leaf curl Sichuan virus (ALCSsV) inhibits gibberellin (GA) signaling hormone which is involved in plant growth and defence system. This ALCSsVencoded C4 interaction with GA associated genes in N. benthamiana interferes plant signaling pathway and develop virus symptoms during the infection (Li et al., 2018). Considering tomato yellow leaf curl disease (TYLCD), which effects tomato crop worldwide at large scale (Anfoka et al., 2016; Aguilar et al., 2017). Recently, this virus showed devastating improvement in drought tolerance for tomato and N. benthamiana (Gorovits et al., 2019). Since various reports have provided the evidences about viral infection to enhance plant tolerance against abiotic stresses. In order to answer this question, C4 expression was studied in transgenic A. thaliana plants that promotes drought tolerance through hormone abscisic acid (ABA) signaling (Corrales-Gutierrez et al., 2020). To determine the role of geminiviruses during abiotic stress, C4 has shown its role for xylem patterning in the root of plants. Proper xylem patterning is done through RLKs BAM1 and BAM2 (Barley and meristem 1,2), that regulates controlled production of miRNAs during intracellular trafficking (Fan et al., 2019). Previously, these BAM1 and BAM2 receptor like kinases were identified as an interactor of C4 protein at PM and PD that interferes with cell-to-cell spread of RNAi resulting in a deformation of xylem tissues required for proper leaf growth (Rosas-Diaz et al., 2018). Moreoever, C4 was found as a pathogenic determinant based on the interaction with multiple members of BAM including BAM1-3, brassinosteroid receptors BRL3, and brassinosteroid insensitive 1 BRI1 in several viruses (Li et al., 2018; Garnelo Gómez et al., 2019). Summarizing the role of C4 as manipulates host defence mechanism, induces the symptoms and act as silencing suppressor. This type of study highlights the multifunction of C4 protein during geminivirus infection Figure 4.

In addition to the C4, there is another ORF present on complementary sense strand referred to as C5 which encodes for almost 105 amino acids in downstream of REn protein. The C5 ORF is present in selected monoand bipartite begomoviruses (Ilyas *et al.*, 2010). Though role of C5 in geminivirus is less studied and its function still needs to be investigated. Mutagenesis study on C5 encoded by OW bipartite begomoviruses including MYMIV (Raghavan *et al.*, 2004), *Watermelon chlorotic stunt virus* (WmCSV) and *tomato chlorotic mottle virus* (ToCMoV) indicates that it does not constitute any role in geminivirus infection and its enhancement (Kheyr-Pour*et al.*, 2000; Fontenelle *et al.*, 2007). A previous report on C5 null mutant shows tomato leaf deformation virus (ToLDeV) from NW accumulate high level of virus DNA in infectious plants and enhance symptoms in the presence of ToLDeV-C5 (Melgarejo *et al.*, 2013). Another study on MYMIV-C5 shows C5 typically suppresses single stranded RNA fragment of either miRNA or siRNA in RNA-induced silencing pathway to modulates antiviral defense strategy in its host, suggesting C5 role as a pathogenicity determinant in viral infection (Li *et al.*, 2015). Subcellular localization studies shows that C5 accumulates heavily in the nucleus and cytoplasm of the *N. benthamiana* that moves along the microfilaments to localize in plasmodesmeta (PD) for the intercellular movement of the virus. This virus movement is fascilitated through C5 interaction with another geminivirus protein V2 to make C5-V2 complex in the cytoplasm and PD (Wang *et al.*, 2019).

Plant defense mechanism and V2 protein

V2 act as a silencing suppressor against host cellular defense mechanism and has a significant role in host methylation cycle by inhibiting silencing signals. It impairs the binding complex of suppressor of gene silencing 3 (SGS3) with RDR6 and DCLs to repress host antidefense mechanism (Glick *et al.*, 2008). SGS3 is required for sense-RNA induced PTGS (S-PTGS) during RNA-triggered systemic silencing in plants. Inhibition of S-PTGS pathway promotes geminivirus infection. However, overexpression of calmodulin proteins (CaM) degrades SGS3 accumulation in the cytoplasm and downregulates phosphatidylinositol 3-kinase (PI3K) complex in autophagy pathway, resulted into an inhibition of geminivirus infection (Li *et al.*, 2017). In nature, RNA-directed DNA methylation (RdDM) mediated TGS pathway responds to the antiviral defense mechanism in plants. Recently, V2 of CLCuMV has shown interaction with AGO4 in *N.benthamiana* to suppress RdDM mediated TGS pathway. Silencing of RdDM component enhanced the viral methyl cycle to encounter geminivirus infection (Wang *et al.*, 2019). Simultaneously, V2 encoded by TYLCV interacts with histone deacetylase 6 (HDA6) in conserved cytosine DNA methylation process that impairs the corporation of HDA6 with methyltransferase 1 (MET1). This V2-HDA6 binding enhances viral genome methylation after inhibiting TGS of infected plant cells (Wang *et al.*, 2018).

Papain-like cysteine proteases (PLCPs) family that enhances plants immunity system based on hypersensitive response (HR). V2 inhibits the enzymatic activity of PLCP members that delays the normal cell death response. One of the member CYP1, a known pathogen inhibitor in plants against viruses, bacteria and fungi (Avrova *et al.*, 1999; Van Der Hoorn, 2008), is found in interaction with V2 of TYLCV that modulates RNAi machinery to spread virus in tomato. However, enzymatic activity on CYP1-V2 shows V2 effects directly this cysteine protease protein but this interaction did not impart its role in post translational modifications. Recent study on V2 encoded by *tomato leaf curl Gujrat virus* (ToLCGV) enhanced methylation activity of the virus promoter which produced severe symptoms due to the binding with RNA-dependent RNA polymerase 1 (RDR1) (Bar-Ziv *et al.*, 2015).

Pathogenicity through Alpha- and Betasatellites

Alphasatelites belonging to the family geminivirus are characterized as Geminialphasatellitinae to differentiate it from Nanoalphasatellitinae, a subfamily of alphasatellites in Nanoviruses (Briddon et al., 2018). Past data lack knowledge about biological role of alphasatellites, and are either involved to enhance virus accumulation or reduce viral symptoms during the infection (Mar et al., 2017). A clear reduction in virus infection was observed in CLCuRaV-betasatellite infected N. benthamiana leaves, showing Rep gene present in alphasatellite functions with betasatellites for symptom enhancement (Nawaz-ul-Rehman & Fauquet, 2009). Due to their relevance with different viruses such as CLCuMV (Pakistan and India), TYLCV (China), AYVV (Africa and South East Asia), it has been assumed that alphasatellites are highly conserved and plays its role in RNAi to weakens host defense mechanism and suppresses PTGS pathway (Nawaz-ul-Rehman et al., 2010). However, a recent report has shown its positive role in host defense mechanism. Alphasatellite associated with TYLCCNV positively upregulates host genes to provide resistance against this virus in the presence of betasatellites. Silencing of TYLCCNA responsive differentially expressed genes (DEGs) accumulates high DNA amount and cause severe symptoms during the infection. Whereas, over expression of these DEGs reduced the virus infection (Luo *et al.*, 2019). The N -acetylation of TYLCCNB- β C1 is crucial for its self-interaction in the nucleus and viral pathogenesis. Removal of N -acetylation of TYLCCNB- β C1 could attenuate virus-induced symptoms and lead to ubiquitination and degradation of TYLCCNB- β C1 (Wang et al., 2023).

The interference of betasatellite encoded β C1 in DNA methylation, ubiquitination and nutrients metabolism

shows its function in the nucleus as well as cytoplasm for virus movement and transmission (Jia et al. 2016). Ubiquitination is a three-step enzymatic reaction to activate, conjugate and then ligation of ubiquitin protein with its substrate during PTGS pathway. E2 and E3 ligase proteins are very crucial in its function for determination of specific substrate for its targeted protein (Catic & Ploegh, 2005; Marino et al., 2012). Co-localization and yeast two hybrid study shows cotton leaf curl Multan betasatellite (CLCuMB) interfere with one of the E2 conjugated protein in S. lycopersicum (SIUBC3) during 26S/proteasome pathway to accumulate high DNA level of CLCuMV (Eini et al., 2009). Also, CLCuMB interacts with E3 ligase protein, known as S-phase kinase associated protein (SKP1) during ubiquitination. SKP1 is one the most abundant protein produced during ligation step in ubiquitin pathway. This protein acts as a bridge between two E3 ubiquitin ligase proteins Cullin 1 (CUL1) and F-box to form a SCF complex which is involved in plants hormone signaling (Kepinski & Leyser, 2005; Xu et al., 2009; Hua & Vierstra, 2011). The binding of β C1 with either SKP1 or CUL1 impairs the SCF complex that results into a retarded leaf growth and abnormal development with severe disease symptoms (Jia et al., 2016). At the same time, β C1 also interacts with E3 ligase protein in the cytoplasm. TYLCCNV encoded β C1 binds with and overexpresses Ring Finger Protein (RFP1) in tobacco plants, suggesting NtRFP1 is involved in degradation of β C1 through ubiquitin-26S proteasome system (UPS) and attenuate disease symptoms during geminivirus infection (Shen et al., 2016).

It was observed that C2-SAMDC1 interaction facilitates the binding of β C1 with another methyl cycle enzyme SAHH (S-adenosyl homocysteine hydrolase). TYLCCNB interferes with DNA methylation by inhibiting SAHH activity and enhances successful virus replication and transcription in the nucleus (Yang *et al.*, 2011). This complex C2-SAMDC1- β C1-SAHH further mediates the binding of Rep with SnRK1 and GRIK protein to suppress DNA methylation in the host (Shen & Hanley-Bowdoin, 2006; Ascencio-Ibánez *et al.*, 2008). A comprehensive report of SnRK1 binding at domain level has been studied with β C1 of cotton leaf curl Multan virus (CLCuMV) (Kamal et al., 2019b). SnRK1 binds with and phosphorylates TYLCCNB protein in tomato and attenuates geminivirus infection (Shen *et al.*, 2011).

Signaling pathways have evolved in plants that sense the invading pathogen and initiate appropriate defense responses. Asymmetric leaves 1 (AS1) and Asymmetric leaves 2 (AS2) interacts with each other that forms a complex AS1-AS2 and regulates normal leaf development in A. thaliana. β C1, associated with TYLCCNV interacts directly with AS1 gene and partially with AS2 gene. This β C1/AS1-AS2 interaction prevent normal leaf development and usurp cellular resources by interfering with jasmonic acid (JA) responsive genes to induce infection by insect vector B. tabaci (Yang *et al.*, 2011). Homo-oligomerization of transcription factor MYC2 is involved in terpene biosynthesis. β C1 interferes directly with MYC2 expression which down-regulates terpene synthase (TPS) gene and disrupts transcription level of JA responsive genes (Li *et al.*, 2014).

Calmodulin (CaM) and calmodulin like protein (CML) is a highly conserved protein family that provides calcium as a source of energy and triggers immune system by monitoring intracellular Ca+2 concentration. Geminiviruses encodes VSRs (viral suppressor of RNA silencing) in response to the ESRs (endogenous suppressor of RNA silencing) present in the host to suppress PTGS against geminiviruses (Li *et al.*, 2014). The VSR β C1 encoded by TYLCCNV overexpresses NbrgsCaM to target RNA-dependent RNA polymerase (RDR6) which is involved in RNA silencing pathway. The β C1-NbrsgCaM binding provides energy supplement to geminivirus which weakens antiviral system in the host by repressing RDR6 expression. CLCuMV associated β C1 binds with CML11 in G. hirsutum ultimately provides calcium as a nutrient source for virus pathogenicity and symptom enhancement (Kamal *et al.*, 2019).

Virus trafficking using DNA B- MP and NSP in Bipartite begomoviruses

Bipartite begomoviruses encodes two proteins NSP and MP, non-structural proteins that facilitates virus movement between the cytoplasm and the nucleus as well as cell to cell movement (Krenz *et al.*, 2012). Both proteins are present on DNA-B component. NSP encodes almost 281 amino acid with size of 31 kDa while MP encodes 268 amino acid with expected size of 30.5 kDa (Noueiry *et al.*, 1994; Frischmuth*et al.*, 2007). It has been studied that NSP function is similar to CP and MP functions mainly just like V2 protein.

However, NSP and MP plays its role in case of bipartite viruses (Poornima Priyadarshini et al., 2011).

NSP which promotes intracellular movement of the virus between nuclei and the cytoplasm, induces AS2 gene expression. AS2 gene is involved in mRNA decapping activity for degradation and endogenous suppression of virus silencing. NSP deregulates AS2 function by its forceful export from nuclei to cytosol where it binds with DCP2, a protein subunit that controls 5' cap structure for mRNA stability during translation. This NSP-AS2-DCP2 complex reduces siRNA production that weaken the antiviral defense system in plants (Ye et al. , 2015). On the other hand, MP can bind with heat shock protein 70 (HSP70) (Krenz et al. , 2010) and SYTA (Lewis & Lazarowitz, 2010; Uchiyama et al. , 2014), regulates virus transport with chaperone like proteins.

Furthermore, CabLCV NSP directly interacts within the nucleus with jasmonate insensitive 1 (JIN1 or MYC2) to inhibit its transcriptional activity. JIN1/MYC2 is a conserved interaction partner shared by β C1 of tomato yellow leaf curl China virus and CabLCV NSP proteins. JIN1/MYC2 is a transactivation factor that upregulates genes involved in terpene syntheses, such as terpene synthase 10 (TPS10) and terpene synthase 4 (TPS04). Accordingly, CabLCV infections result in reduced terpene synthesis, which, in turn, enhances the performance of Bemisia tabaci, the vector of CabLCV. Terpenes possess insecticidal, repellent, and attractive properties for natural enemies, thus serving as an effective defense strategy against B. tabaci. Further investigations are necessary to fully understand the role of NSP in vector–plant interactions and the complex synergistic relationship between the vector and the virus (Breves *et al.*, 2023).

NSP and MP belonging to the Bean dwarf mosaic virus (BDMV) interacts with histone H3 through nuclear pore complex and plasmodesmata cells to export virus to cell periphery and then transmission across the cells (Yang *et al.*, 2011). Both proteins have also been found in interaction with NSP-interacting GTPase (NIG) protein, a cytosolic GTP-binding protein that assess GTPase activity in the cell. NSP and MP binds with NIG protein for intracellular movement of the virusz (Carvalho *et al.*, 2008). NSP monitors nuclear export of viral DNA through binding with acetyltransferase in A. thaliana (AtNSI), acting as a small GTPase for CaLCuV trafficking (Carvalho & Lazarowitz, 2004; Carvalho *et al.*, 2008). It has capability to develop symptoms in infected cells through binding with a PERK-like protein (proline rich extension-like receptor protein kinase) called NSP-associated protein (NsAK) (Florentino *et al.*, 2006). Another protein NSP-interacting kinase (NIK) is a known receptor-like kinase which plays its role in plants defense mechanism. NSP binds with this NIK protein which inhibits its kinase activity and promotes virus movement in the cell (Fontes*et al.*, 2004). In conclusion, this small DNA virus family adopts multitasking role for successful infection in host plants.

ADVANCES IN GENOME EDITING FOR GEMINIVIRUSES

To combat this huge family of plant viruses, genome editing approach CRISPR/Cas9 was under consideration to target huge species under begomoviruses and its associated satellites. In recent years, this molecular technique CRISPR/Cas9 was introduced for modification in the cotton genome. This approach has showed some promising results in regulation of the genes related to the higher quality traits that can give a positive response against plant pathogens (Sattar et al., 2019, Khan et al., 2021). As we know that cotton leaf curl virus is one of the widely spread infection at global level. Hense, transgenic cotton varieties based on CRISPR/Cas9 will provide a better yield and pathogen free cotton in near future. Recently, cap snatching technique was introduced with the help of Rice stripe virus (RSV) to mapp the 5' of viral mRNAs belonging to CLCuMuV, Corchorus yellow vein virus (CoYVV), and Ramie mosaic virus (RamV). Using this approach, RSV was able to snatch the capped RNA from host mRNAs and co-infected begomoviruses (Arif et al., 2020). Due to the diversity in guide RNA (gRNA) sequence, there is still a need of potential targeting to the multiple viruses rather than a single virus (Agrahari et al., 2020, Mishra et al., 2017). Using combination of different molecular tools including GWAS, CRISPR/Cas9 and transcriptome data could explore better plant immune system to dileante virus-host interaction.

CONCLUSION AND PERSPECTIVES

This review provides new insights into geminivirus-host interactions at the molecular level and lays foundation

for further studies on structure-function relationships. This insect transmissible virus has caused considerable yield loss at an alarming rate in several newer hosts including crops and weeds worldwide. As geminiviruses encodes fewer proteins which cannot afford independent completion of their infection cycle. Therefore, their small genome size proteins perform multifunctional roles to hijack host cellular machinery to suppress their defense mechanism to create a favorable environment for virus propagation and its transmission. Only two to three geminviral proteins redirects host replication process via DNA polymerase complex and further transcribe in the nucleus for viral genome amplification. Modifying host protein binding site such as targeting SnRK1 will affect the binding of Rep, TrAP and β C1. It will show negative impact on virus binding further with RLKs resulting into an impaired signal transduction during infection cycle and delayed symptom development. Additionally, RNAi-mediated pathways are major key players to regulate gene expression under TGS and PTGS mechanism to provide resistance against virulence factors. These plant pathogens are targeted through the production of small interfering RNAs (siRNAs) generated from viral genome and plant-derived micro RNAs (miRNAs). However, TrAP, C4, V2 and β C1 proteins acts as RNAi suppressors to interfere host miRNA regulatory pathway that eventually block protein network related to the defense system in the plants. To target AGO protein in the host will revert the VSR function of these viral proteins and restoring the normal production of siRNA through proper activity of RDR6-SGS3-DCL4 complex in the host. Moreover, modification of histone (H3) protein function using crisper-cas technology will subvert NSP-MP-H3 interaction complex which will restrict virus export through plasmodesmata cells into their neighboring cells

In conclusion, it is crucial to identify strong interactors in the host that are involved in direct response to the viral genome versus those playing secondary role during pathogenicity. Thus, data based on R (resistant) genes in host plants exhibits a deep insight the strategy involved in antiviral immunity system. These emerging plant pathogens are spreading to non-endemic new locations through mixed infection to overcome resistant varieties or using recombinant phenomenon for susceptible genes. Therefore, a real challenge still lies to develop a stable crop genotype that confers a remarkable resistance against geminivirus infection. Hence, "omics" approaches could provide a better source to understand this trade off in the plant developmental processes during geminivirus host interaction.

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REFERENCES

Adams MJ, King AMQ, Carstens EB . 2013 . Ratification vote on taxonomic proposals to the International Committee on Taxonomy of Viruses (2013). Archives of virology 158 : 2023–2030.

Aguilar E, Cutrona C, Del Toro FJ, Vallarino JG, Osorio S, Pérez-Bueno ML, Baron M, Chung B, Canto T, Tenllado F . 2017 . Virulence determines beneficial trade-offs in the response of virus-infected plants to drought via induction of salicylic acid. *Plant, Cell & Environment* 40 : 2909–2930.

Alemandri V, Vaghi Medina CG, DumOn AD, Arguello Caro EB, Mattio MF, Garcia Medina S, Lopez Lambertini PM, Truol G . 2015. Three members of the Bemisia tabaci (Hemiptera: Aleyrodidae) cryptic species complex occur sympatrically in Argentine horticultural crops. *Journal of Economic Entomology* 108 : 405–413.

Amin I, Patil BL, Briddon RW, Mansoor S, Fauquet CM .2011 . Comparison of phenotypes produced in response to transient expression of genes encoded by four distinct begomoviruses in Nicotiana

benthamiana their correlation with the levels of developmental miRNAs. Virology Journal 8: 1-24.

Amrao L, Amin I, Shahid MS, Briddon RW, Mansoor S .2010. Cotton leaf curl disease in resistant cotton is associated with a single begomovirus that lacks an intact transcriptional activator protein. *Virus research* 152 : 153–163.

Anfoka G, Moshe A, Fridman L, Amrani L, Rotem OR, Kolot M, Zeidan M, Czosnek H, Gorovits R . 2016 . Tomato yellow leaf curl virus infection mitigates the heat stress response of plants grown at high temperatures. *Scientific Reports* 6 : 19715.

Ascencio-Ibanez JT, Sozzani R, Lee T-J, Chu T-M, Wolfinger RD, Cella R, Hanley-Bowdoin L . 2008. Global analysis of Arabidopsis gene expression uncovers a complex array of changes impacting pathogen response and cell cycle during geminivirus infection. *Plant physiology* 148 : 436–454.

Avrova AO, Stewart HE, De Jong W, Heilbronn J, Lyon GD, Birch PRJ . 1999 . A cysteine protease gene is expressed early in resistant potato interactions with Phytophthora infestans. *Molecular plantmicrobe interactions* 12 : 1114–1119.

Bagewadi B, Chen S, Lal SK, Choudhury NR, Mukherjee SK .2004 . PCNA interacts with Indian mung bean yellow mosaic virus rep and downregulates Rep activity. *Journal of virology*78 : 11890–11903.

Bahder BW, Zalom FG, Jayanth M, Sudarshana MR. **2016**. Phylogeny of geminivirus coat protein sequences and digital PCR aid in identifying Spissistilus festinus as a vector of grapevine red blotch-associated virus. *Phytopathology* **106**: 1223–1230.

Baliji S, Lacatus G, Sunter G . 2010. The interaction between geminivirus pathogenicity proteins and adenosine kinase leads to increased expression of primary cytokinin-responsive genes. *Virology* 402 : 238–247.

Bar-Ziv A, Levy Y, Citovsky V, Gafni Y. **2015**. The Tomato yellow leaf curl virus (TYLCV) V2 protein inhibits enzymatic activity of the host papain-like cysteine protease CYP1. *Biochemical and biophysical research communications* **460**: 525–529.

Barbosa L da F, Marubayashi JM, De Marchi BR, Yuki VA, Pavan MA, Moriones E, Navas-Castillo J, Krause-Sakate R . 2014 . Indigenous American species of the Bemisia tabaci complex are still widespread in the Americas. *Pest Management Science* **70** : 1440–1445.

De Barro PJ, Liu S-S, Boykin LM, Dinsdale AB . 2011 . Bemisia tabaci: a statement of species status. Annual review of entomology 56 : 1–19.

Baumann P. **2005**. Biology of bacteriocyte-associated endosymbionts of plant sap-sucking insects. *Annu. Rev. Microbiol.***59**: 155–189.

Breves, S. S., Silva, F. A., Euclydes, N. C., Saia, T. F., Jean-Baptiste, J., Andrade Neto, E. R. and Fontes, E. P. (2023) Begomovirus-Host Interactions: Viral Proteins Orchestrating Intra and Intercellular Transport of Viral DNA While Suppressing Host Defense Mechanisms. *Viruses*, **15**, 1593.

Bernardo P, Muhire B, Francois S, Deshoux M, Hartnady P, Kraberger S, Filloux D, Fernandez E, Galzi S, Ferdinand R .2016. Molecular characterization and prevalence of two capulaviruses: Alfalfa leaf curl virus from France and Euphorbia caput-medusae latent virus from South Africa. *Virology*493 : 142–153.

Berry SD, Fondong VN, Rey C, Rogan D, Fauquet CM, Brown JK .2004. Molecular evidence for five distinct Bemisia tabaci (Homoptera: Aleyrodidae) geographic haplotypes associated with cassava plants in sub-Saharan Africa. *Annals of the Entomological Society of America* **97**: 852–859.

Bi H, Fan W, Zhang P . 2017 . C4 protein of sweet potato leaf curl virus regulates brassinosteroid signaling pathway through interaction with AtBIN2 and affects male fertility in Arabidopsis. *Frontiers in Plant Science* 8 : 1689.

Bing X-L, Yang J, Zchori-Fein E, Wang X-W, Liu S-S .2013. Characterization of a newly discovered symbiont of the whitefly Bemisia tabaci (Hemiptera: Aleyrodidae). *Applied and environmental microbiology* **79**: 569–575.

Boulton MI. **2002**. Functions and interactions of mastrevirus gene products. *Physiological and molecular* plant pathology **60**: 243–255.

Briddon RW, Bull SE, Amin I, Mansoor S, Bedford ID, Rishi N, Siwatch SS, Zafar Y, Abdel-Salam AM, Markham PG . 2004. Diversity of DNA 1: a satellite-like molecule associated with monopartite begomovirus–DNA β complexes. *Virology* 324 : 462–474.

Briddon RW, Mansoor S, Bedford ID, Pinner MS, Saunders K, Stanley J, Zafar Y, Malik KA, Markham PG . 2001 . Identification of DNA components required for induction of cotton leaf curl disease. *Virology* 285 : 234–243.

Briddon RW, Markham PG . 2001 . Complementation of bipartite begomovirus movement functions by topocuviruses and curtoviruses. Archives of virology 146 : 1811–1819.

Briddon RW, Martin DP, Roumagnac P, Navas-Castillo J, Fiallo-Olivé E, Moriones E, Lett J-M, Zerbini FM, Varsani A .2018. Alphasatellitidae: a new family with two subfamilies for the classification of geminivirus-and nanovirus-associated alphasatellites. *Archives of virology* 163 : 2587–2600.

Briddon RW, Pinner MS, Stanley J, Markham PG . 1990. Geminivirus coat protein gene replacement alters insect specificity. *Virology* 177 : 85–94.

Brown JK, Bird J. **1992**. Whitefly-transmitted geminiviruses and associated disorders in the Americas and the Caribbean Basin. *Plant Disease* **76** : 220–225.

Buchmann RC, Asad S, Wolf JN, Mohannath G, Bisaro DM .2009. Geminivirus AL2 and L2 proteins suppress transcriptional gene silencing and cause genome-wide reductions in cytosine methylation. *Journal* of virology 83 : 5005–5013.

Bull SE, Briddon RW, Sserubombwe WS, Ngugi K, Markham PG, Stanley J. 2007. Infectivity, pseudorecombination and mutagenesis of Kenyan cassava mosaic begomoviruses. *Journal of general virology* 88: 1624–1633.

Butler NM, Baltes NJ, Voytas DF, Douches DS . 2016 . Geminivirus-mediated genome editing in potato (Solanum tuberosum L.) using sequence-specific nucleases. *Frontiers in plant science* 7 : 1045.

Campos-Olivas R, Louis JM, Clérot D, Gronenborn B, Gronenborn AM . 2002a . The structure of a replication initiator unites diverse aspects of nucleic acid metabolism. *Proceedings of the National Academy of Sciences* 99 : 10310–10315.

Campos-Olivas R, Louis JM, Clérot D, Gronenborn B, Gronenborn AM. **2002b**. 1 H, 13 C, and 15 N assignment of the N-terminal, catalytic domain of the replication initiation protein from the geminivirus TYLCV. *Journal of Biomolecular NMR* **24** : 73–74.

Cappadocia L, Lima CD . 2018 . Ubiquitin-like protein conjugation: structures, chemistry, and mechanism. *Chemical reviews* 118 : 889–918.

Carvalho CM, Fontenelle MR, Florentino LH, Santos AA, Zerbini FM, Fontes EPB . 2008 . A novel nucleocytoplasmic traffic GTPase identified as a functional target of the bipartite geminivirus nuclear shuttle protein. *The Plant Journal* 55 : 869–880.

Carvalho MF, Lazarowitz SG. 2004. Interaction of the movement protein NSP and the Arabidopsis acetyltransferase AtNSI is necessary for cabbage leaf curl geminivirus infection and pathogenicity. *Journal of virology* **78**: 11161–11171.

Castillo-Gonzalez C, Liu X, Huang C, Zhao C, Ma Z, Hu T, Sun F, Zhou Y, Zhou X, Wang X-J. 2015. Geminivirus-encoded TrAP suppressor inhibits the histone methyltransferase SUVH4/KYP to counter host defense. *Elife* 4 : e06671.

Castillo AG, Collinet D, Deret S, Kashoggi A, Bejarano ER .2003 . Dual interaction of plant PCNA with geminivirus replication accessory protein (Ren) and viral replication protein (Rep). *Virology* **312** : 381–394.

Catic A, Ploegh HL . 2005 . Ubiquitin–conserved protein or selfish gene? *Trends in biochemical sciences* 30 : 600–604.

Chellappan P, Vanitharani R, Fauquet CM. **2004**. Short interfering RNA accumulation correlates with host recovery in DNA virus-infected hosts, and gene silencing targets specific viral sequences. *Journal of virology* **78**: 7465–7477.

Chen X, Cheng J, Chen L, Zhang G, Huang H, Zhang Y, Xu L .2016 . Auxin-independent NAC pathway acts in response to explant-specific wounding and promotes root tip emergence during de novo root organogenesis in Arabidopsis. *Plant Physiology* 170 : 2136–2145.

Chen H, Zhang Z, Teng K, Lai J, Zhang Y, Huang Y, Li Y, Liang L, Wang Y, Chu C . 2010 . Up-regulation of LSB1/GDU3 affects geminivirus infection by activating the salicylic acid pathway. *The Plant Journal* 62 : 12–23.

Chen Z-Q, Zhao J-H, Chen Q, Zhang Z-H, Li J, Guo Z-X, Xie Q, Ding S-W, Guo H-S. 2020. DNA geminivirus infection induces an imprinted E3 ligase gene to epigenetically activate viral gene transcription. *Plant Cell* 32: 3256–3272.

Chevalier D, Walker JC . 2005. Functional genomics of protein kinases in plants. *Briefings in Functional Genomics* 3 : 362–371.

Chiel E, Gottlieb Y, Zchori-Fein E, Mozes-Daube N, Katzir N, Inbar M, Ghanim M . 2007 . Biotype-dependent secondary symbiont communities in sympatric populations of Bemisia tabaci. *Bulletin* of Entomological Research 97 : 407–413.

Chi, Y., Pan, L.-L., Liu, S.-S., Mansoor, S. and Wang, X.-W. (2021) Implication of the whitefly protein vps twenty associated 1 (Vta1) in the transmission of cotton leaf curl multan virus. *Microorganisms*, 9, 304.

Chodon, A., Karanthamalai, J., Pandi, G. and Tennyson, J. (2022) The begomovirus-host interplay in viral replication and movement. In: *Geminivirus: Detection, Diagnosis and Management.* Elsevier, pp. 397-419.

Chikoti PC, Mulenga RM, Tembo M, Sseruwagi P . 2019 . Cassava mosaic disease: a review of a threat to cassava production in Zambia. *Journal of Plant Pathology* 101 : 467–477.

Chung HY, Lacatus G, Sunter G . 2014. Geminivirus AL2 protein induces expression of, and interacts with, a calmodulin-like gene, an endogenous regulator of gene silencing. *Virology*460 : 108–118.

Coco D, Calil IP, Brustolini OJB, Santos AA, Inoue-Nagata AK, Fontes EPB . 2013 . Soybean chlorotic spot virus, a novel begomovirus infecting soybean in Brazil. *Archives of Virology*158 : 457–462.

Corrales-Gutierrez M, Medina-Puche L, Yu Y, Wang L, Ding X, Luna AP, Bejarano ER, Castillo AG, Lozano-Duran R . 2020 . The C4 protein from the geminivirus Tomato yellow leaf curl virus confers drought tolerance in Arabidopsis through an ABA-independent mechanism. *Plant Biotechnology Journal* 18 : 1121.

Cui X, Wan F, Xie M, Liu T . 2008. Effects of heat shock on survival and reproduction of two whitefly species, Trialeurodes vaporariorum and Bemisia tabaci biotype B. *Journal of Insect Science* 8 : 24.

Desvoyes B, Ramirez-Parra E, Xie Q, Chua N-H, Gutierrez C .2006. Cell type-specific role of the retinoblastoma/E2F pathway during Arabidopsis leaf development. *Plant physiology*140: 67–80.

Dogra SC, Eini O, Rezaian MA, Randles JW. **2009**. A novel shaggy-like kinase interacts with the Tomato leaf curl virus pathogenicity determinant C4 protein. *Plant molecular biology***71**: 25–38.

Dong X, van Wezel R, Stanley J, Hong Y. **2003**. Functional characterization of the nuclear localization signal for a suppressor of posttranscriptional gene silencing. *Journal of virology* **77**: 7026–7033.

Douglas AE. **1998**. Nutritional interactions in insect-microbial symbioses: aphids and their symbiotic bacteria Buchnera. *Annual review of entomology* 43 : 17-37.

Dry IB, Rigden JE, Krake LR, Mullineaux PM, Rezaian MA .1993. Nucleotide sequence and genome organization of tomato leaf curl geminiviru. *Journal of General Virology* 74 : 147–151.

Eini O, Dogra S, Selth LA, Dry IB, Randles JW, Rezaian MA .2009 . Interaction with a host ubiquitin-conjugating enzyme is required for the pathogenicity of a geminiviral DNA β satellite.*Molecular plant-microbe interactions* 22 : 737–746.

Elmer JS, Brand L, Sunter G, Gardiner WE, Bisaro DM, Rogers SG .1988. Genetic analysis of the tomato golden mosaic virus II. The product of the AL1 coding sequence is required for replication. *Nucleic acids research* 16 : 7043–7060.

Esterhuizen LL, Mabasa KG, Van Heerden SW, Czosnek H, Brown JK, Van Heerden H, Rey MEC . 2013 . Genetic identification of members of the Bemisia tabaci cryptic species complex from South Africa reveals native and introduced haplotypes. *Journal of applied entomology* 137 : 122–135.

Fan P, Wang H, Xue H, Rosas-Diaz T, Tang W, Zhang H, Xu L, Lozano-Duran R . 2019. The receptor-like kinases BAM1 and BAM2 promote the cell-to-cell movement of miRNA in the root stele to regulate xylem patterning. *BioRxiv* : 603415.

Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA .2005 . Virus taxonomy: VIIIth report of the International Committee on Taxonomy of Viruses . Academic Press.

Fedorkin ON, Solovyev AG, Yelina NE, Zamyatnin Jr AA, Zinovkin RA, Mäkinen K, Schiemann J, Yu. Morozov S . 2001 . Cell-to-cell movement of potato virus X involves distinct functions of the coat protein. *Journal of General Virology* 82 : 449–458.

Fiallo-Olivé E, Trenado HP, Louro D, Navas-Castillo J .2019 . Recurrent speciation of a tomato yellow leaf curl geminivirus in Portugal by recombination. *Scientific reports* 9 : 1332.

Fiallo-Olive E, Tovar R, Navas-Castillo J . 2016 . Deciphering the biology of deltasatellites from the New World: maintenance by New World begomoviruses and whitefly transmission. *New Phytologist* 212 : 680–692.

Firdaus S, Vosman B, Hidayati N, Jaya Supena ED, GF Visser R, van Heusden AW . 2013. The Bemisia tabaci species complex: additions from different parts of the world. *Insect Science* 20: 723–733.

Florentino LH, Santos AA, Fontenelle MR, Pinheiro GL, Zerbini FM, Baracat-Pereira MC, Fontes EPB . 2006 . A PERK-like receptor kinase interacts with the geminivirus nuclear shuttle protein and potentiates viral infection. *Journal of virology* 80 : 6648–6656.

Fondong VN, Reddy RVC, Lu C, Hankoua B, Felton C, Czymmek K, Achenjang F. 2007. The consensus N-myristoylation motif of a geminivirus AC4 protein is required for membrane binding and pathogenicity. *Molecular plant-microbe interactions* **20**: 380–391.

Fontenelle MR, Luz DF, Gomes APS, Florentino LH, Zerbini FM, Fontes EPB . 2007 . Functional analysis of the naturally recombinant DNA-A of the bipartite begomovirus Tomato chlorotic mottle virus. *Virus research* **126** : 262–267. Fontes EP, Eagle PA, Sipe PS, Luckow VA, Hanley-Bowdoin L .1994. Interaction between a geminivirus replication protein and origin DNA is essential for viral replication. *Journal of Biological Chemistry* 269 : 8459–8465.

Fontes EPB, Santos AA, Luz DF, Waclawovsky AJ, Chory J .2004. The geminivirus nuclear shuttle protein is a virulence factor that suppresses transmembrane receptor kinase activity. *Genes & development* 18: 2545–2556.

Farooq, T., Lin, Q., She, X., Chen, T., Li, Z., Yu, L., *et al.* (2022) Cotton leaf curl Multan virus differentially regulates innate antiviral immunity of whitefly (Bemisia tabaci) vector to promote cryptic species-dependent virus acquisition. *Frontiers in Plant Science*, **13**, 1040547.

Frischmuth S, Wege C, Hulser D, Jeske H. **2007**. The movement protein BC1 promotes redirection of the nuclear shuttle protein BV1 of Abutilon mosaic geminivirus to the plasma membrane in fission yeast. *Protoplasma* **230**: 117–123.

Frohlich DR, Torres-Jerez I, Bedford ID, Markham PG, Brown JK .1999 . A phylogeographical analysis of the Bemisia tabaci species complex based on mitochondrial DNA markers. *Molecular ecology* 8 : 1683–1691.

Garcia-Andres S, Tomas DM, Sanchez-Campos S, Navas-Castillo J, Moriones E . 2007 . Frequent occurrence of recombinants in mixed infections of tomato yellow leaf curl disease-associated begomoviruses. *Virology* **365** : 210–219.

Gareau JR, Lima CD . 2010 . The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. *Nature reviews Molecular cell biology* 11 : 861–871.

Garnelo Gomez B, Zhang D, Rosas-Diaz T, Wei Y, Macho AP, Lozano-Duran R . 2019. The C4 protein from tomato yellow leaf curl virus can broadly interact with plant receptor-like kinases. *Viruses* 11 : 1009.

Ghosh S, Bouvaine S, Maruthi MN. **2015**. Prevalence and genetic diversity of endosymbiotic bacteria infecting cassava whiteflies in Africa. *BMC microbiology* **15** : 1–17.

Gilbertson RL, Batuman O, Webster CG, Adkins S. 2015. Role of the insect supervectors Bemisia tabaci and Frankliniella occidentalis in the emergence and global spread of plant viruses. *Annual review of virology* 2: 67–93.

Glab N, Oury C, Guerinier T, Domenichini S, Crozet P, Thomas M, Vidal J, Hodges M. **2017**. The impact of Arabidopsis thaliana SNF 1-related-kinase 1 (Sn RK 1)-activating kinase 1 (Sn AK 1) and Sn AK 2 on Sn RK 1 phosphorylation status: characterization of a Sn AK double mutant. *The Plant Journal* **89**: 1031–1041.

Glick E, Zrachya A, Levy Y, Mett A, Gidoni D, Belausov E, Citovsky V, Gafni Y . 2008. Interaction with host SGS3 is required for suppression of RNA silencing by tomato yellow leaf curl virus V2 protein. *Proceedings of the National Academy of Sciences*105 : 157–161.

Gopal P, Kumar PP, Sinilal B, Jose J, Yadunandam AK, Usha R .2007. Differential roles of C4 and β C1 in mediating suppression of post-transcriptional gene silencing: evidence for transactivation by the C2 of Bhendi yellow vein mosaic virus, a monopartite begomovirus. *Virus research* **123** : 9–18.

Gorovits R, Czosnek H . 2017. The involvement of heat shock proteins in the establishment of Tomato yellow leaf curl virus infection. *Frontiers in plant science* 8 : 355.

Gorovits R, Sobol I, Altaleb M, Czosnek H, Anfoka G .2019 . Taking advantage of a pathogen: understanding how a virus alleviates plant stress response. *Phytopathology Research* 1 : 1–6.

Gottlieb Y, Zchori-Fein E, Mozes-Daube N, Kontsedalov S, Skaljac M, Brumin M, Sobol I, Czosnek H, Vavre F, Fleury F . 2010 . The transmission efficiency of tomato yellow leaf curl virus by

the whitefly Bemisia tabaci is correlated with the presence of a specific symbiotic bacterium species. *Journal* of virology 84: 9310–9317.

Götz M, Popovski S, Kollenberg M, Gorovits R, Brown JK, Cicero JM, Czosnek H, Winter S, Ghanim M . 2012 . Implication of Bemisia tabaci heat shock protein 70 in Begomovirus-whitefly interactions. *Journal of virology* 86 : 13241–13252.

Gray S, Cilia M, Ghanim M . 2014 . Circulative, "nonpropagative" virus transmission: an orchestra of virus-, insect-, and plant-derived instruments. In: Advances in virus research. Elsevier, 141–199.

Gueguen G, Vavre F, Gnankine O, Peterschmitt M, Charif D, Chiel E, Gottlieb Y, Ghanim M, ZCHORI-FEIN E, Fleury F . 2010 . Endosymbiont metacommunities, mtDNA diversity and the evolution of the Bemisia tabaci (Hemiptera: Aleyrodidae) species complex. *Molecular Ecology* 19 : 4365–4376.

Guerra-Peraza O, Kirk D, Seltzer V, Veluthambi K, Schmit AC, Hohn T, Herzog E . 2005. Coat proteins of Rice tungro bacilliform virus and Mungbean yellow mosaic virus contain multiple nuclear-localization signals and interact with importin α . *Journal of general virology* **86** : 1815–1826.

Guerrero, J., Regedanz, E., Lu, L., Ruan, J., Bisaro, D. M. and Sunter, G. (2020) Manipulation of the plant host by the geminivirus AC2/C2 protein, a central player in the infection cycle. *Frontiers in plant science*, **11**,591.

Gutierrez C . 1999 . Geminivirus DNA replication. Cellular and Molecular Life Sciences CMLS 56 : 313–329.

Hanley-Bowdoin L, Bejarano ER, Robertson D, Mansoor S .2013 . Geminiviruses: masters at redirecting and reprogramming plant processes. *Nature Reviews Microbiology* 11 : 777–788.

Hanley-Bowdoin L, Settlage SB, Orozco BM, Nagar S, Robertson D .1999. Geminiviruses: models for plant DNA replication, transcription, and cell cycle regulation. *Critical Reviews in Plant Sciences* 18: 71–106.

Hanley-Bowdoin L, Settlage SB, Robertson D . 2004 . Reprogramming plant gene expression: a prerequisite to geminivirus DNA replication. *Molecular Plant Pathology* 5 : 149–156.

Harrison BD, Swanson MM, Fargette D. 2002. Begomovirus coat protein: serology, variation and functions. *Physiological and molecular plant pathology* **60**: 257–271.

Hayward AP, Tsao J, Dinesh-Kumar SP . 2009. Autophagy and plant innate immunity: Defense through degradation. In: Seminars in cell & developmental biology. Elsevier, 1041–1047.

Himler AG, Adachi-Hagimori T, Bergen JE, Kozuch A, Kelly SE, Tabashnik BE, Chiel E, Duckworth VE, Dennehy TJ, Zchori-Fein E .2011 . Rapid spread of a bacterial symbiont in an invasive whitefly is driven by fitness benefits and female bias. *science* **332** : 254–256.

Hoogstraten RA, Hanson SF, Maxwell DP. **1996**. Mutational analysis of the putative nicking motif in the replication-associated protein (AC1) of bean golden mosaic geminivirus. *Molecular Plant-Microbe Interactions: MPMI* **9**: 594–599.

Van Der Hoorn RAL . 2008 . Plant proteases: from phenotypes to molecular mechanisms. Annu. Rev. Plant Biol.59 : 191–223.

Hua Z, Vierstra RD . 2011 . The cullin-RING ubiquitin-protein ligases. Annual review of plant biology62 : 299–334.

Huang W, Miao M, Kud J, Niu X, Ouyang B, Zhang J, Ye Z, Kuhl JC, Liu Y, Xiao F. 2013. Sl NAC 1, a stress-related transcription factor, is fine-tuned on both the transcriptional and the post-translational level. *New Phytologist* 197 : 1214–1224.

Hulsmans S, Rodriguez M, De Coninck B, Rolland F .2016 . The SnRK1 energy sensor in plant biotic interactions. *Trends in Plant Science* 21 : 648–661.

Ilyas M, Qazi J, Mansoor S, Briddon RW . 2010 . Genetic diversity and phylogeography of begomoviruses infecting legumes in Pakistan. *Journal of General Virology* **91** : 2091–2101.

Ilyina T V, Koonin E V . 1992 . Conserved sequence motifs in the initiator proteins for rolling circle DNA replication encoded by diverse replicons from eubacteria, eucaryotes and archaebacteria. *Nucleic acids research* 20 : 3279–3285.

Inoue-Nagata AK, Lima MF, Gilbertson RL . 2016. A review of geminivirus diseases in vegetables and other crops in Brazil: current status and approaches for management. *Horticultura Brasileira* 34: 8–18.

Ismayil A, Haxim Y, Wang Y, Li H, Qian L, Han T, Chen T, Jia Q, Yihao Liu A, Zhu S . 2018 . Cotton Leaf Curl Multan virus C4 protein suppresses both transcriptional and post-transcriptional gene silencing by interacting with SAM synthetase. *PLoS pathogens*14 : e1007282.

Jia Q, Liu N, Xie K, Dai Y, Han S, Zhao X, Qian L, Wang Y, Zhao J, Gorovits R . 2016 . CLCuMuB β Cl subverts ubiquitination by interacting with NbSKP1s to enhance geminivirus infection in Nicotiana benthamiana. *PLoS pathogens* 12 : e1005668.

Jiang R, Qi L-D, Du Y-Z, Li Y-X . 2017 . Thermotolerance and heat-shock protein gene expression patterns in Bemisia tabaci (Hemiptera: Aleyrodidae) mediterranean in relation to developmental stage. *Journal of economic entomology* 110 : 2190–2198.

Jiu M, Hu J, Wang L-J, Dong J-F, Song Y-Q, Sun H-Z .2017 . Cryptic species identification and composition of Bemisia tabaci (Hemiptera: Aleyrodidae) complex in Henan province, China. *Journal of Insect Science* 17 : 78.

Kaliappan K, Choudhury NR, Suyal G, Mukherjee SK .2012 . A novel role for RAD54: this host protein modulates geminiviral DNA replication. *The FASEB Journal* 26 : 1142–1160.

Kamal H, Minhas F-AA, Farooq M, Tripathi D, Hamza M, Mustafa R, Khan MZ, Mansoor S, Pappu HR, Amin I . 2019 . In silico prediction and validations of domains involved in Gossypium hirsutum SnRK1 protein interaction with cotton leaf curl Multan betasatellite encoded β C1. Frontiers in Plant Science 10 : 656.

Kanakala S, Ghanim M. 2016. Implication of the whitefly Bemisia tabaci cyclophilin B protein in the transmission of Tomato yellow leaf curl virus. Frontiers in Plant Science 7: 1702.

Kanakala S, Kontsedalov S, Lebedev G, Ghanim M . 2019 . Plant-mediated silencing of the whitefly Bemisia tabaci cyclophilin B and heat shock protein 70 impairs insect development and virus transmission. *Frontiers in Physiology* 10 : 557.

Kepinski S, Leyser O . 2005 . The Arabidopsis F-box protein TIR1 is an auxin receptor. *Nature* 435 : 446–451.

Kheyr-Pour A, Bananej K, Dafalla GA, Caciagli P, Noris E, Ahoonmanesh A, Lecoq H, Gronenborn B . 2000 . Watermelon chlorotic stunt virus from the Sudan and Iran: sequence comparisons and identification of a whitefly-transmission determinant. *Phytopathology* **90** : 629–635.

Kil E-J, Kim S, Lee Y-J, Byun H-S, Park J, Seo H, Kim C-S, Shim J-K, Lee J-H, Kim J-K . 2016 . Tomato yellow leaf curl virus (TYLCV-IL): a seed-transmissible geminivirus in tomatoes. *Scientific reports* 6 : 19013.

King AMQ, Lefkowitz E, Adams MJ, Carstens EB . 2011 . Virus taxonomy: ninth report of the International Committee on Taxonomy of Viruses . Elsevier.

Kong L-J, Hanley-Bowdoin L . 2002 . A geminivirus replication protein interacts with a protein kinase and a motor protein that display different expression patterns during plant development and infection. *The Plant Cell* 14 : 1817–1832.

Kong L-J, Orozco BM, Roe JL, Nagar S, Ou S, Feiler HS, Durfee T, Miller AB, Gruissem W, Robertson D . 2000 . A geminivirus replication protein interacts with the retinoblastoma protein through a novel domain to determine symptoms and tissue specificity of infection in plants. *The EMBO journal* 19 : 3485–3495.

Kontsedalov S, Zchori-Fein E, Chiel E, Gottlieb Y, Inbar M, Ghanim M . 2008. The presence of Rickettsia is associated with increased susceptibility of Bemisia tabaci (Homoptera: Aleyrodidae) to insecticides. *Pest management science: formerly Pesticide Science*64: 789–792.

Krenz B, Jeske H, Kleinow T . 2012 . The induction of stromule formation by a plant DNA-virus in epidermal leaf tissues suggests a novel intra-and intercellular macromolecular trafficking route. Frontiers in plant science 3: 291.

Krenz B, Windeisen V, Wege C, Jeske H, Kleinow T .2010 . A plastid-targeted heat shock cognate 70 kDa protein interacts with the Abutilon mosaic virus movement protein. *Virology* 401 : 6–17.

Kushwaha NK, Bhardwaj M, Chakraborty S. 2017. The replication initiator protein of a geminivirus interacts with host monoubiquitination machinery and stimulates transcription of the viral genome. *PLoS pathogens* 13: e1006587.

Kwade Z, Swiaatek A, Azmi A, Goossens A, Inzé D, Van Onckelen H, Roef L . 2005. Identification of four adenosine kinase isoforms in tobacco BY-2 cells and their putative role in the cell cycle-regulated cytokinin metabolism. *Journal of Biological Chemistry* **280** : 17512–17519.

Lacatus G, Sunter G . 2009. The Arabidopsis PEAPOD2 transcription factor interacts with geminivirus AL2 protein and the coat protein promoter. *Virology* **392**: 196–202.

Laufs J, Traut W, Heyraud F, Matzeit V, Rogers SG, Schell J, Gronenborn B. 1995. In vitro cleavage and joining at the viral origin of replication by the replication initiator protein of tomato yellow leaf curl virus. *Proceedings of the National Academy of Sciences* 92: 3879–3883.

Legg JP, Fauquet CM . 2004 . Cassava mosaic geminiviruses in Africa. *Plant molecular biology* 56 : 585–599.

Legg JP, Sseruwagi P, Boniface S, Okao-Okuja G, Shirima R, Bigirimana S, Gashaka G, Herrmann H-W, Jeremiah S, Obiero H .2014 . Spatio-temporal patterns of genetic change amongst populations of cassava Bemisia tabaci whiteflies driving virus pandemics in East and Central Africa. *Virus research* 186 : 61–75.

Leke WN, Mignouna DB, Brown JK, Kvarnheden A . 2015 . Begomovirus disease complex: emerging threat to vegetable production systems of West and Central Africa. *Agriculture & Food Security* 4 : 1–14.

Lewis JD, Lazarowitz SG . 2010 . Arabidopsis synaptotagmin SYTA regulates endocytosis and virus movement protein cell-to-cell transport. *Proceedings of the National Academy of Sciences* 107 : 2491–2496.

Li F, Ding S-W . 2006 . Virus counterdefense: diverse strategies for evading the RNA-silencing immunity. *Annu. Rev. Microbiol.* 60 : 503–531.

Li F, Huang C, Li Z, Zhou X . 2014 . Suppression of RNA silencing by a plant DNA virus satellite requires a host calmodulin-like protein to repress RDR6 expression. *PLoS pathogens* 10 : e1003921.

Li F, Wang Y, Zhou X . 2017a . SGS3 cooperates with RDR6 in triggering geminivirus-induced gene silencing and in suppressing geminivirus infection in Nicotiana benthamiana. *Viruses*9 : 247.

Li F, Xu X, Huang C, Gu Z, Cao L, Hu T, Ding M, Li Z, Zhou X .2015. The AC 5 protein encoded by Mungbean yellow mosaic India virus is a pathogenicity determinant that suppresses RNA silencing-based antiviral defenses. *New Phytologist* 208 : 555–569.

Li H, Zeng R, Chen Z, Liu X, Cao Z, Xie Q, Yang C, Lai J .2018 . S-acylation of a geminivirus C4 protein is essential for regulating the CLAVATA pathway in symptom determination. *Journal of experimental botany* 69 : 4459–4468.

Li F, Zhao N, Li Z, Xu X, Wang Y, Yang X, Liu S-S, Wang A, Zhou X . 2017b . A calmodulin-like protein suppresses RNA silencing and promotes geminivirus infection by degrading SGS3 via the autophagy pathway in Nicotiana benthamiana. *PLoS pathogens* 13 : e1006213.

Lozano-Duran R, Rosas-Diaz T, Gusmaroli G, Luna AP, Taconnat L, Deng XW, Bejarano ER . 2011a . Geminiviruses subvert ubiquitination by altering CSN-mediated derubylation of SCF E3 ligase complexes and inhibit jasmonate signaling in Arabidopsis thaliana. *The Plant Cell* 23 : 1014–1032.

Lozano-Duran R, Rosas-Diaz T, Luna AP, Bejarano ER .2011b . Identification of host genes involved in geminivirus infection using a reverse genetics approach. *PloS one* **6** : e22383.

Lozano G, Trenado HP, Fiallo-Olive E, Chirinos D, Geraud-Pouey F, Briddon RW, Navas-Castillo J . 2016 . Characterization of non-coding DNA satellites associated with sweepoviruses (genus Begomovirus, Geminiviridae)–definition of a distinct class of begomovirus-associated satellites. *Frontiers in Microbiology* 7 : 162.

Luo C, Wang ZQ, Liu X, Zhao L, Zhou X, Xie Y . 2019 . Identification and analysis of potential genes regulated by an alphasatellite (TYLCCNA) that contribute to host resistance against tomato yellow leaf curl China virus and its betasatellite (TYLCCNV/TYLCCNB) infection in Nicotiana benthamiana. *Viruses*11 : 442.

Luque A, Sanz-Burgos AP, Ramirez-Parra E, Castellano MM, Gutierrez C . 2002 . Interaction of geminivirus Rep protein with replication factor C and its potential role during geminivirus DNA replication. *Virology* **302** : 83–94.

Mansoor S, Briddon RW, Zafar Y, Stanley J . 2003 . Geminivirus disease complexes: an emerging threat. Trends in plant science 8: 128-134.

Mar TB, Mendes IR, Lau D, Fiallo-Olive E, Navas-Castillo J, Alves MS, Murilo Zerbini F. 2017. Interaction between the New World begomovirus Euphorbia yellow mosaic virus and its associated alphasatellite: effects on infection and transmission by the whitefly Bemisia tabaci. *Journal of General Virology* 98: 1552–1562.

Marino D, Peeters N, Rivas S . 2012 . Ubiquitination during plant immune signaling. *Plant physiology* 160 : 15–27.

Martin DP, Lemey P, Lott M, Moulton V, Posada D, Lefeuvre P .2010 . RDP3: a flexible and fast computer program for analyzing recombination. *Bioinformatics* 26 : 2462–2463.

Marubayashi JM, Yuki VA, Rocha KCG, Mituti T, Pelegrinotti FM, Ferreira FZ, Moura MF, Navas-Castillo J, Moriones E, Pavan MA .2013. At least two indigenous species of the Bemisia tabaci complex are present in Brazil. *Journal of Applied Entomology*137 : 113–121.

McGRATH PF, Harrison BD . 1995 . Transmission of tomato leaf curl geminiviruses by Bemisia tabaci: effects of virus isolate and vector biotype. *Annals of Applied Biology* **126** : 307–316.

Mei Y, Wang Y, Hu T, Yang X, Lozano-Duran R, Sunter G, Zhou X .2018a . Nucleocytoplasmic shuttling of geminivirus C4 protein mediated by phosphorylation and myristoylation is critical for viral pathogenicity. *Molecular Plant* 11 : 1466–1481.

Mei Y, Yang X, Huang C, Zhang X, Zhou X . 2018b . Tomato leaf curl Yunnan virus-encoded C4 induces cell division through enhancing stability of Cyclin D 1.1 via impairing NbSK η -mediated phosphorylation in Nicotiana benthamiana. *PLoS Pathogens*14 : e1006789.

Melgarejo TA, Kon T, Rojas MR, Paz-Carrasco L, Zerbini FM, Gilbertson RL . 2013 . Characterization of a new world monopartite begomovirus causing leaf curl disease of tomato in Ecuador and Peru reveals a new direction in geminivirus evolution. *Journal of virology* 87 : 5397–5413.

Miao M, Niu X, Kud J, Du X, Avila J, Devarenne TP, Kuhl JC, Liu Y, Xiao F . 2016. The ubiquitin ligase SEVEN IN ABSENTIA (SINA) ubiquitinates a defense-related NAC transcription factor and is involved in defense signaling. *New Phytologist* 211 : 138–148.

Mills-Lujan K, Andrews DL, Chou C, Deom CM . 2015. The roles of phosphorylation and SHAGGYlike protein kinases in geminivirus C4 protein induced hyperplasia. *PLoS One* **10** : e0122356.

Miozzi L, Napoli C, Sardo L, Accotto GP . 2014 . Transcriptomics of the interaction between the monopartite phloem-limited geminivirus tomato yellow leaf curl Sardinia virus and Solanum lycopersicum highlights a role for plant hormones, autophagy and plant immune system fine tuning during infection. *PLoS One* 9 : e89951.

Moffatt BA, Stevens YY, Allen MS, Snider JD, Pereira LA, Todorova MI, Summers PS, Weretilnyk EA, Martin-McCaffrey L, Wagner C .2002. Adenosine kinase deficiency is associated with developmental abnormalities and reduced transmethylation. *Plant Physiology* **128** : 812–821.

Morin S, Ghanim M, Sobol I, Czosnek H . 2000. The GroEL protein of the whitefly Bemisia tabaci interacts with the coat protein of transmissible and nontransmissible begomoviruses in the yeast two-hybrid system. *Virology* **276** : 404–416.

Morin S, Ghanim M, Zeidan M, Czosnek H, Verbeek M, van den Heuvel JFJM . 1999 . A GroEL homologue from endosymbiotic bacteria of the whiteflyBemisia tabaciis implicated in the circulative transmission of tomato yellow leaf curl virus. *Virology*256 : 75–84.

Moshe A, Belausov E, Niehl A, Heinlein M, Czosnek H, Gorovits R . 2015 . The Tomato yellow leaf curl virus V2 protein forms aggregates depending on the cytoskeleton integrity and binds viral genomic DNA. *Scientific reports* 5 : 9967.

Mugerwa H, Seal S, Wang H-L, Patel M V, Kabaalu R, Omongo CA, Alicai T, Tairo F, Ndunguru J, Sseruwagi P . 2018 . African ancestry of New World, Bemisia tabaci-whitefly species. *Scientific reports* 8 : 2734.

Nagar S, Pedersen TJ, Carrick KM, Hanley-Bowdoin L, Robertson D. 1995. A geminivirus induces expression of a host DNA synthesis protein in terminally differentiated plant cells. *The Plant Cell* 7: 705–719.

Naqvi RZ, Zaidi SS-A, Mukhtar MS, Amin I, Mishra B, Strickler S, Mueller LA, Asif M, Mansoor S . 2019 . Transcriptomic analysis of cultivated cotton Gossypium hirsutum provides insights into host responses upon whitefly-mediated transmission of cotton leaf curl disease. *PloS one* 14 : e0210011.

Nawaz-ul-Rehman MS, Fauquet CM . 2009 . Evolution of geminiviruses and their satellites. *FEBS letters* 583 : 1825–1832.

Nawaz-ul-Rehman MS, Nahid N, Mansoor S, Briddon RW, Fauquet CM .2010 . Post-transcriptional gene silencing suppressor activity of two non-pathogenic alphasatellites associated with a begomovirus. *Virology* **405** : 300–308.

Nezames CD, Deng XW . 2012 . The COP9 signalosome: its regulation of cullin-based E3 ubiquitin ligases and role in photomorphogenesis. *Plant physiology* 160 : 38–46.

Noueiry AO, Lucas WJ, Gilbertson RL . 1994. Two proteins of a plant DNA virus coordinate nuclear and plasmodesmal transport. *Cell* 76 : 925–932.

Pan L-L, Chen Q-F, Zhao J-J, Guo T, Wang X-W, Hariton-Shalev A, Czosnek H, Liu S-S . 2017 . Clathrin-mediated endocytosis is involved in Tomato yellow leaf curl virus transport across the midgut barrier of its whitefly vector. *Virology* 502 : 152–159.

Park J, Hwang H, Shim H, Im K, Auh C-K, Lee S, Davis KR .2004 . Altered cell shapes, hyperplasia, and secondary growth in Arabidopsis caused by beet curly top geminivirus infection. *Molecules and Cells* 17 : 117–124.

Patil BL, Fauquet CM. **2009**. Cassava mosaic geminiviruses: actual knowledge and perspectives. *Molecular plant pathology* **10**: 685–701.

Piroux N, Saunders K, Page A, Stanley J. **2007**. Geminivirus pathogenicity protein C4 interacts with Arabidopsis thaliana shaggy-related protein kinase $AtSK\eta$, a component of the brassinosteroid signalling pathway. *Virology* **362**: 428–440.

Polston JE, De Barro P, Boykin LM. **2014**. Transmission specificities of plant viruses with the newly identified species of the Bemisia tabaci species complex. *Pest management science***70**: 1547–1552.

Poornima Priyadarshini CG, Ambika M V, Tippeswamy R, Savithri HS. 2011. Functional characterization of coat protein and V2 involved in cell to cell movement of Cotton leaf curl Kokhran virus-Dabawali. *PloS one* **6** : e26929.

Qin S, Ward BM, Lazarowitz SG. **1998**. The bipartite geminivirus coat protein aids BR1 function in viral movement by affecting the accumulation of viral single-stranded DNA. *Journal of virology* **72**: 9247–9256.

Raghavan V, Malik PS, Choudhury NR, Mukherjee SK .2004. The DNA-A component of a plant geminivirus (Indian mung bean yellow mosaic virus) replicates in budding yeast cells. *Journal of virology* 78 : 2405–2413.

Raja P, Sanville BC, Buchmann RC, Bisaro DM . 2008 . Viral genome methylation as an epigenetic defense against geminiviruses. *Journal of virology* 82 : 8997–9007.

Rajeswaran R, Sunitha S, Shivaprasad P V, Pooggin MM, Hohn T, Veluthambi K. 2007. The mungbean yellow mosaic begomovirus transcriptional activator protein transactivates the viral promoterdriven transgene and causes toxicity in transgenic tobacco plants. *Molecular plant-microbe interactions* 20 : 1545–1554.

Ramesh S V, Sahu PP, Prasad M, Praveen S, Pappu HR .2017 . Geminiviruses and plant hosts: a closer examination of the molecular arms race. *Viruses* 9 : 256.

Rana VS, Singh ST, Priya NG, Kumar J, Rajagopal R .2012. Arsenophonus GroEL interacts with CLCuV and is localized in midgut and salivary gland of whitefly B. tabaci.

Richter KS, Ende L, Jeske H . 2015 . Rad54 is not essential for any geminiviral replication mode in planta. *Plant molecular biology* 87 : 193–202.

Rigden JE, Krake LR, Rezaian MA, Dry IB . 1994 . ORF C4 of tomato leaf curl geminivirus is a determinant of symptom severity. *Virology* 204 : 847–850.

Rogers SG, Bisaro DM, Horsch RB, Fraley RT, Hoffmann NL, Brand L, Elmer JS, Lloyd AM . 1986 . Tomato golden mosaic virus A component DNA replicates autonomously in transgenic plants. *Cell*45 : 593–600.

Rojas MR, Jiang H, Salati R, Xoconostle-Cázares B, Sudarshana MR, Lucas WJ, Gilbertson RL . 2001 . Functional analysis of proteins involved in movement of the monopartite begomovirus, Tomato

yellow leaf curl virus. Virology 291 : 110–125.

Rosas-Díaz T, Macho AP, Beuzón CR, Lozano-Durán R, Bejarano ER .2016. The C2 protein from the geminivirus Tomato yellow leaf curl Sardinia virus decreases sensitivity to jasmonates and suppresses jasmonate-mediated defences. *Plants* **5** : 8.

Rosas-Diaz T, Zhang D, Fan P, Wang L, Ding X, Jiang Y, Jimenez-Gongora T, Medina-Puche L, Zhao X, Feng Z . 2018 . A virus-targeted plant receptor-like kinase promotes cell-to-cell spread of RNAi. *Proceedings of the National Academy of Sciences*115 : 1388–1393.

Roumagnac P, Granier M, Bernardo P, Deshoux M, Ferdinand R, Galzi S, Fernandez E, Julian C, Abt I, Filloux D . 2015 . Alfalfa leaf curl virus: An aphid-transmitted geminivirus. *Journal of virology* 89 : 9683–9688.

Sablowski RWM, Meyerowitz EM . 1998 . A homolog of NO APICAL MERISTEM is an immediate target of the floral homeotic genes APETALA3/PISTILLATA. *Cell* 92 : 93–103.

Saeed ST, Samad A . 2017 . Emerging threats of begomoviruses to the cultivation of medicinal and aromatic crops and their management strategies. *VirusDisease* 28 : 1-17.

Saeed M, Zafar Y, Randles JW, Rezaian MA . 2007 . A monopartite begomovirus-associated DNA β satellite substitutes for the DNA B of a bipartite begomovirus to permit systemic infection. *Journal of General Virology* 88 : 2881–2889.

Sankaranarayanan S, Jamshed M, Kumar A, Skori L, Scandola S, Wang T, Spiegel D, Samuel MA . 2017 . Glyoxalase goes green: the expanding roles of glyoxalase in plants. *International journal of molecular sciences* 18 : 898.

Saunders K, Bedford ID, Briddon RW, Markham PG, Wong SM, Stanley J. 2000. A unique virus complex causes Ageratum yellow vein disease. *Proceedings of the National Academy of Sciences*97: 6890–6895.

Selth LA, Dogra SC, Rasheed MS, Healy H, Randles JW, Rezaian MA . 2005 . A NAC domain protein interacts with tomato leaf curl virus replication accessory protein and enhances viral replication. *The Plant Cell* 17 : 311–325.

Settlage SB, See RG, Hanley-Bowdoin L . 2005 . Geminivirus C3 protein: replication enhancement and protein interactions. *Journal of virology* **79** : 9885–9895.

Sharma P, Ikegami M . 2009 . Characterization of signals that dictate nuclear/nucleolar and cytoplasmic shuttling of the capsid protein of Tomato leaf curl Java virus associated with DNA β satellite. Virus research 144 : 145–153.

Shen W, Bobay BG, Greeley LA, Reyes MI, Rajabu CA, Blackburn RK, Dallas MB, Goshe MB, Ascencio-Ibáñez JT, Hanley-Bowdoin L .2018 . Sucrose nonfermenting 1-related protein kinase 1 phosphorylates a geminivirus Rep protein to impair viral replication and infection. *Plant Physiology* 178 : 372–389.

Shen W, Hanley-Bowdoin L. **2006**. Geminivirus infection up-regulates the expression of two Arabidopsis protein kinases related to yeast SNF1-and mammalian AMPK-activating kinases. *Plant Physiology* **142**: 1642–1655.

Shen Q, Hu T, Bao M, Cao L, Zhang H, Song F, Xie Q, Zhou X .2016 . To bacco RING E3 ligase NtRFP1 mediates ubiquitination and proteasomal degradation of a geminivirus-encoded β C1. *Molecular plant* 9 : 911–925.

Shen Q, Liu Z, Song F, Xie Q, Hanley-Bowdoin L, Zhou X .2011 . Tomato SlSnRK1 protein interacts with and phosphorylates β C1, a pathogenesis protein encoded by a geminivirus β -satellite.*Plant physiology* 157 : 1394–1406.

Shen W, Reyes MI, Hanley-Bowdoin L. **2009**. Arabidopsis protein kinases GRIK1 and GRIK2 specifically activate SnRK1 by phosphorylating its activation loop. *Plant physiology***150**: 996–1005.

Shibata M, Shinga J, Yasuhiko Y, Kai M, Miura K, Shimogori T, Kashiwagi K, Igarashi K, Shiokawa K . 2003 . Overexpression of S-adenosylmethionine decarboxylase (SAMDC) in early Xenopus embryos induces cell dissociation and inhibits transition from the blastula to gastrula stage. *International Journal of Developmental Biology*42 : 675–686.

Shivaprasad P V, Akbergenov R, Trinks D, Rajeswaran R, Veluthambi K, Hohn T, Pooggin MM . 2005 . Promoters, transcripts, and regulatory proteins of Mungbean yellow mosaic geminivirus. *Journal of virology* **79** : 8149–8163.

Singh CM, Singh P, Pratap A, Pandey R, Purwar S, Douglas CA, Baek K-H, Mishra AK . 2019 . Breeding for enhancing Legumovirus resistance in mungbean: current understanding and future directions. *Agronomy* 9 : 622.

Souza-Dias JAC, Sawazaki HE, Pernambuco-Fo PCA, Elias LM, Maluf H. **2008**. Tomato severe rugose virus: another begomovirus causing leaf deformation and mosaic symptoms on potato in Brazil. *Plant Disease* **92**: 487.

Stanley J, Latham JR. **1992**. A symptom variant of beet curly top geminivirus produced by mutation of open reading frame C4. *Virology* **190** : 506–509.

Sun Y-W, Tee C-S, Ma Y-H, Wang G, Yao X-M, Ye J . 2015 . Attenuation of Histone Methyltransferase KRYPTONITE-mediated transcriptional gene silencing by Geminivirus. *Scientific Reports* 5 : 16476.

Sunter G, Bisaro DM . 1991 . Transactivation in a geminivirus: AL2 gene product is needed for coat protein expression. *Virology* 180 : 416–419.

Sunter G, Gardiner WE, Rushing AE, Rogers SG, Bisaro DM .1987. Independent encapsidation of tomato golden mosaic virus A component DNA in transgenic plants. *Plant Molecular Biology* 8 : 477–484.

Susi H, Laine A-L, Filloux D, Kraberger S, Farkas K, Bernardo P, Frilander MJ, Martin DP, Varsani A, Roumagnac P . 2017. Genome sequences of a capulavirus infecting Plantago lanceolata in the Åland archipelago of Finland. *Archives of Virology* 162 : 2041–2045.

Tan PHN, Wong SM, Wu M, Bedford ID, Saunders K, Stanley J .1995. Genome organization of ageratum yellow vein virus, a monopartite whitefly-transmitted geminivirus isolated from a common weed. *Journal of General Virology* 76 : 2915–2922.

Teng K, Chen H, Lai J, Zhang Z, Fang Y, Xia R, Zhou X, Guo H, Xie Q . 2010 . Involvement of C4 protein of beet severe curly top virus (family Geminiviridae) in virus movement. *PloS one* 5 : e11280.

Tiendrebeogo F, Lefeuvre P, Hoareau M, Harimalala MA, De Bruyn A, Villemot J, Traore VSE, Konaté G, Barro N, Reynaud B . 2012 . Evolution of African cassava mosaic virus by recombination between bipartite and monopartite begomoviruses.[S02-11].

Trinks D, Rajeswaran R, Shivaprasad P V, Akbergenov R, Oakeley EJ, Veluthambi K, Hohn T, Pooggin MM . 2005 . Suppression of RNA silencing by a geminivirus nuclear protein, AC2, correlates with transactivation of host genes. *Journal of virology* **79** : 2517–2527.

Torres-delosSantos, R., Arévalo-Monterrubio, L. D., Torres-Acosta, R. I. and Martínez-Montoya, H. (2022) The other face of pollinating insects and their relationship to geminivirus transmission. In: *Geminivirus: Detection, Diagnosis and Management.* Elsevier, pp. 253-259.

Uchiyama A, Shimada-Beltran H, Levy A, Zheng JY, Javia PA, Lazarowitz SG . 2014. The Arabidopsis synaptotagmin SYTA regulates the cell-to-cell movement of diverse plant viruses. *Frontiers in plant science* 5 : 584.

Unseld S, Höhnle M, Ringel M, Frischmuth T . 2001 . Subcellular targeting of the coat protein of African cassava mosaic geminivirus. *Virology* 286 : 373–383.

Vaghi Medina CG, Teppa E, Bornancini VA, Flores CR, Marino-Buslje C, López Lambertini PM . 2018 . Tomato apical leaf curl virus: a novel, monopartite geminivirus detected in tomatoes in Argentina. *Frontiers in Microbiology* 8 : 2665.

Vanitharani R, Chellappan P, Pita JS, Fauquet CM .2004. Differential roles of AC2 and AC4 of cassava geminiviruses in mediating synergism and suppression of posttranscriptional gene silencing. *Journal of virology***78**: 9487–9498.

Varsani A, Roumagnac P, Fuchs M, Navas-Castillo J, Moriones E, Idris A, Briddon RW, Rivera-Bustamante R, Murilo Zerbini F, Martin DP .2017. Capulavirus and Grablovirus: two new genera in the family Geminiviridae. *Archives of Virology* 162: 1819–1831.

Vinutha T, Kumar G, Garg V, Canto T, Palukaitis P, Ramesh S V, Praveen S . 2018 . Tomato geminivirus encoded RNAi suppressor protein, AC4 interacts with host AGO4 and precludes viral DNA methylation. *Gene* 678 : 184–195.

Wang H, Buckley KJ, Yang X, Buchmann RC, Bisaro DM .2005. Adenosine kinase inhibition and suppression of RNA silencing by geminivirus AL2 and L2 proteins. *Journal of virology***79**: 7410–7418.

Wang H, Hao L, Shung C-Y, Sunter G, Bisaro DM . 2003 . Adenosine kinase is inactivated by geminivirus AL2 and L2 proteins. *The Plant Cell* 15 : 3020–3032.

Wang L-L, Wang X-R, Wei X-M, Huang H, Wu J-X, Chen X-X, Liu S-S, Wang X-W . 2016. The autophagy pathway participates in resistance to tomato yellow leaf curl virus infection in whiteflies. *Autophagy* 12: 1560–1574.

Wang Y, Wu Y, Gong Q, Ismayil A, Yuan Y, Lian B, Jia Q, Han M, Deng H, Hong Y . 2019. Geminiviral V2 protein suppresses transcriptional gene silencing through interaction with AGO4. *Journal of virology* 93 : 10–1128.

Wang B, Yang X, Wang Y, Xie Y, Zhou X \therefore 2018. Tomato yellow leaf curl virus V2 interacts with host histone deacetylase 6 to suppress methylation-mediated transcriptional gene silencing in plants. *Journal of virology* 92 : 10–1128.

Wang, L. and Lozano-Durán, R.(2023) Manipulation of plant RNA biology by geminiviruses. *Journal of Experimental Botany*, 74, 2311-2322.

Wang, Y., Hu, T., He, Y., Su, C., Wang, Z. and Zhou, X. (2023) N-terminal acetylation of the β C1 protein encoded by the betasatellite of tomato yellow leaf curl China virus is critical for its viral pathogenicity. *Virology*,**586**, 1-11.

Wei N, Serino G, Deng X-W . 2008 . The COP9 signalosome: more than a protease. Trends in biochemical sciences 33 : 592–600.

Wurzinger B, Nukarinen E, Nägele T, Weckwerth W, Teige M .2018. The SnRK1 kinase as central mediator of energy signaling between different organelles. *Plant physiology* **176** : 1085–1094.

Xie Q, Frugis G, Colgan D, Chua N-H . 2000 . Arabidopsis NAC1 transduces auxin signal downstream of TIR1 to promote lateral root development. *Genes & development* 14 : 3024–3036.

Xu G, Ma H, Nei M, Kong H . 2009 . Evolution of F-box genes in plants: different modes of sequence divergence and their relationships with functional diversification. *Proceedings of the National Academy of Sciences* 106 : 835–840.

Yaakov N, Levy Y, Belausov E, Gaba V, Lapidot M, Gafni Y .2011 . Effect of a single amino acid substitution in the NLS domain of Tomato yellow leaf curl virus-Israel (TYLCV-IL) capsid protein (CP) on

its activity and on the virus life cycle. Virus research 158:8-11.

Yang L, Fang Y, An C, Dong L, Zhang Z, Chen H, Xie Q, Guo H .2013 . C 2-mediated decrease in DNA methylation, accumulation of si RNA s, and increase in expression for genes involved in defense pathways in plants infected with beet severe curly top virus. *The Plant Journal* **73** : 910–917.

Yang X, Xie Y, Raja P, Li S, Wolf JN, Shen Q, Bisaro DM, Zhou X \cdot 2011 \cdot Suppression of methylation-mediated transcriptional gene silencing by β C1-SAHH protein interaction during geminivirus-betasatellite infection. *PLoS pathogens* 7 : e1002329.

Ye J, Yang J, Sun Y, Zhao P, Gao S, Jung C, Qu J, Fang R, Chua N-H . 2015 . Geminivirus activates ASYMMETRIC LEAVES 2 to accelerate cytoplasmic DCP2-mediated mRNA turnover and weakens RNA silencing in Arabidopsis. *PLoS pathogens* 11 : e1005196.

Youn J-H, Kim T-W . 2015 . Functional insights of plant GSK3-like kinases: multi-taskers in diverse cellular signal transduction pathways. *Molecular Plant* 8 : 552–565.

Zaidi SS-A, Tashkandi M, Mansoor S, Mahfouz MM . 2016 . Engineering plant immunity: using CRISPR/Cas9 to generate virus resistance. *Frontiers in plant science* 7 : 1673.

Zeng H, Xu L, Singh A, Wang H, Du L, Poovaiah BW .2015 . Involvement of calmodulin and calmodulin-like proteins in plant responses to abiotic stresses. *Frontiers in plant science* 6 : 600.

Zerbini FM, Briddon RW, Idris A, Martin DP, Moriones E, Navas-Castillo J, Rivera-Bustamante R, Roumagnac P, Varsani A, Consortium IR . 2017 . ICTV virus taxonomy profile: Geminiviridae. Journal of general virology 98 : 131–133.

Zhang Z, Chen H, Huang X, Xia R, Zhao Q, Lai J, Teng K, Li Y, Liang L, Du Q . 2011 . BSCTV C2 attenuates the degradation of SAMDC1 to suppress DNA methylation-mediated gene silencing in Arabidopsis. *The Plant Cell* 23 : 273–288.

Zhang J, Dong J, Xu Y, Wu J. **2012**. V2 protein encoded by Tomato yellow leaf curl China virus is an RNA silencing suppressor. *Virus research* **163** : 51–58.

Zhang L, Yao L, Zhang N, Yang J, Zhu X, Tang X, Calderón-Urrea A, Si H . 2018 . Lateral root development in potato is mediated by stu-mi164 regulation of NAC transcription factor. *Frontiers in plant science* 9 : 383.

FIGURE LEGENDS:

Figure 1 |Begomoviruses possess 5-7 proteins to cause infection in several host. Begomoviruses possess few proteins that interplay a role of interaction on intraspecies level and sometimes causes self-interaction to make a loop structure to prevent degradation from antiviral system in the host. These viruses interact with the host using replication associated proteins, membrane-based proteins and its satellite molecules for virus propagation in different hosts.

Figure 2 Geminivirus-host interaction network. This bioinformatics approach combining existing data highlights the mutualistic interaction to differentiate healthy and infected plants. Geminiviruses are transmitted through *B. tabaci* (whitefly), and during this transmission phase, CP of geminivirus binds with GroEL and HSP family of *B. tabaci* and transmitted during whitefly feeding cycle through healthy plant phloem cells. When geminivirus enters plant cell, it immediately starts using plant machinery for its multipurpose functions. This network depicts geminivirus proteins interaction with its targeted proteins (members in blue circle) in various hosts that needs to be verifying to understand geminivirus cell cycle and its movement.

Figure 3 A detail of geminiviruses encoded proteins-interaction with proteins of the host plant. Describing virus cycle, dark color in the figure indicates specific virus protein function after binding with well-known host proteins at each step and grey color shows protein is partially involved or has completed its role during cell cycle. During geminivirus infection, each virus protein performs its function after binding

with host proteins that are usually involve in normal leaf cell development, energy metabolism, plant signaling pathway, gene silencing and defense mechanism including biotic and abiotic stress. For virus replication and transcription in the nucleus, virus protein Rep/C1, TrAP/C2, REN/C3, C4, C5, β C1, NSP/MP (bipartite) executes proper replication and transcription using proof reading enzymes in the host. During this process, these viral proteins usually interact with plant proteins that are involved in cell cycle for normal leaf development. After using host transcription machinery, virus is being transmitted to cytosol into the cytoplasm where it binds with most of the defense related genes to help virus for cell to cell movement. Here, MP starts its function with β C1 protein for virus transmission within the cell and across the cell. TrAP and betasatellite shares host proteins in the nucleus as well as in the cytoplasm to cause pathogenicity and infection in the plant cell. At this phase, both proteins interact with defense related host proteins like sucrose non-fermenting related kinase protein (SnRK1), calmodulin like proteins and dicer like protein family to suppress host defense mechanism. MP plays its role using number of heat shock proteins like hsp70, hsc70 and H3. It is shown that C4 supports viral proteins C2, β C1 and MP protein to accumulate virus DNA at high level in the cytoplasm. The V2 protein replaces MP role in monopartite viruses and function with C4 for virus movement. Virus completes its cell cycle and packaging and is being transmitted to another plant cell to cause infection.

Figure 4 | Role of C4 during signal transduction and hormone signaling. Plasma membrane localized RLKs and SKs induces endogenous and exogenous signals for leaf shoot meristem growth, its development and defense mechanism. The C4 plays a main role in CLAVATA signaling during cell division to control the expression of WUS, a known gene required for homeostatic maintenance of stem cell and flower meristems. Additionally, C4 binds with BR-signaling kinases and RLKs to phosphorylate and control negatively downstream signaling components for embryo development. Through LRR-RLK, C4 disrupts a network of MAPK cascade which regulates stomata development and inflorescence growth. MAPK cascade constitute three activated kinase domains (MAPK kinase kinase MAPKKK/MEKK; MAPK kinase MAPKK/MKK; MAPK MPK). Phosphorylation of C4 through PAMP derived MAPK network controls plant immunity system by modulating ROS production, ethylene induction and hypersensitive cell death response. Inhibiting the activity of S-adenosyl homocysteine hydrolase-SAHH enzyme in the methyl cycle suppresses the DNA methylation dependent TGS pathway. The C4 protein also dephosphorylates several transcription factors (WRKY, MYB) in the nucleus that are essential for pollen development and floral abscission. It also hijacks TGS and PTGS pathway along-with phosphorylation and ubiquitination to contribute to the viral transcript production. Thereby, C4 interacts with various host genes to overcome plant growth and anti-geminiviral immunity.

Figure 1







Figure 3



Figure 4

