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Dual functionality of pathogenesis-related proteins: defensive role in plants versus immunosuppressive role in pathogens

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Plants respond to pathogen exposure by activating the expression of a group of defense-related proteins known as Pathogenesis-Related (PR) proteins, initially discovered in the 1970s. These PR proteins are categorized into 17 distinct families, denoted as PR1-PR17. Predominantly secreted, most of these proteins execute their defensive roles within the apoplastic space. Several PR proteins possess well-defined enzymatic functions, such as β-glucanase (PR2), chitinases (PR3, 4, 8, 11), proteinase (PR7), or RNase (PR10). Enhanced resistance against pathogens is observed upon PR protein overexpression, while their downregulation renders plants more susceptible to pathogen infections. Many of these proteins exhibit antimicrobial activity *in vitro*, and due to their compact size, some are classified as antimicrobial peptides. Recent research has unveiled that phytopathogens, including nematodes, fungi, and phytophthora, employ analogous proteins to bolster their virulence and suppress plant immunity. This raises a fundamental question: how can these conserved proteins act as antimicrobial agents when produced by the host plant but simultaneously suppress plant immunity when generated by the pathogen? In this hypothesis, we investigate PR proteins produced by pathogens, which we term “PR-like proteins,” and explore potential mechanisms by which this class of virulence factors operate. Preliminary data suggests that these proteins may form complexes with the host’s own PR proteins, thereby interfering with their defense-related functions. This analysis sheds light on the intriguing interplay between plant and pathogen-derived PR-like proteins, providing fresh insights into the intricate mechanisms governing plant-pathogen interactions.

KEYWORDS

plant immunity, fungal pathogens, secretion, apoplast, virulence, immune signaling, sperm coating proteins (SCPs), venom allergen-like proteins (VALs/VAPs)

Introduction

Plants are constantly challenged by various organisms, including fungi, oomycetes, bacteria, and viruses, which can compromise the plant's fitness and survival (Teixeira et al., 2019). Plant pathogens affect forest plantations and most staple crops, decreasing productivity worldwide and severely compromising food security (Fones et al., 2020). The situation is expected to get worse, given the current rate of growth of the human population, the effect of climate change, the prevalence of monocultures, and the rise in pathogen resistance (Singh et al., 2023).

To combat the incursion of pathogens, plants have developed an intricate defense strategy comprising both inherent and inducible mechanisms (Jones and Dangl, 2006; Han, 2019). Constitutive defenses, operating as the foremost line of protection, encompass features like cutin, waxes, robust lignin deposition on cell walls, and the synthesis of antimicrobial small molecules, such as phytoanticipins (Li et al., 2020). The inducible defense mechanisms can be broadly categorized into two main types: Pathogen-associated molecular pattern (PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI). Furthermore, plants can develop systemic acquired resistance (SAR), a sophisticated response that fortifies defense throughout the plant following localized pathogen attack (Zhou and Zhang, 2020; Tanaka and Heil, 2021; Ngou et al., 2022).

Pathogenesis-related proteins

Amidst the spectrum of plant defense mechanisms, PR proteins stand as a prominent line of primary defense. These proteins are categorized into various families, denoted as PR1 to PR17 and beyond, based on their unique structural and functional characteristics (van Loon and van Kammen, 1970). Typically, PR proteins are induced in response to pathogen invasion and complement the action of small organic defense compounds that primarily serve to fend off herbivores but also exhibit antimicrobial activities (Westrick et al., 2021).

The discovery of PR proteins traces back to pioneering studies in the 1970s, where their robust induction in response to tobacco mosaic virus infection was first observed (Gianinazzi et al., 1970; van Loon and van Kammen, 1970). Subsequent research extended this finding to various plant species facing diverse pathogens, including oomycetes, fungi, bacteria, viruses, viroids, nematodes, and insect pests (van Loon et al., 1987; Stintzi et al., 1993; Van Loon and Van Strien, 1999; Edreva, 2005; van Loon et al., 2006; Jain and Khurana, 2018; Zribi et al., 2021). The transcripts encoding PR proteins show rapid accumulation following PTI and ETI, with their expression often regulated by the signaling molecule salicylic acid (SA). Notably, PR1 proteins are distinguished as crucial molecular markers for heightened plant defense due to the induction of SAR (Vlot et al., 2009).

PR proteins exhibit distinct biochemical properties, such as low molecular weight (ranging from 6 to 43 kDa), extractability and stability at low pH (below 3, a condition under which most other proteins denature), thermostability, and resistance to proteases (Van Loon and Van Strien, 1999). They are found throughout various plant organs, with leaves being particularly rich in these proteins, where they can constitute up to 5-10% of total leaf proteins. The PR1 family, for example, can comprise 1-2% of total leaf proteins (Van Loon and Van Strien, 1999). In plants, multiple genes usually represent each PR protein family, enabling the synthesis of diverse protein isoforms. For example, *Arabidopsis thaliana* has 22 genes encoding PR1 homologs, and rice contains 39 PR1-type genes (Mitsuhara et al., 2008). Some of these PR1 genes are constitutively expressed in roots or floral tissues, implying roles in plant development. This wide distribution of defense-related proteins across monocots and dicots underscores their multifaceted functions beyond defense (van Loon et al., 2006).

PR proteins can be categorized based on their isoelectric points, with acidic variants primarily induced upon immune activation and secreted to the apoplast. In contrast, those with a basic isoelectric point are often involved in developmental processes, showing limited induction upon pathogen infection, and typically localizing intracellularly, particularly in vacuoles (Farvardin et al., 2020; Zribi et al., 2021). Certain PR proteins also respond to various abiotic stressors like wounding, dehydration, salt, or cold stress, while others possess anti-freeze activity, reflecting their roles under adverse environmental conditions (Griffith and Yaish, 2004; Islam et al., 2023). Importantly, several PR proteins present in pollen, fruits, and vegetables can trigger allergic reactions in humans, making them significant contributors to plant allergens (Arora et al., 2020).

Over the past five decades, extensive research has been dedicated to characterizing individual PR proteins, elucidating their basic enzymatic activities, and establishing their direct role in defense against microbial pathogens (van Loon et al., 2006; Ferreira et al., 2007; Ali et al., 2018; Dos Santos and Franco, 2023) (see Table 1). For instance, PR1 proteins exhibit lipid-binding activity and inhibit the growth of sterol auxotrophic oomycetes (Gamir et al., 2017; Han et al., 2023). PR1 proteins also harbor a C-terminal peptide known as CAP-derived peptide 1 (CAPE1), which, when cleaved from the full-length PR1 protein, stimulates plant immune defense (Chen et al., 2014; Breen et al., 2017; Chen et al., 2023). PR2 proteins share sequence homology with β-1,3-glucanases and can hydrolyze β-1,3-glucans, which are present in the cell walls of microbes, generating oligomers that serve as elicitors. PR3, PR8, and PR11 exhibit chitinase activity, often synergizing with PR2, and PR4 binds chitin, a key component of fungal cell walls (Levy et al., 2007; Balasubramanian et al., 2012; Perrot et al., 2022). PR5 encompasses thaumatin-like proteins (TLPs) that exert antimicrobial activity by rapidly permeabilizing microbial plasma membranes (Zhang et al., 2018b; de Jesús-Pires et al., 2020; Sharma et al., 2021). PR6 encodes a protease inhibitor and shows synergy with thionins (PR13) (Ryan, 1989; Terras et al., 1993; Sels et al., 2008; Grosse-Holz and van der Hoorn, 2016; Rawlings et al., 2018). PR7 encodes a subtilisin-like endoprotease, believed to attack and degrade microbial cell wall proteins. However, these proteolytic enzymes are also important for peptide signaling, for example, by releasing serine rich endogenous peptides (SCOOPs) in *Brassicacea*, which are then perceived by the leucine-rich repeat receptor kinase male discovery 1-interacting receptor-like kinase 2 (MIK2) to elicit immunity

TABLE 1 Summary of properties of PR protein families.

Family	Pfam	Activity	Function/Properties	References*
PR1	PF00188	Immune signaling, Lipid-binding	• Antimicrobial • Abundant induced protein in the apoplast	(Chen et al., 2014; Breen et al., 2017; Gamir et al., 2017; Han et al., 2023)
PR2	PF00332	β-1,3-glucanase	• Antimicrobial • Cell wall degradation	(Levy et al., 2007; Balasubramanian et al., 2012; Perrot et al., 2022)
PR3 PR4 PR8 PR11	PF00182 PF00967 PF00704 PF00704	Chitinase (GH19) Chitin binding Chitinase (GH18) Chitinase (GH18)	• Antimicrobial • Cell wall degradation • Synergistic with PR2	(Oyeleye and Normi, 2018; Fukamizo and Shinya, 2019; Poria et al., 2021)
PR5	PF00314	Thaumatin/ Osmotin/ Zeamatin-like	• Antifungal • Glucan binding • Plasma membrane permeability • Sweet tasting • Anti-freeze activity	(Zhang et al., 2018; de Jesús-Pires et al., 2020; Sharma et al., 2021)
PR6	PF00280	Protease inhibitor MEROPS family	• Nematocidal • Insecticidal • Synergistic with PR13	(Terras et al., 1993; Ryan, 1989; Sels et al., 2008; Grosse-Holz and van der Hoorn, 2016; Rawlings et al., 2018)
PR7	PF00082	Subtilisin-like endoprotease	• Antifungal • Dissociation of microbial cell wall •Phytocytokine signaling	(Figueiredo et al., 2018; Schaller et al., 2018; Yang et al., 2023)
PR9	PF00141	Heme-containing peroxidase	• Lignin-forming peroxidase	(Passardi et al., 2004; Almagro et al., 2009; Liu et al., 2018; Cesarino, 2019)
PR10	PF00407	Ribonuclease-like, large hydrophobic cavity	• Antimicrobial • Cytoplasmic protein • Related to Bet v 1, a major birch pollen allergen	(Radauer et al., 2008; Choi et al., 2012; Fernandes et al., 2013; Aglas et al., 2020)
PR12	PF00304	Plant defensin	• Antimicrobial • Induction of ion efflux • Interaction with fungal sphingolipids	(Terras et al., 1995; Thevissen et al., 2000; Sels et al., 2008; Tam et al., 2015; Parisi et al., 2019)
PR13	PF00321	Thionin	• Antimicrobial • Membrane permeating • Synergistic with PR14	(Stec, 2006; Sels et al., 2008; Tam et al., 2015; Höng et al., 2021)
PR14	PF00234	Non-specific lipid-transfer protein Protease inhibitor Seed storage	• Antimicrobial	(Sels et al., 2008; Liu et al., 2015; McLaughlin et al., 2021; Gao et al., 2022; Melnikova et al., 2022)
PR15 PR16	PF00190 PF00190	Oxalate oxidase Oxalate oxidase-like	• Antimicrobial • ROS generation • Germin • Cupin family	(Mittler, 2002; Dunwell et al., 2004; Farvardin et al., 2020; Joshi et al., 2021)
PR17	PF04450	Putative aminopeptidase	• Poorly characterized	(Okushima et al., 2000; Christensen et al., 2002; Joshi et al., 2021)

*We predominantly reference review articles in this table, aiming to provide a comprehensive overview of the individual members within the PR class of proteins. This approach is taken due to the extensive nature of the original literature encompassing these 17 distinct protein families, spanning over 50 years, and involving numerous plant species as well as specific types of pathogen interactions. Notably, the PR18 and PR19 proteins, although recently incorporated, are omitted from this compilation. This omission arises from their limited characterization thus far, with their enzymatic activity and mode of action yet to be elucidated (Ali et al., 2018).

(Yang et al., 2023). PR9 exhibits heme-dependent peroxidase activity, crucial for lignification, wound healing, and oxidative degradation of phenolic compounds (Passardi et al., 2004; Almagro et al., 2009; Liu et al., 2018; Cesarino, 2019). PR10 proteins are members of the major latex-like family and have been reported to possess ribonuclease activity, but this might be attributed to copurifying RNase contaminations (Fernandes et al., 2013; Aglas et al., 2020; Longsaward et al., 2023). PR10 has a hydrophobic cavity capable of binding various lipids, including steroids and fatty acids (Radauer et al., 2008). Intriguingly, PR10 members are localized in the cytoplasm, but secreted into the apoplastic space when complexed with and activated by leucine-rich repeat protein 1 (LRR1) (Choi et al., 2012).

PR12 comprises plant defensins, small proteins with antimicrobial activity but an uncharacterized mode of action (Terras et al., 1995; Thevissen et al., 2000; Sels et al., 2008; Tam et al., 2015; Parisi et al., 2019). PR6, PR12, PR13, and PR14, due to their low molecular weight and antimicrobial activity, are classified as antimicrobial peptides (Sels et al., 2008). PR13 belongs to the class of thionins, small, basic, and cysteine-rich peptides that, like PR12 peptides, cause the permeabilization of microbial cell membranes. PR13 exhibits synergistic antimicrobial activity with PR14 (Stec, 2006; Sels et al., 2008; Tam et al., 2015; Höng et al., 2021). PR14 proteins can transfer phospholipids between membranes *in vitro* and, due to their low substrate specificity, are known as non-specific lipid transfer proteins (ns-LTPs) (Sels et al., 2008; Liu et al., 2015; Gao et al., 2022; Melnikova et al., 2022). PR15 and PR16, oxalate oxidase and oxalate oxidase-like proteins, contribute to the generation of apoplastic reactive oxygen species (ROS), initiating signal transduction cascades and activating plant defense mechanisms (Mittler, 2002; Dunwell et al., 2004; Farvardin et al., 2020; Joshi et al., 2021). Lastly, PR17, the least understood class, is postulated to possess aminopeptidase activity (Okushima et al., 2000; Christensen et al., 2002; Joshi et al., 2021).

Numerous PR proteins display antimicrobial activity *in vitro*, and their overexpression in plants enhances resistance to various pathogens across diverse plant species (Alexander et al., 1993; Niderman et al., 1995; Epple et al., 1997; Anand et al., 2004; van Loon et al., 2006; Ferreira et al., 2007; Sels et al., 2008; Dos Santos and Franco, 2023). Conversely, silencing the expression of PR1 or PR5 renders plants more susceptible to pathogens (Riviere et al., 2008; Zhang et al., 2018b). Despite their antimicrobial activity, the precise functions of many PR proteins in defense responses remain incompletely understood, extending beyond direct pathogen inhibition to encompass roles in cell wall reinforcement, scavenging of ROS, and modulation of defense signaling pathways (van Loon et al., 2006; Islam et al., 2023). Given the protective effects conferred by the induction and accumulation of PR proteins, their overexpression, and heterologous expression are currently explored as strategies to establish stress-tolerant plants (Ali et al., 2018; Boccardo et al., 2019; Islam et al., 2023).

Pathogenesis-related-like proteins produced by pathogens

While PR proteins are typically produced by plants in response to pathogen infection as part of their defense mechanism, recent findings have unveiled a fascinating twist: pathogens themselves synthesize pathogenesis-related-like proteins, which we will refer to as PR-like proteins, that play crucial roles in promoting pathogen virulence (Han et al., 2023). Unlike the induction and secretion of antimicrobial proteins by the host plant upon pathogen attack, which are well studied, the precise function and contribution of PR-like proteins to pathogen virulence remain enigmatic.

Among PR-like proteins, the PR1-like family is perhaps the most extensively characterized. PR1 proteins belong to a large protein superfamily, also known as CAP proteins (CRISP/Ag5/PR1) or SCPs (sperm coating proteins) and are related to VALs/VAPs (venom allergen-like proteins made by nematodes) (Gibbs et al., 2008; Cantacessi and Gasser, 2012; Wilbers et al., 2018; Han et al., 2023). Recent research has unveiled PR1-like proteins from various pathogenic nematodes and fungi as novel virulence factors. For example, PR1-like proteins from hemibiotrophic *Fusarium* species, including Fpr1 from *Fusarium oxysporum*, FgPR1L-4 from *Fusarium graminearum*, as well as FvSCP1 from *Fusarium verticillioides*, have all been shown to enhance fungal virulence in their respective host plants (Prados-Rosales et al., 2012; Lu and Edwards, 2018; Zhang et al., 2018a). More recently, a family of three highly related PR1-like proteins was identified in the necrotrophic fungal pathogens *Cytospora chrysosperma* and *Valsa mali*, causal agents of canker disease in poplar and apple, respectively. Deletion of CcCAP1 in *C. chrysosperma* reduced fungal virulence and increased sensitivity to ROS, highlighting its importance (Han et al., 2021). Additionally, two of the three *V. mali* PR1-like proteins, VmPR1a and VmPR1c, were found to be essential for pathogen virulence (Wang et al., 2021). Recent host-induced gene silencing experiments further demonstrated that three out of six PR1-like proteins from the wheat stripe rust fungus *Puccinia striiformis* f. sp. *tritici* are necessary for fungal virulence (Zhao et al., 2023).

Furthermore, in susceptible tomato plants, GrVAP1 secreted by the potato cyst nematode (*Globodera rostochiensis*) is required for successful infection (Lozano-Torres et al., 2014). However, in other cultivars, GrVAP1 interacts with the tomato papain-like cysteine protease Rcr3, activating the membrane-localized immune receptor Cf-2, thereby inducing the host's immune response (Lozano-Torres et al., 2012). Similarly, a PR1-like protein from *Phytophthora sojae* has been found to trigger an immune response in *Nicotiana benthamiana*, dependent on its recognition by the leucine-rich repeat receptor-like protein (LRR-RLP) RCAP1. This recognition involves the shared immune coreceptors BAK1 and SOBIR1 and leads to increased plant resistance against Phytophthora (Gust and Felix, 2014; Liebrand et al., 2014; Jiang et al., 2023). PsCAP1, the Phytophthora PR1-like protein, contains an N-terminal PAN domain and exhibits immune-stimulatory activities such as triggering ROS bursts, activating mitogen-activated protein kinase (MAPK), and inducing cell death. Importantly, these activities are mediated by the PAN domain, which is distinct from the CAP domain found in canonical PR1 proteins. The PAN domain has been proposed to facilitate protein-protein and protein-carbohydrate interactions, but its precise role in plant-microbe interactions remains a subject of study (Jiang et al., 2023). This PAN domain containing PsCAP1 protein is conserved among phytopathogenic oomycetes but absent in the genomes of plants, diatoms, bacteria, or fungi (Jiang et al., 2023).

Interestingly, heterologous expression of PR1-like proteins from pathogens, such as GrVAP1 from *G. rostochiensis* or CcCAP1 from *C. chrysosperma*, in host plants suppresses the plant's PTI response. Expression of CcCAP1 in tobacco inhibits pathogen-induced induction of PR1 and PR4 and the expression of GrVAP1 selectively suppresses the activation of the programmed cell death by surface-localized immune receptors (Lozano-Torres et al., 2014; Han et al., 2021). These observations suggest that these proteins possess potent immune modulatory activity, rendering plants hypersensitive to various unrelated pathogens (Lozano-Torres et al., 2014; Han et al., 2021).

The corn smut *Ustilago maydis* UmPR1-like protein has recently been shown to sense plant-derived phenolic compounds to eliciting hyphal-like growth to guide fungal invasion in plants. In addition, secretion of UmPR1-like promotes fungal virulence by hijacking a plant cysteine protease to release a UmCAPE-like signaling peptide from UmPR1-like and suppress plant immunity (Lin et al., 2023).

These PR1-like proteins from pathogens appear to function in ways similar to plant hormones produced by pathogenic and symbiotic fungi. They may have dual roles: (i) perturbing plant processes, either positively or negatively, to promote invasion and nutrient uptake by the pathogens; and (ii) serving as signals for the fungi to engage in appropriate developmental and physiological processes adapted to their environment (Chanclud and Morel, 2016).

Building upon these insights into PR1-like proteins, we explored the genomes of various plant pathogens for the presence of other PR-like genes. Remarkably, we found that not only PR1-like genes are prevalent in phytopathogen genomes but that many other PR-like protein family members are also present. Except for PR4 (chitinase), PR6 (protease inhibitor), PR10 (ribonuclease-like), PR12 (plant defensin), PR13 (thionin), and PR14 (non-specific lipid transfer protein), multiple copies of genes encoding PR-like proteins are frequently identified in the genomes of model phytopathogens, particularly in those of fungi and oomycetes (Dean et al., 2012; Kamoun et al., 2015). Notable examples include the rice blast fungus *Magnaporthe oryzae* (Tan et al., 2023), the gray mold fungus *Botrytis cinerea* (Bi et al., 2023), the rust fungus *Puccinia* spp (Avasthi et al., 2023), the soil-borne ascomycete *Fusarium oxysporum* (Srinivas et al., 2019), the causative agent of wilt disease *Verticillium dahliae* (Klosterman et al., 2009), the corn smut fungus *Ustilago maydis* (Yu et al., 2023), as well as the oomycetes *Phytophthora infestans* (Whisson et al., 2016), which cause late blight disease on potato and tomato, the downy mildew causing *Hyaloperonospora arabidopsidis* (Coates and Beynon, 2010), and the sudden oak death disease causing *Phytophthora ramorum* (Grünwald et al., 2008) (see Table 2; Supplementary Materials Table S1). These intriguing observations suggests that the phenomena described for PR1-like proteins likely extend to other PR-like protein families as well. Consequently, some of the key questions that arise are: What functions do these PR-like proteins serve in phytopathogens? Do their deletions impact pathogen virulence? Can their heterologous expression in plants render them more susceptible to a broader spectrum of pathogens? What are the mechanisms of action employed by pathogen-produced PR-like proteins?

The role of PR-like proteins in pathogen vegetative growth, virulence, or their function as effectors modulating the host's immune response are not well characterized, except for the cell wall remodeling enzymes including β-1,3-glucanases, such as Bgl2 in *Candida albicans*, and chitinases, which have established roles in filamentous growth, conidial germination, or haustorium establishment (Sarthy et al., 1997; Chen et al., 2017; Han et al., 2019; Guo et al., 2023). However, these cell wall remodeling enzymes may function primarily as morphogenetic factors rather than classical effectors, even though chitin can induce strong PTI, and its immune modulation involves processes such as shielding through lectin binding or deacetylation to chitosan (Gong et al., 2020). Interestingly, PR8 and PR11 chitinases belong the glycosyl hydrolase family 18 (GH18), a bacterial type of endochitinase, which are widely distributed in almost all organisms including plant pathogens (Bradley et al., 2022) (Table 2). PR3, on the other hand, belongs to the glycosyl hydrolase family 19 (GH19), which are mostly found in plants, and possess a specific chitin binding domain, which is absent in the bacterial type of enzyme (Henrissat and Bairoch, 1993). Members of this family are thought to be produced as part of a defense response against fungal pathogens. The overall structures and catalytic domains of these two classes of chitinase differ greatly. The GH19 family chitinases have an α-helix-rich lysozyme-like domain characterized by a deep cleft, whereas GH18 chitinases are characterized by a catalytic region that consists of a triosephosphate isomerase (TIM) $(\beta/\alpha)_8$-barrel domain (Oyeleye and Normi, 2018; Fukamizo and Shinya, 2019; Poria et al., 2021) (Figure 1). Interestingly, oomycetes express the GH19 plant type of chitinase as well, whereas most of the fungal pathogens do not (Klinter et al., 2019). This is particularly intriguing given that the cell wall of oomycetes is primarily composed of cellulose and β-glucans rather than chitin (Mélida et al., 2013; Wanke et al., 2021). These GH19 family chitinases in oomycetes have likely been acquired by horizontal gene transfer and been proposed to be important for the degradation of complex carbohydrates present in fungal cell walls during mycoparasitism (Liang et al., 2020; Bělonožníková et al., 2022).

On the other hand, silencing of the PR5-like thaumatin-like protein from the pine wood nematode *Bursaphelenchus xylophilus* has been shown to reduce the pathogen's reproduction and pathogenicity. When expressed in tobacco, it induces a robust cell death response (Meng et al., 2019; Kirino et al., 2020; Meng et al., 2022). Thaumatin-like proteins have been reported to bind β-1,3-glucans, exhibit endo-β-1,3-glucanase activity, inhibit α-amylase, or permeabilize cell membranes, yet their precise antimicrobial mechanisms remain ambiguous (Roberts and Selitrennikoff, 1990; Abada et al., 1996; Trudel et al., 1998; Grenier et al., 1999; Koiwa et al., 1999; Franco et al., 2002; Menu-Bouaouiche et al., 2003; de Jesús-Pires et al., 2020; Sharma et al., 2021). Thaumatin-like proteins are found in fungi, nematodes, and insects but are absent in vertebrates (Brandazza et al., 2004; Sakamoto et al., 2006; Belaish et al., 2008; Meng et al., 2019; de Jesús-Pires et al., 2020; Kirino et al., 2020).

Discussion

Several studies have highlighted the interactions between plant and fungal PR1 and PR1-like proteins, shedding light on their potential roles in modulating the host's immune response. Notably, some of these proteins form homodimers, exemplified by the wheat protein TaPR1-5, Fpr1 from the soilborne fungal pathogen *F. oxysporum*, and *S. cerevisiae* Pry1 (Prados-Rosales et al., 2012; Lu

TABLE 2 Genes Encoding PR-Like Proteins in Filamentous Phytopathogens.

Family	Pfam	Activity	*Magnaporthe oryzae*	*Botrytis cinerea*	*Puccinia spp.*	*Fusarium oxysporum f.sp.*	*Verticillium dahliae*	*Ustilago maydis*	*Phytophthora infestans*	*Hyaloperonospora arabidopsidis*	*Phytophthora ramorum*	*Key References*
PR1	PF00188	Immune signaling Lipid-binding	6	4	6	7	4	2	29	13	21	(Han et al., 2023; Lin et al., 2023; Jiang et al., 2023; Zhao et al., 2023; Han et al., 2021; Lozano-Torres et al., 2014; Teixeira et al., 2012; Prados-Rosales et al., 2012)
PR2	PF00332	β-1,3-glucanase	3	4	2	4	6	2	7	3	7	(Sarthy et al., 1997; Chen et al., 2017)
PR3	PF00182	Chitinase (GH19)	/	/	/	/	/	/	3	1	1	(Bělonožníková et al., 2022; Guo et al., 2023)
PR4	PF00967	Chitin-binding	/	/	/	/	/	/	/	/	/	
PR5	PF00314	Thaumatin	1	2	4	1	1	1	2	/	/	(Meng et al., 2019; Kirino et al., 2020)
PR6	PF00280	Protease inhibitor	/	/	/	/	/	/	/	/	/	
PR7	PF00082	Subtilisin-like endoprotease	30	13	16	32	18	5	13	6	7	(Monod et al., 2002; Shi et al., 2014; Xu et al., 2020; Liu et al., 2020)
PR8/ PR11	PF00704	Chitinase (GH18))	16	7	15	28	18	3	2	2	2	(Han et al., 2019; Bradley et al., 2022; Bělonožníková et al., 2022; Guo et al., 2023)
PR9	PF00141	Heme-containing peroxidase	10	4	2	10	7	3	4	4	6	(Mir et al., 2015)
PR10	PF00407	Ribonuclease-like	/	/	/	/	/	/	/	/	/	

(Continued)

TABLE 2 Continued

Family	Pfam	Activity	*Magnaporthe oryzae*	*Botrytis cinerea*	*Puccinia spp.*	*Fusarium oxysporum f.sp.*	*Verticillium dahliae*	*Ustilago maydis*	*Phytophthora infestans*	*Hyaloperonospora arabidopsidis*	*Phytophthora ramorum*	*Key References*
PR12	PF00304	Plant defensin	/	/	/	/	/	/	/	/	/	
PR13	PF00321	Thionin	/	/	/	/	/	/	/	/	/	
PR14	PF00234	Non-specific lipid-transfer protein	/	/	/	/	/	/	/	/	/	
PR15/ PR16	PF00190	Oxalate oxidase Oxalate oxidase-like	1	3	/	7	6	/	/	/	/	(El Hadrami et al., 2015; Liang et al., 2015; Fan et al., 2021; Yan et al., 2022)
PR17	PF04450	Putative aminopeptidase	1	1	/	1	1	/	/	/	/	

The table gives an overview of the number of PR-like proteins that are present in fungal (left-hand part) and oomycetes (right-hand part) phytopathogens. /, indicates that there is no gene present that matches the annotation of the respective plant PR protein family. PR-like families that are absent from the genomes of fungal or oomycetes are shaded in light green, i.e., PR3-, PR4-, PR6-, PR10-, PR12-, PR13-, PR14-, PR17-like. Genes were identified by screening sequences of individual plant PR family members against the genome sequences of *Magnaporthe oryzae* (*Pyricularia oryzae* 70-15, v3.0), *B. cinerea* (B05.10), *Puccinia* spp. (*Puccinia striiformis* f.sp. *tritici* PST-78, v1.0), *Fusarium oxysporum* (*Fusarium oxysporum* f.sp. *lycopersici* 4287, v2), *Verticillium dahliae* (VdLs.17), *Ustilago maydis* (521, v2.0), *Phytophthora infestans* (T30-4), *Hyaloperonospora arabidopsidis* (Emoy2, v2.0), and *Phytophthora ramorum* (v1.1) in the PhytoPath database (https://phytopathdb.org/) (Pedro et al., 2016). Gene identifiers for all these PR-like family members are provided in Supplementary Materials, Table S1.

Gray shading is used to differentiate between rows.

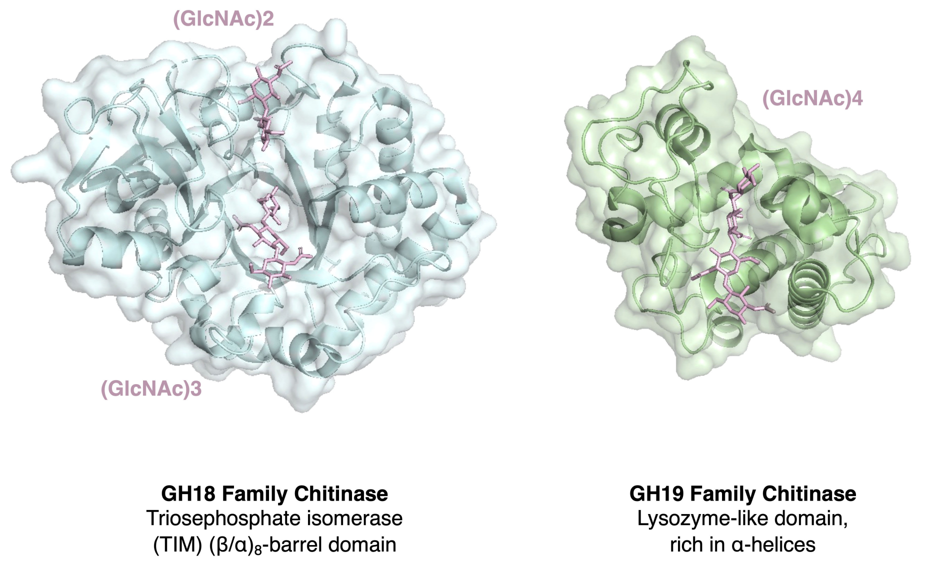

FIGURE 1
Comparison of the structure of chitinases belonging to two major families. Structural comparison of the ubiquitous chitinases belonging to the glycoside hydrolase family 18 (GH18) and the more plant-specific GH19 family. PR8 and PR11 are members of the bacterial/fungal GH18 family whereas PR3 is a member of the GH19 family and has structural similarity to some lysozymes (Monzingo et al., 1996). Shown are the structures of the triosephosphate isomerase (TIM) $(\beta/\alpha)_8$-barrel domain-containing GH18 family chitinase from *Cycas revoluta* in complex with the chitin dimer (GlcNAc)2 and chitin trimer (GlcNAc)3 (PDB 4MNK), and the α-helix-rich lysozyme-like GH19 family chitinase from *Bryum coronatum* in complex with the chitin tetramer (GlcNAc)4 (PDB 4IJ4; Ohnuma et al., 2014).

et al., 2013; Darwiche et al., 2016). Furthermore, it has been shown that the dimeric form of TaPR1-5 is a specific target of ToxA, a host-selective virulence factor secreted by the causal agent of wheat tan spot disease, *Pyrenophora tritici-repentis* and the leaf/glume blotch fungus *Stagonospora nodorum* (*Sn*) (Lu et al., 2014). The binding of SnToxA to TaPR1-5 appears to compromise the immune-protective function of PR1 in wheat, thereby promoting necrosis (Ciuffetti et al., 2010).

Intriguingly, a second effector protein, SnTox3, secreted by *S. nodorum*, interacts with a broader range of wheat PR1 isoforms than SnToxA. SnTox3 effectively inhibits the release of CAPE1, thus suppressing the plant's immune defense mechanisms (Breen et al., 2016; Sung et al., 2021). These findings suggest a multifaceted strategy by phytopathogens to subvert the host's immune response, utilizing distinct effectors to target different components of the plant's defense system.

Beyond the interactions with pathogenic effectors, PR1 has been shown to form heteromeric complexes with other PR proteins, particularly PR5 and PR14. The thaumatin-like PR5 is secreted into the apoplastic space and rapidly accumulates in response to various stressors, both biotic and abiotic (Hakim et al., 2018; Zhang et al., 2018b). Notably, wheat PR5 (TaTLP1) directly interacts with TaPR1, and the antimicrobial activity of the resulting heteromeric complex surpasses that of either PR5 or PR1-4 alone. This synergy suggests that these proteins act cooperatively to enhance the plant's defense against invading pathogens (Wang et al., 2020, 2022).

On the other hand, PR14 belongs to the ns-LTP family. These extracellular ns-LTPs are known to bind to and transfer lipids between membranes *in vitro*. *In vivo*, they may serve as lipid sensors or sequester lipids to modulate their potential signaling functions (Missaoui et al., 2022). Wheat PR14 (TaLTP3) associates with TaPR1 in the apoplast, and plants overexpressing both proteins activate multiple signaling cascades, including the SA, jasmonic acid, and auxin pathways, and they exhibit enhanced production of ROS during the defense response. This interaction, together with the fact that purified PR14 exhibits antimicrobial activity *in vitro*, highlights the role of PR14 in reinforcing plant immunity (McLaughlin et al., 2021; Zhao et al., 2021).

These reported protein interactions suggest that the association between PR1-like proteins and their various PR family members may function to modulate plant-pathogen interactions. Given that PR1-like proteins from certain pathogens, such as the nematode *G. rostochiensis* (GrVAP1) or the fungal pathogen *C. chrysosperma* (CcCAP1), have been shown to reduce host immunity when expressed in plants (Lozano-Torres et al., 2014; Han et al., 2021), these PR1-like proteins may interfere with the immune-stimulating actions of endogenous PR1 proteins, similarly to the effectors SnToxA or SnTox3. This interference may occur through the disruption of protein complexes between plant's own PR1 and PR5 and/or PR14 or by impeding the CAPE1-mediated signaling of PR1 (Breen et al., 2017; Han et al., 2023).

Consistent with the potential mode of action of PR-like proteins, *in silico* docking experiments suggest that PR1-like proteins from pathogens can indeed form protein complexes with plant endogenous PR5 and PR14, thus potentially undermining the host's PR-based defense mechanisms (Figure 2). The prediction of protein complexes is emerging as a new powerful tool to identify potential microbial effectors. A recent bioinformatics screen using

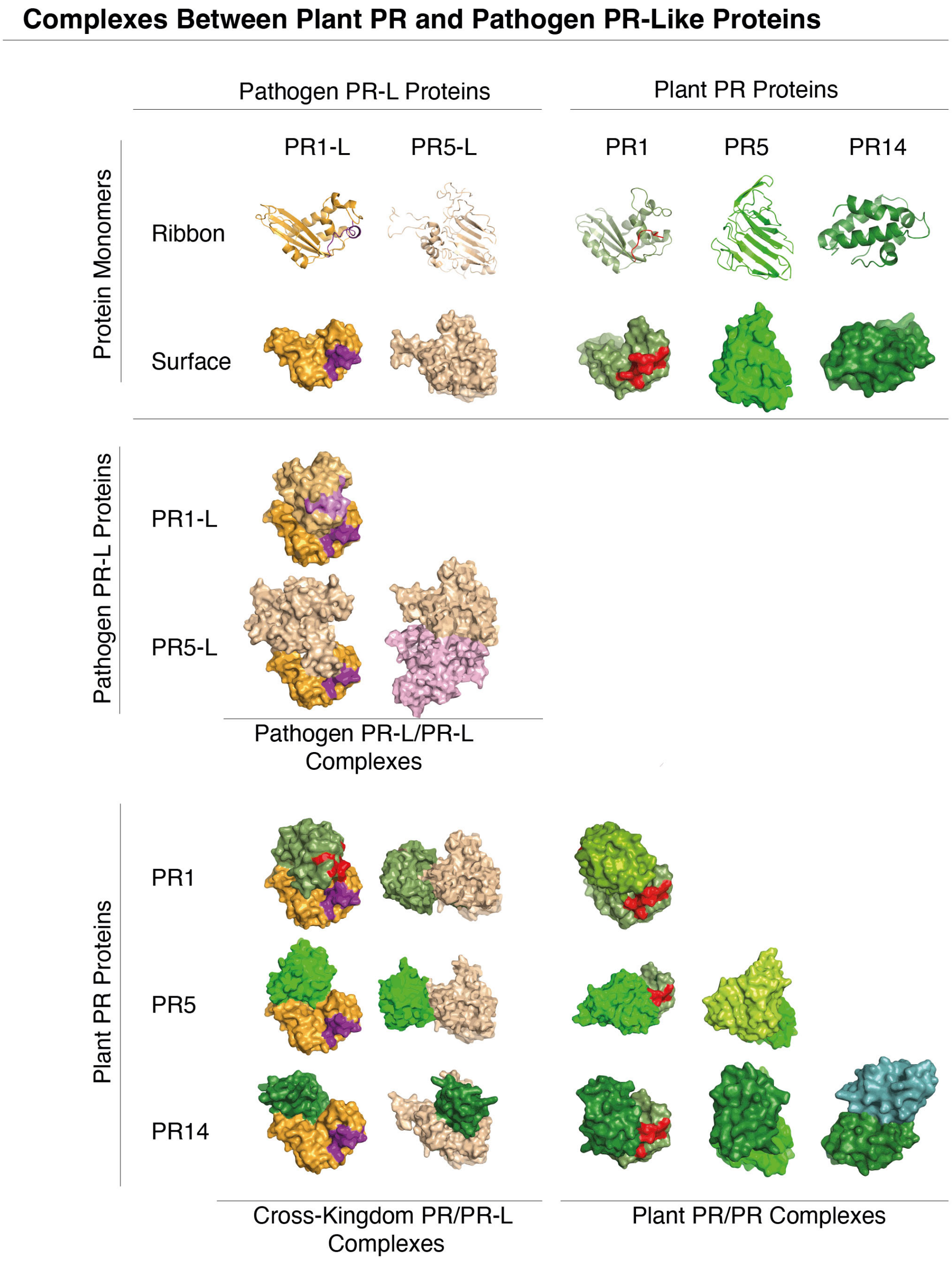

FIGURE 2
Molecular docking of phytopathogen PR1-like and PR5-like proteins with plant PR1, PR5 and PR14. Predicted molecular interactions between PR1-like and PR5-like proteins (orange) from phytopathogens and plant PR1, PR5, and PR14 (green) are visualized in the matrix. Notably, PR-like (PR-L) proteins from phytopathogens can interact both with themselves, and with host plant PR proteins. The docking simulations of PR1-like and PR5-like proteins from *Botrytis cinerea* with plant PR1, PR5, and PR14 (*Arabidopsis thaliana*) were performed using UCSF Chimera (Pettersen et al., 2004). The pathogen's CAPE-like and the plant's CAPE immune stimulatory peptides in the C-terminal end of PR1 and PR1-like are indicated in violet and red, respectively. Structures of monomeric proteins shown in the top two rows are represented both by ribbon diagrams and as space-filling models.

AlphaFold-Multimer, for example, has identified PR7, a subtilisin-like endoprotease PR7 (also known as P69 subtilase), as an effector hub targeted by different microbial kingdoms (Homma et al., 2023). This discovery lends further support to the notion that PR-like proteins may play pivotal roles in manipulating the plant's immune response through the formation of cross-kingdom heteromeric protein complexes (Figure 3).

In conclusion, accumulating evidence suggests that phytopathogens have evolved strategies involving PR-like proteins to subdue their host's immune response. These proteins appear to have coopted elements of the plant's innate defense mechanisms, our hypothesis is that these proteins potentially interfere with the formation of protein complexes involving PR1, PR5, and PR14 within the apoplastic space and with key signaling pathways

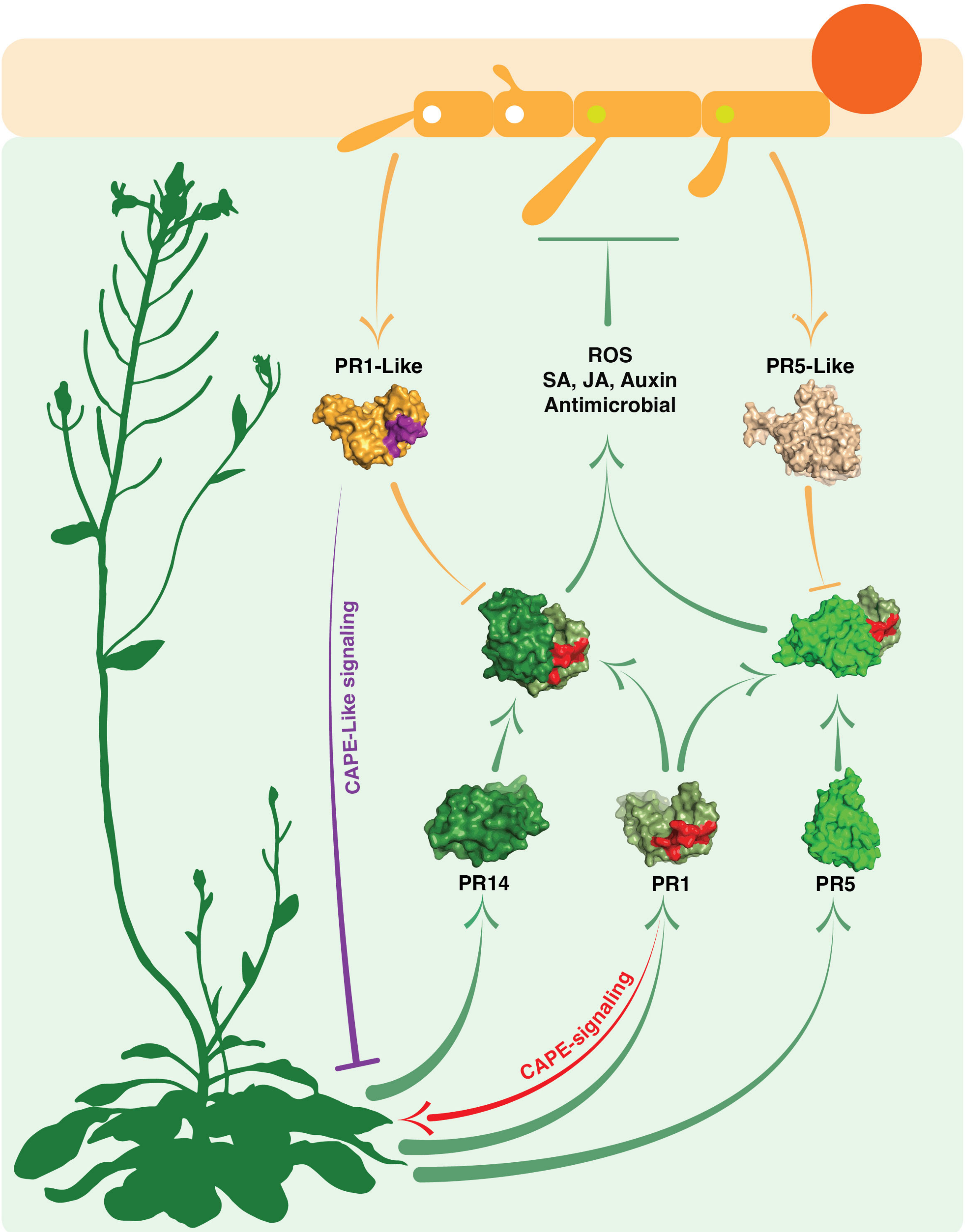

FIGURE 3
Interactions between plant defense-related PR proteins and phytopathogen PR-like proteins. This schematic diagram illustrates the complex interactions occurring in the apoplastic space of host plants (light green shaded space). It showcases the interplay between the host plant's own PR1, PR5, and PR14 proteins (depicted by green arrows and green space-filling models) and the PR1-like and PR5-like proteins secreted by invading phytopathogens (depicted by orange arrows and orange space-filling models). The light green shading represents the host's apoplastic space. The figure displays the structures of heteromeric complexes formed by plant PR1 with PR5 or PR14 proteins. The formation of these complexes contributes to immune stimulatory processes (involving SA, salicylic acid; JA, jasmonic acid; and auxin) as well as antimicrobial responses (including ROS production and direct antimicrobial activity). Importantly, the figure also suggests that these interactions can be disrupted by pathogen-derived PR-like proteins. Furthermore, it highlights CAPE immune stimulatory signaling by plant PR1 (indicated by the red arrow) and CAPE-like inhibitory signaling mediated by the pathogen's PR1-like protein (indicated by the violet blunt arrow).

mediated by the CAPE peptide of PR1. While these findings offer valuable insights, it is important to emphasize that further experimental validation is necessary to establish the exact mechanisms underlying the interactions between PR and PR-like proteins and their impact on plant immunity.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

ZH: Conceptualization, Data curation, Funding acquisition, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. RS: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpls.2024.1368467/full#supplementary-material

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