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COMPREHENSIVE REVIEW

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Plasmodesmata-located proteins: The molecular hubs in noncell-autonomous immunity

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Abstract

Plasmodesmata (PD) are unique connection structures between plant cells that play a key role in the transportation of signal molecules and metabolites. In noncell-autonomous immunity, PD function as battlegrounds against intruders, including viral, fungal and bacterial pathogens. Recent studies have demonstrated that a variety of proteins, including catalytic enzymes involved in callose metabolism, callose-binding proteins, receptor kinases, lipid-associated proteins, and tether proteins, serve as critical molecular hubs in plant defense responses by facilitating the closure of PD. Here, we present a comprehensive overview of the regulation mechanisms of PD-related proteins in the process of plant disease resistance. Moreover, we discuss the challenges currently encountered in PD regulation and highlight critical questions for future investigation. Addressing these issues will further enhance our understanding of intercellular communication in plant defense system and promote its application in agriculture.

KEYWORDS

non-cell-autonomous immunity, PD-related proteins, plasmodesmata

1 | INTRODUCTION

The Chinese proverb, “Many hands make light work,” illustrates the limitations of individual efforts in various activities. Similar to human social behaviors, nearly all multicellular organisms, whether composed of animal or plant cells, exhibit the phenomenon of information and material exchange between cells. Plasmodesmata (PD), membranous junction structures unique to plant cells, serve as the main path for the transmission of substances and signals in planta. PD are jointly constructed by the plasma membrane (PM) and the cell wall of adjacent cells, forming microchannels with a diameter of approximately 20–40 nm.[1] These structures cross the cell wall and integrate the cytoplasm of neighboring cells into a unified symplastic system. Through PD, plant cells facilitate the direct exchange of various biological macromolecules and small molecules, including proteins, small RNA molecules, plant hormones, and organic metabolites.[2] Therefore, PD play a core role in regulating plant growth and development, as well as in responding to environmental stimuli.[2–4]

Over the course of long-term interactions with pathogens, plants have evolved a complex and sophisticated defense system that encompasses both cell-autonomous and noncell-autonomous immunity. Cell-autonomous immunity relies on the sense of pathogen-associated molecular patterns (PAMPs) by PM-located pattern recognition receptors (PRRs) and the subsequent activation of downstream signal cascades including cytosolic calcium bursts, mitogen activated protein kinase (MAPK) phosphorylation, and reactive oxygen species (ROS) production. Noncell-autonomous immunity coordinates systemic defense through intercellular signal transmission, in which PD

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play a central role in regulating systemic immune signal transduction through the symplastic route. PD are under dynamic control by fine-tuning its pore size (i.e., permeability) at specific developmental stages or in response to external stimuli. During pathogen and insect invasion, plants can rapidly close PD to restrict cell-to-cell communication. Up to now, various proteins that show a stable physical association with PD have been identified, with distinct roles in plasmodesmal construction, callose metabolism, lipid binding and transport, etc. Some of them serve as critical molecular hubs that respond to immune signals and execute defense regulatory functions by closing the PD.

Recently, investigations into the regulatory mechanisms of PD-related proteins have emerged as a key focus in plant immunity research. Here, we provide a comprehensive review of various types of PD-associated proteins and their functions in immune signal perception, calcium signaling activation, and callose metabolism, with a focus on how they participate in plant resistance to bacteria, fungi, and viruses by dynamically regulating plasmodesmal permeability. Future research directions in this field are also discussed.

2 | CALLOSE-RELATED PROTEINS

Callose, a polysaccharide molecule composed of glucose residues linked by β-1,3-bonds, is a key regulator of plasmodesmal permeability.[5] In response to the infection of various pathogens, callose reversibly and temporarily deposits on the cell walls in the neck region of the PD, forming extracellular ring structures that compress the cytoplasmic membrane, thereby dynamically regulating the permeability of PD.[6]

PD callose binding proteins (PDCBs) are a subfamily of proteins that target PD, with an N-terminal X8 domain that binds callose and a C-terminal glycosylphosphatidylinositol (GPI) signal anchoring to the PM.[7] PDCBs are involved in regulating callose deposition and intercellular communication in plants.[8] Overexpression of *PDCB1* results in an increase in callose accumulation and a decrease in the diffusion ability of green fluorescent protein (GFP) through PD.[7] Based on the conservation analysis of amino acids, PDCB1 has two homologous proteins, namely PDCB2 and PDCB3. Localization observations of PDCB2 and PDCB3 fused with yellow fluorescent protein indicate that PDCB2 and PDCB3 exhibit similar localization to PDCB1 at PD.[7] Subsequent research studies also confirmed that the mutant of *PDCB2* shows a reduction in callose deposition at PD.[8]

In plant cells, callose synthase (CALS) and β-1,3-glucanase (BG) are identified as the enzymes responsible for callose synthesis and degradation, respectively, thereby regulating the dynamic balance of callose.[6] CALSs are considered processive glycosyltransferases that catalyze the polymerization of UDP-glucose into a β-1,3-glucan backbone. In *Arabidopsis*, CALSs consist of 12 members, named CALS1–12, each performing distinct functions in different organs or signaling pathways.[6] *CalS1* and *CalS8* are key genes involved in altering plasmodesmal permeability upon pathogen infection.[9] Defense hormone salicylic acid (SA) and ROS function as defense signals to induce PD' closure via the distinct regulation of callose deposition. In the *CalS1* mutant, no significant changes of plasmodesmal callose accumulation and CF dye movement were observed after SA treatment or infection by *Pseudomonas*.[9] The *CalS8* mutant was defective in ROS- or wounding-induced callose accumulation and plasmodesmal regulation.[9] Similar to the PDCBs, most PD-located β-1,3-glucanases (BGs) are also GPI-anchored proteins.[10,11] AtBG_ppap (putative plasmodesmal associated protein) with the neck location at PD has been proven to be involved in the degradation of callose.[10] Compared to wild-type (WT) plants, the callose level at PD was increased in *AtBG_ppap* mutant, whereas the GFP cell-to-cell movement and the spread of tobamoviruses were reduced,[10,12] indicating the role of BGs in plasmodesmal permeability and plant defense regulation.

3 | PLASMODESMATA-LOCATED PROTEINS

Plasmodesmata-located proteins (PDLPs) are characterized as type I membrane proteins with the C-terminal located in the cytoplasm and the N-terminal located in the extracellular region. PDLPs can be targeted to the PD through specific exocytosis pathways and participate in regulating its permeability, thereby regulating systemic resistance against viruses, pathogens and insects.[13–15]

As two significant members of PDLPs, both PDLP1 and PDLP5 negatively regulate the intercellular transport by modulating plasmodesmal callose deposition.[13,14] When *PDLP1* and *PDLP5* were overexpressed, the diffusion of GFP between cells was significantly inhibited.[4,13] PDLP1 is transferred to the PD through Brefeldin A (BFA)-sensitive and coat protein complex II (COPII)-dependent secretion pathway and co-localizes with the callose in the PD.[13,15] The *pdlp1* mutant could not close PD when treated by flagellin peptide (flg22) and SA, suggesting that PDLP1 is required for elicitor-triggered signaling cascades.[15] PDLP5 is located in the central region of the PD channel and is associated with the PD in the primary pit field of the cell wall.[4] In response to flg22 or chitin treatment, the plasmodesmal permeability of *pdlp5* exhibited no significant difference compared to that under resting state.[15] Upon bacterial infection, *PDLP5*

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overexpression resulted in an enhanced defense, whereas the *PDLP5* mutant showed increased susceptibility, which may account for the PD-dependent movement of bacterial effectors.[4,14] Moreover, PDLP5 is also involved in the regulation of systemic signaling in response to herbivore attack. Upon mechanical wounding, the propagating $[Ca^{2+}]_{cyt}$ in the target leaf was limited to the regions adjacent to the vasculature in *PDLP5* overexpression line, although the leaf-to-leaf transmission of the $[Ca^{2+}]_{cyt}$ increase was not affected.[16]

PDLP7 plays a crucial role in callose accumulation and the PD-dependent movement of molecules.[14] Overexpression of *PDLP7* in *Nicotiana benthamiana* leaves affects the intercellular movement of the *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst* DC3000) effector, HopAF1.[14] Furthermore, recent studies have shown that PDLP7 dynamically regulates the opening and closing of PD through its interaction with BG10, thereby regulating the plant's resistance to turnip mosaic virus (TuMV) and cucumber mosaic virus (CMV).[17] PDLP7 is the only PDLP member that is significantly upregulated upon TuMV and CMV infections.[17] When viruses attack, the highly expressed PDLP7 interacts specifically with BG10 through its GnK2-1 domain to inhibit callose hydrolysis.[17] As a result, increased deposition of callose occurs at PD to mediate its closure, thereby enhancing resistance against viral invasion.[17]

4 | PLASMA-MEMBRANE-LOCATED PROTEIN KINASES

Plants employ a two-layered innate immune system to cope with pathogen invasion. As the first layer of immune system, PM-located PRRs sense PAMPs to activate pattern-triggered immunity (PTI). In addition to classical intracellular signaling pathways, PAMPs such as chitin and flg22, could induce the synthesis of callose through specific receptor kinases and downstream regulatory factors, thereby triggering the closure of PD and establishing a specific PD-dependent immune response.

The receptor kinase LysM domain-containing glycosylphosphatidylinositol-anchored protein 2 (LYM2), the *Arabidopsis* homolog of a rice chitin receptor-like protein, is a PM-located protein with PD association.[18] Upon chitin treatment, LYM2 recruits LysM-containing receptor-like kinase 4 (LYK4) and the downstream calcium-dependent protein kinases CPK6 and CPK11, which become enriched at the plasmodesmatal PM region.[19] This complex phosphorylates the Ser^{347} and Ser^{133} sites of NADPH oxidase respiratory burst oxidase homolog D (RbohD) to produce ROS and induce localized callose synthesis, finally leading to plasmodesmal closure.[19] Additionally, compared with WT plants, the mutant of *LYM2* exhibited susceptibility to the fungal pathogen *Botrytis cinerea* with increased spread of cell death of leaf cells,[18] indicating that chitin-triggered regulation of molecular flux between cells is essential for defense responses. In contrast, the chitin-recognition receptor chitin elicitor receptor kinase 1 (CERK1) could not mediate PAMP-triggered reduction in plasmodesmal flux but is specifically responsible for chitin-triggered MAPK activation.[18] These data reveal an independent signaling cascade that is executed in PD, distinct from classic PM signaling.

Plasmodesmal closure triggered by flg22 relies on its receptor, flagellin-sensitive 2 (FLS2), and the downstream calmodulin-like protein, calmodulin-like 41 (CML41).[20] The *fls2* mutant exhibited no alteration in red fluorescent protein diffusion in response to flg22, indicating that FLS2 functions in plasmodesmal regulation after PAMP treatment.[18] CML41 is specifically localized at PD, where it senses flg22-induced Ca^{2+} signals, facilitates callose deposition, and induces plasmodesmal closure.[20] *CML41-amiRNA* lines showed increased sensitivity to *Pst* DC3000 (cor^{-}) with higher bacterial proliferation, whereas overexpression lines exhibited enhanced resistance with less bacterial growth, suggesting that CML41 is required for a complete defense response against *Pseudomonas* infection.

Nonrace specific disease resistance/hin1 hairpin-induced-like protein 3 (NHL3) is an important protein that functions in plasmodesmal immune signaling.[15] Recent research studies demonstrated that the complex formed by PDLP1/5 and NHL3 serves as an integrative node, relaying immune signals such as chitin and flg22 to activate CALS1, thereby promoting callose deposition and plasmodesmal closure.[15] In detail, the *nhl3* mutant failed to close PD in response to flg22 or chitin treatment. The enhanced callose deposition at PD in *PDLP5* overexpression lines was reverted to WT levels in the *nhl3* mutant background. Similarly, the absence of NHL3 also reverted the lower PD permeability of *PDLP1* overexpression plants to WT levels, indicating that NHL3 is required for the function of PDLP1/5.

5 | LIPID-RELATED PROTEINS

The PM lipid composition of PD is an important factor regulating its permeability. Similar to the specific nanodomains of PM, the regions of PD are rich in highly ordered lipid structures formed by phospholipids and sphingolipids with saturated fatty acid chains, and sterols.[11] Due to the enrichment of ordered lipids, the nanodomain marker protein, remorin (REM), is also recruited to the PM of PD region.[11,21–23]

Sphingolipids are formed by a fatty acid bonded to a long-chain base (LCB) through an amide bond and a

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head group.[24] In *Arabidopsis* leaves, 85%–90% of sphingolipid LCBs contain a *cis* or *trans* D8 double bond, which is produced by sphingoid LCB Δ8 desaturase (SLD).[24] SLD1 exhibits desaturase activity, which is responsible for introducing a double bond between the 8th and 9th carbon atoms of the sphingosine skeleton through an oxidation reaction, resulting in the formation of unsaturated sphingosine.[24]

Compared with PM, the proportion of t18:0-based sphingolipids in PD was significantly increased, and the content of sphingolipids containing saturated very long-chain fatty acids was slightly higher, indicating that t18:0-based sphingolipids may be involved in the regulation of PD function.[25] The total amounts of t18:0-based sphingolipids were significantly elevated in the *sld1sld2* mutant, which facilitates the recruitment of PDLP5, known for its specific binding affinity to t18:0.[25] The level of plasmodesmal callose is increased by the enrichment of PDLP5, thereby decreasing the PD permeability.[25] In addition, there was a significant enhancement in resistance to *Pst* DC3000 and *Verticillium dahliae* in *sld1sld2* mutant. The deletion of PDLP5 in *sld1sld2* mutant could revert plasmodesmal morphological defects and the defense phenotypes observed in this mutant.[25]

The defense hormone SA causes PD closure through a lipid raft-dependent way.[26] In detail, SA induces the aggregation of the 14-3-3 family member general regulatory factor 10 (GRF10) at PD to facilitate the polymerization of REM1.2/1.3 proteins, thereby leading to a higher-ordered lipid phase.[26] The removal of sterols by methyl-β-cyclodextrin (MβCD) counteracted the effect of SA on PD closure, highlighting the necessity of a specific arrangement of the membrane lipid raft.[26] The mutation of REM proteins, crucial regulators of lipid raft formation, resulted in significantly less sensitivity to SA-induced changes in lipid order, thereby leading to wider plasmodesmal apertures and increased plasmodesmal permeability.[26] Moreover, overexpression of REMs in *N. benthamiana* leaves impeded virus spreading among host plant cells.[26] After pathogen infection, multiple chemical signal molecules such as SA, azelaic acid (AzA) and glycerol-3-phosphate (G3P) are synthesized in plant to induce systemic acquired resistance (SAR).[27,28] SA is transported in the phloem through the apoplast; in contrast, AzA and G3P transport occurs through the symplastic route regulated by PD.[28] As lipid transporters, Aza-induced 1 (AZI1) and defective in induced resistance 1 (DIR1) are responsible for the cross-cellular transport of AzA and G3P, respectively.[28] PDLP1 could interact with AZI1 and facilitate its intracellular distribution while PDLP5 could regulate the efficiency of symplastic transport for AzA/G3P by modulating PD aperture, thereby affecting SAR.[28]

6 | ENDOPLASMIC RETICULUM-PLASMA MEMBRANE TETHER PROTEINS

In recent years, with the in-depth research on the interaction of the intracellular membrane system, the concept of "membrane contact sites (MCSs)" has gradually become a significant focus for the study of transmembrane signaling and material transport. MCSs are typically defined as the regions where two intracellular membrane structures form dynamic contacts at nanoscale distances (approximately 30–50 nm apart).[29] These contacts do not involve membrane fusion but allow for the efficient transport of lipids, ions, and small molecules, serving as key nodes in processes such as cellular metabolic integration, signal transduction, and stress responses. In plants, known MCSs include contact sites between endoplasmic reticulum-PM (ER-PM), ER-vacuole, and ER-chloroplast, which play pivotal roles in regulating calcium signals, lipid homeostasis, and hormone signaling.[29]

Notably, recent research studies, for the first time, defined PD as unconventional tubular ER-PM MCSs.[30] Three multiple C2 domain and transmembrane region proteins (MCTPs), namely MCTP3, MCTP4 and MCTP6, form an ER-PM tethering complex within plasmodesmal bridges. Loss of *MCTP* led to looser membrane junctions and increased intercellular molecular flow, which is independent of callose deposition.[30] It was further revealed that the signaling lipid phosphatidylinositol-4-phosphate (PI4P) regulates the anchoring of MCTPs to the PM by binding to their C2 domain. Elevated PI4P levels (such as in *sac7*, which has a mutation in the PI4P 4-phosphatase-coding gene *SAC7*) exhibited tighter ER-PM connection within PD and inhibited molecular movement, whereas low PI4P levels (such as from the overexpression of *SAC7*) promoted ER-PM detachment events within PD and enhanced molecular flow. This discovery demonstrates a noncanonical plasmodesmal regulation mechanism, which may provide a potential function of PD in plant immunity.

Additionally, Synaptotagmin 1 (Syt1) in *Arabidopsis* is also a MCS-located protein which acts as a tether between the ER and PM at sites where both cellular membranes are in close proximity, called ER-PM contact sites (EPCSs).[31] The transmembrane domain of Syt1 is anchored to the cortical ER, whereas the C2 domains (C2A, C2B) facilitate docking to the PM.[32] The permeability of PD in the *syt1-2* mutant was similar to that of WT plants in resting condition, whereas when treated with PAMPs, the *syt1-2* mutant showed no decrease in PD permeability that is observed in WT plants, indicating that Syt1 is involved in PAMP-induced PD closure.[31] The concentration of phosphatidylinositol

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4,5-bisphosphate ($PI(4,5)P_2$) increases in the PD region upon flg22 treatment. Syt1 senses the up-regulated $PI(4,5)P_2$ level through its C2 domain and accumulates at the PD, subsequently recruiting the calcium-permeable transporter annexin 4 (ANN4) and forming the Syt1/ANN4 complex.[31] The *syt1-2* or *ann4* mutants failed to elicit PD-associated Ca^{2+} signatures in response to flg22, suggesting that the Syt1/ANN4 complex facilitates the generation of PD-localized calcium signaling. This process results in callose deposition for PD closure, thereby modulating intercellular communication and restricting the spread of bacterial infection.[31]

7 | EXPLOITATION OF PD-ASSOCIATED PROTEINS BY VIRUSES AND MICROBIAL PATHOGENS

In addition to serving as vital regulators to fine-tune defense responses against pathogen attacks, some PD-located proteins have been uncovered as key nodes hijacked by viruses and microbial pathogens to remodel callose dynamics and plasmodesmal aperture, thereby facilitating their efficient infection and systemic spread.

Viruses could utilize PDs to achieve both local and systemic infection within host plants. *At*OSM34, a pathogenesis-related 5 family protein, functions as a proviral factor through diminishing callose deposition at PD to promote TMV intercellular movement.[33] In rice, two PD-associated proteins, flotillin-1 and importin α4, are induced by rice stripe virus (RSV) to enlarge plasmodesmal apertures, thereby facilitating viral cell-to-cell transport.[34,35] Moreover, the potato PM-localized protein cation binding protein StPCaP1 is recruited to PD by potato virus Y (PVY, *Potyvirus*) and potato virus S (PVS, *Carlavirus*), leading to reduced callose deposition at PD and promoted viral intercellular movement.[36]

Besides viruses, effectors from various pathogens, such as bacteria, oomycetes and fungi, also manipulate plasmodesmal permeability to enhance their spread between cells. The bacterial pathogen *Pst* DC3000 delivers the effector protein HopO1-1 to promote its colonization and invasion through interaction and destabilization of PD-located protein PDLP7.[37] Likewise, the *Phytophthora brassicae* (a type of oomycetes) effector RxLR3 can target three members of the CALS family, CalS1, CalS2 and CalS3, to interfere with plasmodesmal callose deposition, thereby facilitating PD-dependent cell-to-cell trafficking.[38] Additionally, the rice blast fungus *Magnaporthe oryzae* secretes the effector Pwl2 to facilitate host infection by displacing the heavy metal-binding isoprenylated protein HIPP43 from PD.[39]

8 | CONCLUSION

PD represent a unique connection structure of plant cells and have long been regarded as the core channel for the exchange of substances and information between plant cells. In the context of pathogen infection, PD not only serves as the "breakthrough point" for pathogen utilization but also as a vital defense line for plants to regulate the intercellular barrier and restrict the spread of pathogens. In recent years, multiple mechanisms of PD-located proteins in plant immune regulation have gradually been revealed.

PD-localized proteins participate in regulating plant resistance through multiple ways.

First, PD-localized proteins can affect the morphology and aperture of PD, thereby influencing the spread of viral particles and pathogen effectors. The synthase and degrading enzymes of callose jointly maintain the opening or closing of plasmodesmal channels (Figure 1). PDLPs and callose-binding protein PDCBs can modulate the permeability of PD by influencing callose deposition (Figure 1). Furthermore, PD-localized proteins can regulate the long-distance transport of signaling molecules, affecting systemic defense responses. Lipid-related proteins involved in the regulation of lipid composition and fluidity affect the transport capacity of PD, and further influence SAR in plants (Figure 1). Moreover, several PD-located protein kinases and related signaling complexes may serve as hubs for pathogen recognition or signal transduction, triggering downstream defense events such as ROS burst and callose deposition (Figure 1). Additionally, the tether proteins between the ER and PM could dynamically regulate the contact degree of ER-PM in the PD region, enabling opening/closing regulation of PD independent of the callose pathway (Figure 1). Finally, some PD-associated proteins are exploited by viruses and microbial pathogens to alter callose dynamics and PD aperture, thereby promoting their infection and systemic dissemination. Collectively, the regulation of PD aperture and associated defense responses involves coordinated actions of different types of PD-related proteins.

Although the role of PD-localized proteins in plant immunity has been preliminarily demonstrated, several key issues remain to be addressed. Immune signals such as PAMPs can trigger the subcellular relocalization of PD proteins, but the specific regulatory pathways remain unclear. The composition of membrane lipids in the PD region are key to regulate the permeability of PD; however, the roles of lipid metabolic and transport proteins still need to be refined. Recent studies have revealed that PD are tubular MCSs between the ER and PM, but the noncallose-dependent mechanisms by which ER-PM tether proteins regulate the opening and closing of PD still need to be further explored. PD-located proteins (such as PDLPs,

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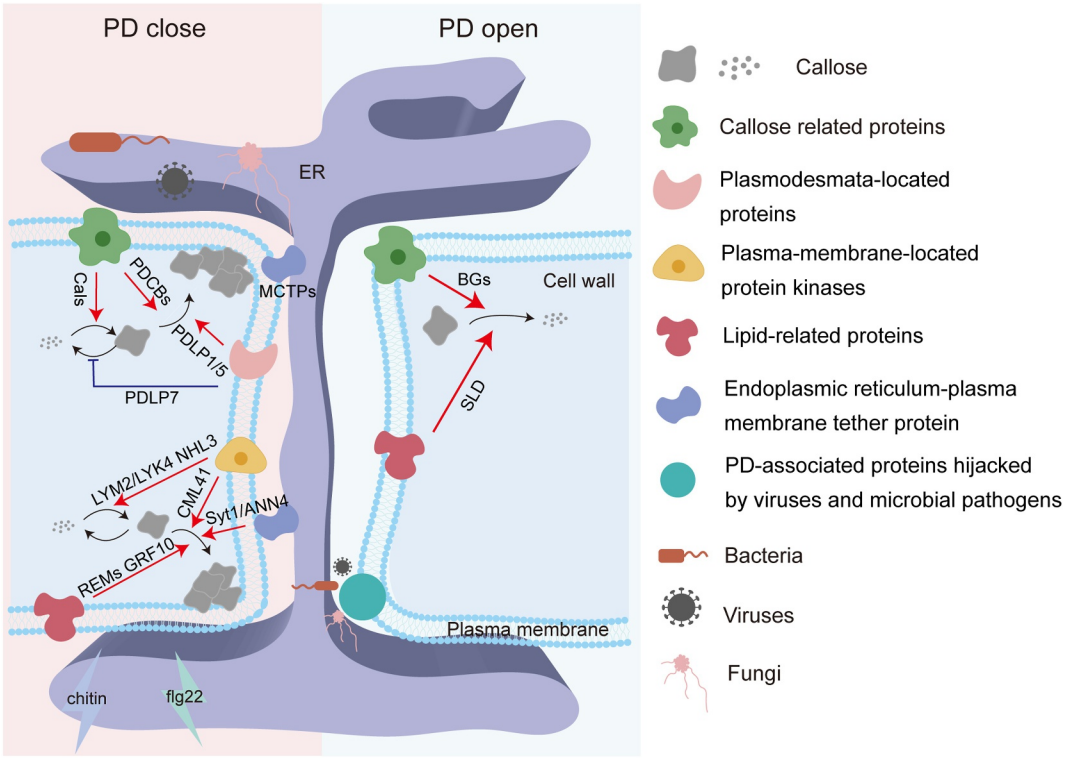

FIGURE 1 The model of plasmodesmata-located proteins regulating the noncell-autonomous immunity.

PDCBs, RLKs, MCTPs, etc.) play a central role in immune regulation, whereas the synergistic mechanisms of multiple PD-associated proteins have not yet been fully elucidated. PD are both spears and shields in the interaction between pathogens and plants, necessitating clarification of the interactions between PD proteins and pathogenic effector proteins as well as their antagonistic responses. Systematically elucidating the regulatory mechanisms of PD-localized proteins in plant defense will not only provide a more comprehensive functional framework for PD and an in-depth paradigm of intercellular communication in plant immunity but also offer a theoretical basis and potential targets for disease-resistant breeding strategies based on plasmodesmal function improvement.

When plants are growing normally, plasmodesmata (PD) are open (right) and used for information exchange between cells. During pathogen and insect invasion, plants can rapidly close PD (left) to restrict cell-to-cell communication by regulation of PD-related proteins. In addition, some PD-located proteins were hijacked by pathogenic microorganism to remodel callose dynamics and plasmodesmal aperture, thereby facilitating their efficient infection and systemic spread.

AUTHOR CONTRIBUTIONS

Zheng Wu: Writing—original draft. **Xiaoyi Shan**: Writing—review and editing; conceptualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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