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A plant kinase plays roles in defense response against geminivirus by phosphorylation of a viral pathogenesis protein

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The plant SNF1-related kinase (SnRK1) is the α-subunit of the SnRK1 heterotrimeric compleses. Although SnRK1 is widely known as a key regulator of plant response to various physiological processes including nutrient- and energy-sensing, regulation of global metabolism, and control of cell cycle, development, as well as abiotics stress, less is known about the function of SnRK1 during pathogen infection. Our previous work has demonstrated that a tomato SNF1-related kinase (SlSnRK1) can interact with and phosphorylate βC1, a pathogenesis protein encoded by tomato yellow leaf curl China betasatellite. Our results also showed that the plant SnRK1 can affect genimivirus infection in plant and reduce viral DNA accumulation. Phosphorylation of βC1 protein negatively impacts its function as a pathogenicity determinant. Here we provide more information on interaction between βC1 and SlSnRK1 and propose a mechanistic model for the SlSnRK1-mediated defense responses against geminiviruses and the potential role of SnRK1 in plant resistance to geminivirus.

Keywords: geminivirus, βC1, SlSnRK1, protein interaction, phosphorylation, plant defense

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SUCROSE NON-FERMENTING1 (SNF1) was initially identified in a mutant yeast (*Saccharomyces cerevisiae*) defective in derepressing the Glc-regulated genes and thus unable to grow on media with sugars other than Glc.[1] The plant SNF1-related kinase (SnRK1) belongs to a conserved kinases family and consists of an α catalytic subunit, and a β and γ regulatory subunit. The plant SnRK1 also shares great homology with the mammalian AMP-activated protein kinase (AMPK).[2,3] Yeast SNF1, mammalian AMPK and plant SnRK1 are all known to function in regulating carbon metabolism and energy balance in eukaryotes,[3-8] and are metabolic sensors of Glc availability as well as the AMP to ATP ratios.[4] Activity of the plant SnRK1 can be stimulated by metabolic stresses including sugar starvation and dark treatment.[9] In addition, the SnRK1 can phosphorylate and negatively regulate key metabolic enzymes such as sucrose-phosphate synthase (SPS), 3-hydroxy-3-methylglutaryl-coenzyme A reductase, nitrate reductase and trehalose-6-phosphate synthase important for modulating plant metabolism.[10-13] Baena-Gonzalez et al. indicated previously that the SnRK1 can act as a master regulator of global gene expression in plant grown under the starvation and energy deprivation conditions. They also indicated that many genes regulated by SnRK1 are involved in plant primary and secondary metabolisms.[9] The plant SnRK1 is also known to play roles in development,[14-19] and in regulation of essential signaling pathways through interacting with proteosome and ubiquitin ligase components.[20] Although the SnRK1-mediated metabolic changes were considered to be important in plant defense against viruses,[21] the molecular role of SnRK1 in plant innate defense systems is largely unknown.

Geminiviridae is a large family of viruses with circular, single-stranded DNA genomes. This virus family contains four genera, and Begomovirus is the largest genus, consisting more than 200 different species, which cause devastating diseases in many economically important crops world-wide.[22,23] Begomoviruses have either monopartite or bipartite single-stranded

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DNA genomes.[22,24] In recent years many monopartite begomoviruses have been identified to have a betasatellite molecule (e.g., a circular, single-stranded DNA molecule of approximately 1,350 nucleotides). The betasatellite molecule is essential component in induction of typical disease symptoms in plants.[25-29] All known betasatellite molecules encode a single protein known as βC1. Many studies have identified the βC1 as the determinant of pathogenicity and suppressor of post-transcriptional gene silencing (PTGS).[30-32] A previous study by Yang et al. showed that the βC1 of tomato yellow leaf curl China betasatellite (TYLCCNB) can interact with Arabidopsis ASYMMETRIC LEAVES1 to cause morphological changes in leaf, and suppress specific jasmonic acid responses.[33] The βC1 of cotton leaf curl Multan betasatellite was shown to interact with a tomato ubiquitin-conjugating enzyme, SlUBC3 and this interaction is required for the βC1 pathogenesis.[34] In addition, the βC1 protein can inhibit methylation-mediated transcriptional gene silencing (TGS) by interacting with and inactivating S-adenosyl homocysteine hydrolase (SAHH), a methyl cycle enzyme required for TGS.[35]

Through yeast two-hybrid screen using a tomato cDNA library, we recently identified a tomato SNF1-related kinase (SlSnRK1) as a novel protein that interacts with βC1. We also determined that the βC1-interaction site is located in a region having an internal Ubiquitin-Associated domain (UBA) and/or a self-regulating AIS domain of SlSnRK1. Interestingly the conserved Serine/Threonine protein kinases catalytic domain (S_TKc) is not involved in the binding with βC1 as previously described.[36]

The catalytic domain is the core region of protein kinases and it consists of two lobes: a smaller N-terminal lobe (N-lobe) and a larger C-terminal lobe (C-lobe). These two lobes form a cleft that serves as a docking site for ATP. An activation segment was reported to present in the C-lobe and it regulates the catalytic activity of many protein kinases through its phosphorylation, except those protein kinases that can form catalytically active conformations in the absence of the activation segment phosphorylation.[37,38] More recently the SNF1 kinase found in the budding yeast was shown to be activated by three related but functionally redundant kinases (e.g., SAK1, TOS3 and ELM1).[7,40,41] In animals the SNF1 homolog, AMP-activated protein kinase (AMPK), was reported to be activated by two upstream protein kinases known as LKB1 and CaMKKβ.[7,42-47] In plants, two Arabidopsis kinases (e.g., GRIK1 and GRIK2) can activate the SnRK1.[48-50] The activation of SNF1 kinase through phosphorylation may occur after a conformational change which leads to a change of the activation loop position and allows the access to the kinase active site. The active site of protein kinase is known to be highly conserved and can be exemplified by the well-characterized cyclin-dependent kinase and mitogen-activated protein kinase (MAPK) cascades. Certain protein kinases can be activated or inhibited by specific polypeptide cofactors. For example, cyclin can partially activate the cyclin-dependent kinase Cdk2 by binding to the C helix and orients the αC helix to form an active conformation.[51] In contrast Src-homology SH2 and SH3 domains can inactivate Src tyrosine kinase by binding to the αC helix and an inhibitory *p*-tyrosine in the C-terminal tail, resulting in an inactive conformation.[52] Many reports have indicated that some proteins produced by plant pathogens can alter functions of certain protein kinases. For example, the AL2 from tomato golden mosaic virus (TGMV; genus Begomovirus) and L2 from beet curly top virus (BCTV; genus Curtovirus) were shown to inhibit the activity of an SNF1-related kinase (SnRK) through protein-protein interactions.[21] The NSP from cabbage leaf curl virus (CaLCuV) was also shown to inhibit protein kinase NIKs by binding to the putative active site within the NIK1 domain, and to the activation loop for Ser/Thr kinase. Binding to these two sites plays critical roles in both controlling the activity of protein kinases and substrate recognition.[53] *Phytophthora infestans* INF1 was also shown to alter NbLRK1 kinase activity by binding to the VIb subdomain and then suppressing its autophosphorylation.[54] These published information together with our previous results, showing that the βC1-interacting domain in the SlSnRK1 is not a kinase domain, suggest that interaction between βC1 and SlSnRK1 may not alter SlSnRK1's kinase activity. To test this hypothesis, we performed yeast complementation assays and our results show that indeed βC1 does not inhibit the kinase activity of SlSnRK1 in yeast cells.[36]

Furthermore, we used the NetPhos 2.0 server (www.cbs.dtu.dk/services/NetPhos/) to predict for the serine, threonine and tyrosine phosphorylation sites in the βC1 protein and our results show that Ser-33 and Thr-78 are likely the phosphorylation sites. Our amino acid sequence analysis revealed that the potential TYLCCNB βC1 phosphorylation site, Ser-33, is conserved among βC1 proteins encoded by different geminiviruses and the Thr-78 site is less conserved (**Fig. 1A**). The amino acid context of the βC1 Thr-78 (**Fig. 1B**) exhibits a substrate recognition motif similar to that reported for the SnRK1.[55] Our results show that the interaction between the βC1 and SlSnRK1 leads to phosphorylation of the βC1 protein but does not inhibit the kinase activity of SlSnRK1. Results of our previous in vitro kinase assay also indicated that the SlSnRK1 protein could phosphorylate βC1 mainly on the threonine at position 78 and serine at position 33.[36]

We demonstrated previously that SnRK1 could impact geminivirus infection and viral DNA accumulation in plant and phosphorylation of the βC1 protein could delay geminivirus infection in plant, attenuate disease symptoms and reduce viral DNA accumulation.[36] With our new findings and previously published results[4,29,31,33,35,56] we propose a mechanistic model for the SlSnRK1-mediated defense response against geminiviruses (**Fig. 2**). This model shows that SlSnRK1 attenuates geminivirus infection by interacting with and phosphorylating the pathogenicity determinant βC1 protein. Future investigations are needed to determine the effect of phosphorylation on βC1 protein's ability to suppress RNA silencing and/or methylation-mediated TGS. An investigation on βC1 protein degradation by the 26S proteasome may provide critical information to this model.

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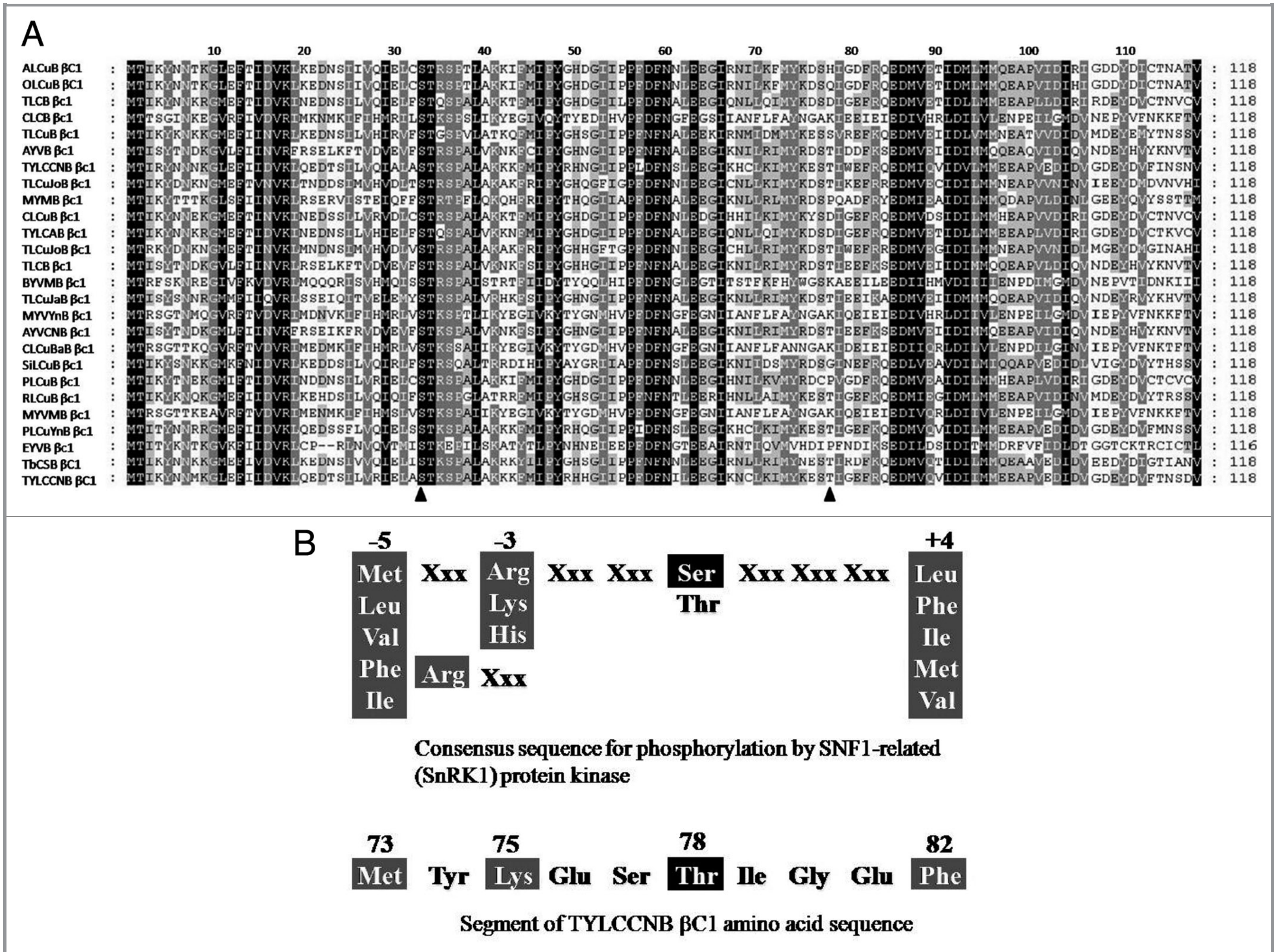

Figure 1. Analyses of TYLCCNB βC1 amino acid sequence. (A) Ser-33 is conserved among the geminivirus βC1 proteins. Predicted βC1 amino acid sequences of Ageratum yellow leaf curl betasatellite (ALCuB) (AJ316027), okra leaf curl betasatellite (OLCuB) (AJ316031), tomato leaf curl betasatellite (TLCB) (AJ316036), cotton leaf curl betasatellite (CLCB) (AJ316038), tomato leaf curl betasatellite (TLCuB) (AJ542492), Ageratum yellow vein betasatellite (AYVB) (AJ542497), tomato yellow leaf curl China betasatellite (TYLCCNB) (AJ781301), tomato leaf curl Joydebpur betasatellite (TLCuJoB) (AJ966244), Malvastrum yellow mosaic betasatellite (MYMB) (AM236769), chilli leaf curl betasatellite (CLCuB) (AM258978), tomato yellow leaf curl associated betasatellite (TYLCAB) (DQ644567), tomato leaf curl Joydebpur betasatellite (TLCuJoB) (EF190216), tomato leaf curl betasatellite (TLCB) (EU286799), Bhendi yellow vein mosaic betasatellite (BYVMB) (NC_003405), tomato leaf curl Java betasatellite (TLCuJaB) (NC_005497), Malvastrum yellow vein Yunnan betasatellite (MYVYnB) (NC_006632), Ageratum yellow vein China betasatellite (AYVCNB) (NC_007067), cotton leaf curl Bangalore betasatellite (CLCuBaB) (NC_007219), Sida leaf curl betasatellite (SiLCuB) (NC_007639), pepper leaf curl betasatellite (PLCuB) (NC_010235), radish leaf curl betasatellite (RLCuB) (NC_010239), Malachra yellow vein mosaic betasatellite (MYVMB) (NC_010328), pepper leaf curl Yunnan betasatellite (PLCuYnB) (NC_010619), Emilia yellow vein betasatellite (EYVB) (NC_012666), tobacco curly shoot betasatellite (TbCSB) (AJ421484) and tomato yellow leaf curl China betasatellite (TYLCCNB) (AJ781299) were aligned using the Clustal method with PAM250 residue weight (DNASTAR Inc.). Shading indicates extent of conservation/similarity. The black triangle represents Ser-33 and Thr-78. (B) A recognition motif for SnRK1 and the amino acid context of βC1 potential phosphorylation sites.

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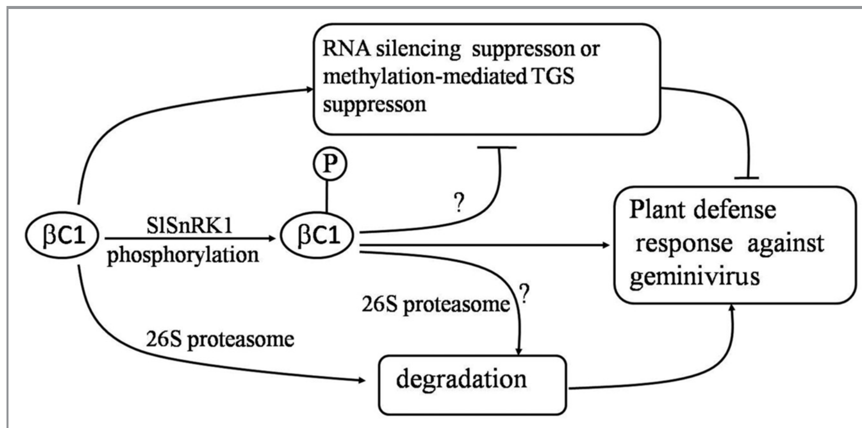

Figure 2. A proposed model for functions of SlSnRK1 in plant defense response against geminivirus. The SlSnRK1 interacts with and phosphorylates the βC1 protein, and phosphorylation of βC1 may negatively affect the βC1 function on RNA silencing suppression or methylation-mediated TGS suppression, which further leads to attenuation of genimivirus infection. Alternatively, SlSnRK1 may phosphorylate βC1 for degradation by the 26S proteasome which also leads to attenuation of disease symptoms and reduction of virus infection. Arrows represent activation and T lines represent repression.

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