Review

Cooperative interaction of antimicrobial peptides with the interrelated immune pathways in plants

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SUMMARY

Plants express a diverse repertoire of functionally and structurally distinct antimicrobial peptides (AMPs) which provide innate immunity by acting directly against a wide range of pathogens. AMPs are expressed in nearly all plant organs, either constitutively or in response to microbial infections. In addition to their direct activity, they also contribute to plant immunity by modulating defense responses resulting from pathogen-associated molecular pattern/effector-triggered immunity, and also interact with other AMPs and pathways involving mitogen-activated protein kinases, reactive oxygen species, hormonal cross-talk and sugar signalling. Such links among AMPs and defense signalling pathways are poorly understood and there is no clear model for their interactions. This article provides a critical review of the empirical data to shed light on the wider role of AMPs in the robust and resource-effective defense responses of plants.

Keywords: antimicrobial peptides, hormonal cross-talk, plant immunity, PTI/ETI, sugar signalling.

INTRODUCTION

Plants respond to pathogens by instigating a series of intricate signalling events, which cause the accumulation of antimicrobial compounds, induce the expression of resistance genes to reinforce plant cell walls, promote the synthesis of pathogenesis-related (PR) proteins and ultimately enhance systemic resistance. Plant innate immune responses (Jones and Dangl, 2006) include the recognition of pathogen/microbe-associated molecular patterns (PAMPs/MAMPs) via plant pattern recognition receptors (PRRs) leading to PAMP-triggered immunity (PTI), as well as an intracellular cascade known as effector-triggered immunity (ETI), which is highly specific and involves the activation of further resistance genes often accompanied by the hypersensitive response (HR) and systemic acquired resistance (SAR). An overlapping set of downstream immune responses results from the PTI/ETI continuum (Thomma et al., 2011). This includes the activation of multiple signalling pathways involving mitogen-activated protein kinases (MAPK), reactive oxygen species (ROS), defence hormones (such as salicylic acid, jasmonic acid and ethylene) and the production of antimicrobial compounds (Jones and Dangl, 2006; Zipfel, 2009).

Within this complex network, antimicrobial peptides (AMPs) provide durable resistance in plants because they act directly against pathogens and therefore complement PTI/ETI (Robinson et al., 2012). Plant AMPs are assigned to different families on the basis of their overall charge, the presence of disulfide bonds and their structural stability (Barbosa Pelegrini et al., 2011). In addition to their direct role against pathogens, plant AMPs can also function as modulators of defence signalling pathways (Rahnamaeian and Vilcinskas, 2012), associate with innate immune responses (Bowdish et al., 2005; Scott et al., 2007) and potentially act as signalling molecules (Salzet, 2002).

The survival of plants in an environment rich in diverse pathogens is also dependent on a defence pathway involving the cross-talk between sugar metabolism and/or signalling and other defence responses, which has been described recently as sweet immunity (Boolouri Moghaddam and Van den Ende, 2013). Although this is poorly understood, there appears to be a close interaction between sugar-mediated responses and other classical signalling pathways that might promote the synthesis and modulation of AMPs or metabolites with comparable activity. Although AMP-related defence signalling is not well characterized in plants, this article aims to summarize what is currently known of the relationships between AMPs and other forms of innate immunity in plant species.

AMPS AND ROS

In many plant species, the early stages of pathogen infection result in a so-called oxidative burst (Ding et al., 2011). This involves the induction of genes that promote the accumulation of ROS, such as the superoxide radical anion (O2•−), the hydroperoxyl radical (HO2), the hydroxyl radical (HO•) and hydro-
gen peroxide (H₂O₂). The accumulation of ROS within infected cells is a central component of plant defence signalling pathways which ultimately promotes apoptosis, and it can be triggered by AMPs against bacterial and fungal pathogens in many plant species (Hwang et al., 2004).

Examples of the AMP-triggered oxidative burst are provided by the defensins HsAFP1 in coral reefs, RsAFP2 in radish, PvD1 in bean and NaD1 in winged tobacco, which induce the accumulation of ROS in response to the fungi Candida albicans and Fusarium oxysporum, thus modulating intracellular signalling cascades and resulting in the permeabilization of the fungal membrane and growth arrest (Aerts et al., 2009, 2011; Mello et al., 2007; Distefano et al., 2009, 2011; van der Weerden et al., 2008). The plant must also scavenge ROS to prevent cell damage, e.g. by the synthesis of antioxidants, such as glutathione and ascorbate, and enzymes that detoxify ROS, such as superoxide dismutases and catalases (Dehghan et al., 2014; Sadeghi et al., 2013). AMPs can also help to regulate directly the cellular redox status. The sweet potato defensin SPD1 regulates the redox status of ascorbate in addition to its antimicrobial activity. SPD1 is a glutathione-dependent dehydroascorbate reductase that converts dehydroascorbate to ascorbic acid in the presence of glutathione (Chen and Gallie, 2006; Huang et al., 2008).

A comprehensive analysis of the latent influence of the insect AMP metchnikowin in transgenic barley plants has revealed that the redox status of metchnikowin-expressing barley plants is potentiated during interactions with the powdery mildew fungus (Rahnamaeian et al., 2009). The higher level of ROS triggered by AMP expression (Aerts et al., 2007; Distefano et al., 2008; Rahnamaeian and Vilcinskas, 2012) suggests that it may act by modulating the redox milieu and encouraging apoptosis (Rahnamaeian, 2011). In this context, a specific vacuolar antioxidant mechanism has been proposed in plants which works in concert with the better known antioxidant mechanisms in the plastids, mitochondria and cytosol (Bolouri-Moghaddam et al., 2010; Van den Ende and Valluru, 2009). There is a clear correlation between mitochondrial hexokinase activity and ROS homeostasis, probably involving signalling pathways leading to antioxidant defence responses (Bolouri-Moghaddam et al., 2010; Camacho-Pereira et al., 2009).

ROS may also accumulate when sugar levels in plants are altered following pathogen attack, and hence contribute to the modulation of sugar signalling pathways under oxidative stress (Bolouri-Moghaddam et al., 2010; Bolouri-Moghaddam and Van den Ende, 2013). AMPs particularly induce the accumulation of H₂O₂ which, in turn, can activate stress-related genes (Fan et al., 2008; Mittler, 2004) independently of the salicylic acid and jasmonic acid pathways (Miller et al., 2009). H₂O₂ also stimulates the biosynthesis of glutathione S-transferase, which activates the salicylic acid pathway (Leon et al., 1995), as well as its roles in plant cell wall defence and the HR (Wang et al., 2009).

Nitric oxide (NO) cooperates with ROS to mediate innate immune responses against plant pathogens (Bellin et al., 2013). The accumulation of NO is induced by PAMPs in stomatal guard cells (Melotto et al., 2006; Zeidler et al., 2004) and it mediates oligogalacturonide-triggered immunity, in which cell wall-derived oligogalacturonides induce plant defence genes in response to fungal pathogens (Xie et al., 2008). NO promotes resistance against Botrytis cinerea in Arabidopsis thaliana (Rasul et al., 2012) and can regulate directly MAPK activity or act indirectly by modifying proteins that interact with MAPK (Wawer et al., 2010). During incompatible plant–pathogen interactions, the combined activity of NO and ROS activates the HR and induces apoptosis (Yoshioka et al., 2011).

The role of NO in the context of AMP activity is not well understood. The exposure of C. albicans to the pea defensin PvD1 causes the intracellular accumulation of ROS and NO (Mello et al., 2011). Similarly, the synthetic fungicidal hexapeptide PAF26 causes the accumulation of intracellular ROS and NO in baker’s yeast (Carmona et al., 2012). NaD1, a floral defensin from tobacco, is taken up by fungi such as C. albicans following membrane permeabilization, where it induces the accumulation of ROS and NO in the cytosol and causes oxidative stress and apoptosis (Hayes et al., 2013). Although such interactions require further investigation, the induction of NO accumulation by AMPs appears to provide a stronger signal for the innate immune system, causing fatal levels of oxidative stress in the pathogen and cooperating with scavenging agents to modulate the cellular redox status and other defence signalling pathways.

**AMPS AND MAPK SIGNALLING**

MAPK cascades transduce extracellular stimuli and trigger appropriate cellular responses in all eukaryotes, including higher plants (Yang et al., 2013). MAPKs phosphorylate their target proteins, including enzymes and transcription factors, in order to control the synthesis of defence hormones and signalling molecules, the expression of genes involved in defence signalling and the synthesis of AMPs. MAPK signalling pathways are induced by ROS and can also regulate the production of ROS (Pitzschke and Hirt, 2009). Plant receptor protein kinases (RPKs) perceive diverse MAMPs and recognize secondary danger-inducible plant peptides and signals produced by the cell wall. Ca²⁺-dependent protein kinases (CDPKs) and MAPK cascades then contribute to the regulation of conserved early target genes in the MAMP signalling pathway (Boudsocq et al., 2010). The 23-amino-acid A. thaliana peptide AtPep1 can activate defence genes associated with the innate immune response (Huffaker et al., 2006) and, together with its paralogues (AtPep2–7), binds to the membrane-anchored leucine-rich repeat (LRR) receptor kinase PEPR1 to amplify the innate immune response (Yamaguchi et al., 2010). AtPep1–3 and AtPep5–6 strongly
induce the transcription of the gene encoding PR-1, whereas AtPep1 (as well as flg22, elf18 and chitin) induce the genes encoding MPK3, PDF1.2, PR-1 and WRKY transcription factors (Huffaker et al., 2006). The induction of defence-related genes and the enhancement of basal resistance by AtPep1 may involve a MAPK cascade comprising MEKK, MKK4/MKK5 and MPK3/MPK6 (Asai et al., 2002; Valerie et al., 2009) following its perception by PEPR1 and PEPR2 (Yamaguchi et al., 2010). MAPKs can also phosphorylate WRKY transcription factors involved in innate immunity, e.g. MPK3/6 phosphorylates WKY33 directly and binds to the promoters of the WKY33 and PAD3 genes, the latter required for the biosynthesis of the antifungal compound camalexin (Qiu et al., 2008). Furthermore, the activation of AtPEPR1 and AtPEP1–3 following the inoculation of A. thaliana with Sclerotinia sclerotiorum may be responsible for the dramatic induction of defensins in response to this pathogen (Stotz et al., 2013).

The interaction between AMPs and transcription factors creates a hub in the AMP–protein interaction network, in which AMPs bind to a COP9 signalosome subunit, MAPK2 and a thioredoxin protein (Damon et al., 2012). The interaction between plant AMPs and MAPKs appears to play a significant role in the innate immune system of plants (Fig. 1) and can also achieve the immunomodulation of other host cells, e.g. as shown when a plant AMP was expressed in bovine endothelial cells (Loeza-Angeles et al., 2011).

Fig. 1 AMPs and cooperative defence responses. The innate immune system of plants includes cellular signalling based on hormones and small metabolites, including sugars (Bolouri Moghaddam and Van den Ende, 2013). Classical immunity (black arrows) includes the recognition of MAMPs by PRRs, whereas sweet immunity (blue arrows) can be activated by changes to the sucrose/hexose ratio (Bolouri Moghaddam and Van den Ende, 2013). Both pathways can elicit an immune response through the MAPK pathway, which phosphorylates target proteins and induces the synthesis of antimicrobial compounds, although the detailed mechanisms remain unclear (broken arrow). Cross-talk between the hormonal, ROS and sugar-dependent pathways (bidirectional arrows) can modulate the production of AMPs, which, in turn, stimulate the production of ROS and NO. ROS can be detoxified in the plant by antioxidants (inhibition arrow). Sugars contribute to the modulation or scavenging of ROS via the HXX-dependent pathway (Bolouri-Moghaddam et al., 2010), and to the production of NO via cell wall-derived OGs, all of which can converge on the MAPK pathway to activate downstream defence genes (Wawer et al., 2010). ABA, abscisic acid; AMP, antimicrobial peptide; AOs, antioxidants; CK, cytokinins; cwINV, cell wall invertase; Glc, glucose; HXX, hexokinase; JA, jasmonic acid; MAMPs, microbe-associated molecular patterns; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NPR1, NONEXPRESSOR OF PR GENES 1; OGs, oligogalacturonides; SA, salicylic acid; Suc, sucrose; Glc, Glucose; cwINV, cell wall invertase; ABA, abscisic acid; CK, cytokinins; JA, jasmonic acid; SA, salicylic acid.

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M KK1 is a MAPK involved in defence signalling, which is activated by both elicitors and ROS, thus making ROS-producing AMPs likely to activate MKK1 and to contribute to other interrelated signalling pathways (Fig. 1). Furthermore, the stress-responsive MAPK MPK4 is specifically phosphorylated and activated by MKK1 (Huang et al., 2000; Mészáros et al., 2006). AMPs can also use the MAPK signalling pathways endogenous to pathogens to control their growth, e.g. MAPK signalling cascades in F. graminearum are activated following exposure to the alfalfa defensin MsDef1 (Ramamoorthy et al., 2007). The activation of MAPKKs can be triggered by physical interactions and/or the phosphorylation of defensin receptors (Ramamoorthy et al., 2007).

**AMPS AND PLANT DEFENCE HORMONES**

Plant hormones act as central players in the innate immune system signalling network downstream of PTI or ETI (Bari and Jones, 2009; Pieterse et al., 2009). Although salicylic acid and jasmonic acid are recognized as major defence hormones, others, including ethylene, abscisic acid, gibberellins, auxins, cytokinins and brassinosteroids, also function as modulators of immunity (Pieterse et al., 2012; and references cited therein). They also modulate each other through a complex regulatory network based on different host–pathogen interactions (Kunkel and Brooks, 2002). In this context, plant hormones also use AMPs to orchestrate immune responses to pathogens (Goyal and Mattoo, 2014).

Pathogens and abiotic stresses, such as drought, salinity and cold, can induce the production of AMPs, and the expression of some defensins is developmentally regulated (van den Heuvel et al., 2001; Meyer et al., 1996; Miroze et al., 2006; Oh et al., 1999). Abscisic acid is thought to prioritize the immune signalling network by modulating the cross-talk between jasmonic acid and salicylic acid (Pieterse et al., 2012). Abscisic acid mediates immune responses against necrotrophic bacteria, oomycetes and fungi, contributing to either resistance or susceptibility (Asselbergh et al., 2008; Cao et al., 2011; Ton et al., 2009). The outcome depends on the infected tissue, the stage of infection and the infection strategy (Ton et al., 2009). The gene encoding the AMP SNAKIN2 is up-regulated by abscisic acid and down-regulated by gibberellins in potato (Berrocal-Lobo et al., 2002). CaAMP1 overexpression in A. thaliana increases salt and drought tolerance through abscisic acid-mediated signalling (Lee and Hwang, 2009). The CaAMP1 promoter sequences that regulate gene expression in response to pathogens, salicylic acid and methyl jasmonate (MeJA) are distinct from those that respond to abscisic acid and osmotic stress, which involve MYB transcription factors (Lee, 2011). Therefore, it seems that biotic and abiotic stress responses mediated by AMPs overlap with those triggered by abscisic acid and may help to coordinate responses to multiple stresses (Bolouri Moghaddam and Van den Ende, 2012).

Abiotic and biotic stresses can also induce the a-hairpin Tk-AMP from wheat (Triticum kiharae) (Utkina et al., 2013). The tomato defensin tgas118 is regulated by gibberellins during flower development (van den Heuvel et al., 2001), and the abundant thionin Th2.1 can be induced in A. thaliana flowers and siliques by the pathogen Fusarium oxysporum, wounding and jasmonic acid (Eppl e et al., 1995).

Jasmonates induce the expression of defensin genes in A. thaliana leaves challenged with fungal pathogens (Tesfaye et al., 2013) and regulate the expression of the hevein-like AMP WJAMP-1 (Kiba et al., 2003). Likewise, jasmonic acid up-regulates the expression of genes encoding insecticidal proteinase inhibitors (Farmer and Ryan, 1992) and enzymes that produce secondary metabolites, such as alkaloids, flavonoids, terpenoids and antimicrobial compounds, as part of systemic defence (Halitschke and Baldwin, 2004; Memelink et al., 2001; Penninckx et al., 1998).

Jasmonic acid also stimulates the activity of plant cell wall invertase to promote sweet immunity (Bolouri Moghaddam and Van den Ende, 2013).

Salicylic acid plays a key role in plant defence against biotrophic and hemibiotrophic pathogens, including Hyaloperonospora parasitica (Bari and Jones, 2009; Glazebrook, 2005). The regulatory protein NONEXPRESSOR OF PR GENES 1 (NPR1) controls many of the signalling events downstream of salicylic acid by acting as a transcriptional co-activator of a large set of defence-related genes, and it can conditionally modulate PDF1.2 expression following treatment with salicylic acid and MeJA (Spoel et al., 2003). CaAMP1 (Capsicum annuum anti-microbial protein 1) is differentially expressed in pepper leaves infected by Xanthomonas campestris pv. vesicatoria or treatments with defence signalling molecules, such as ethylene, salicylic acid and MeJA, as well as environmental stress (Lee et al., 2000).

Salicylic acid and ethylene, but not MeJA, can induce the expression of defensing like (DEFLs) genes in A. thaliana and Sp-AMP (PR-19) in Scots pine, whereas jasmonic acid/ethylene-mediated signalling, rather than salicylic acid signalling, activates PDF1.2 (Penninckx et al., 1996, 1998).

The jasmonic acid and salicylic acid defence pathways can interact antagonistically or synergistically depending on the nature of the pathogen (Beckers and Spoel, 2006; Mur et al., 2006; Spoel et al., 2003; Van der Does et al., 2013). There is an obvious cross-talk between the jasmonic acid and salicylic acid signalling pathways in pepper to control thionin synthesis as part of the PR response and other defence pathways (Lee et al., 2000). Ethylene influences a diverse range of plant growth and developmental processes and contributes to the regulation of defence responses against plant pathogens. In pepper, the ethylene-releasing compound etephon strongly induces the expression of CATHION1, a thionin gene, whereas this expression by salicylic acid and MeJA is time and dose dependent (Lee et al., 2000).
AMPS AND COOPERATIVE DEFENCE RESPONSES

Defence mechanisms based on resistance (R) genes and the recognition of PAMPs are highly effective in plants, but constitutive activation imposes a fitness penalty that leads to growth arrest and, ultimately, death. Therefore, multi-layered regulatory mechanisms have evolved in plants, including RNA silencing at both the transcriptional and post-transcriptional levels through DNA methylation and direct RNA interference mediated by small RNAs (Baulcombe, 2002; Waterhouse et al., 1998). The treatment of A. thaliana plants with salicylic acid or virulent and avirulent Pseudomonas syringae pv. tomato strains leads to the differential methylation of many genomic regions enriched in transposon sequences. Dampening of RNA-directed DNA methylation (RdDM) increases resistance against P. syringae (Pumplin and Voinnet, 2013). Transposon remnants in the vicinity of the promoters upstream of WRKY22 and RMG1 attract the RdDM machinery. Both salicylic acid and the activation of PTI by P. syringae suppress the RdDM pathway, resulting in the appearance of transient differentially methylated regions that prime the WRKY22 transcription factor (Pumplin and Voinnet, 2013). The role of WRKY proteins in the repression or activation of salicylic acid responses highlights their role in salicylic acid-mediated signalling and resistance, both of which affect the production of AMPs (Rushton et al., 2010) through the central immune regulator NPR1 (Pieterse and Van Loon, 2004). SAR is a consequence of the concerted transcriptome remodelling caused by ETI and/or PTI, increasing the intracellular concentration of salicylic acid, activating multiple downstream signalling cascades, and contributing to the synthesis of AMPs (Wang et al., 2006). The accumulation of PR proteins is frequently observed following pathogen infection and is induced by sweet immunity, which provides a direct link between sugar metabolism and plant defence (Bolouri Moghaddam and Van den Ende, 2013). AMPs can also modulate sugar signalling pathways, e.g. the PR maize seed protein PRms acts as a defence regulator through the modulation of Suc-mediated signalling, rather than having a direct antimicrobial effect (Gómez-Ariza et al., 2007; Huffaker et al., 2011).

AMPs are produced constitutively or in response to microbial challenge and show functional interactions to maximize their efficacy (Rahnamaeian and Vilcinskas, 2015; Rahnamaeian et al., 2015); they hold strong promise to serve as anti-infective measures in the era of multiple drug resistance (Rahnamaeian and Vilcinskas, 2015). However, they are not considered as a first line of defence in plants, where ETI, PTI and/or the sweet response act as upstream triggers for AMP synthesis (Stotz et al., 2013). Plant hormones and sugars thus appear to form a system of linked defence reactions that provide a robust and resource-efficient response to pathogens as summarized in Fig. 1.

CONCLUDING REMARKS

Plant innate immunity is a complex network in which there is cross-talk among many signalling pathways. AMPs occupy an important position within this complex network, and may act as modulators of defence signalling pathways based on hormones, ROS and MAPKs, in addition to their direct activity against microbes. Genetic, molecular and biochemical analyses have already begun to unravel this complex system of defence responses, and understanding the cooperative interactions among AMPs and other components of the innate immune system, including the corresponding signalling pathways, would facilitate the development of effective crop protection strategies. However, more fundamental research is needed to elaborate the role of AMPs and their interaction with the wider plant immune system.

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