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The wonderful world of intrinsic and intricate immunity responses in plants against pathogens

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Abstract: Plants, unlike animals, lack specialized mobile immune cells, so they do not have an adaptive immune system. Instead, plants can launch specific, self-tolerant immune responses and establish immune memory. Plants possess defense mechanisms that efficiently detect and ward off potentially dangerous microorganisms. These defense mechanisms start with multiple signalling processes responsible for sensation, recognition, signal collection and conveying information between cells. Recognition occurs when microbial or pathogen-associated molecular patterns (MAMPs or PAMPs) are detected, leading to MAMP- or PAMP-triggered immunity (MTI or PTI). Plant cells also recognize pathogens through effector-triggered immunity (ETI), which relies on the function of the pathogen's avirulence (*Avr*) gene-coded effector proteins and host's resistance (*R*) gene-coded R proteins, resulting in the activation of apoptosis-like cell death, known as the hypersensitive response. In addition, reactive oxygen species (ROS) act as a double-edged sword; they are either toxic or versatile signalling molecules in plants. ROS generation is an integral part of hormone regulation and function in plant defense mechanisms. Plant hormones are also implicated in plant defense signalling pathways; salicylic acid, jasmonic acid, and ethylene have been increasingly studied in plant responses to pathogens. These innate immune system components interact with each other and provide protection against invading pathogens. We review advances in understanding the molecular aspects of plant defense mechanisms and describe the role of ROS, mitogen-activated protein kinase (MAPK) cascades, and hormones in modulating defense responses. We also provide an overview of how these plant defense components interact for a balanced and appropriate defense response.

Keywords: effector-triggered immunity, mitogen-activated protein kinase, PAMP-triggered immunity, phytohormones, reactive oxygen species

Résumé: Les végétaux, contrairement aux animaux, n'ont pas de cellules immunitaires spécialisées mobiles, en conséquence, elles ne possèdent pas de système immunitaire adaptatif. En revanche, ils peuvent amorcer des réponses immunitaires spécifiques autotolérantes et acquérir une mémoire immunitaire. Les végétaux possèdent des mécanismes de défense qui détectent efficacement les microorganismes potentiellement dangereux et qui permettent de les contrer. Ces mécanismes sont amorcés par de multiples processus de signalisation responsables de la sensibilité, de la reconnaissance, de la collecte de signaux et de l'échange d'information entre les cellules. La reconnaissance se produit quand les motifs moléculaires associés à des microbes ou à des agents pathogènes (MAMP ou PAMP) sont détectés, engendrant l'immunité déclenchée par les MAMP ou les PAMP (MTI ou PTI). Les cellules des végétaux reconnaissent également les agents pathogènes grâce à l'immunité déclenchée par des effecteurs (ETI) qui dépend de la fonction des protéines effectrices codées par le gène d'avirulence (*Avr*) de l'agent pathogène et des protéines codées par le gène R de la résistance de l'hôte (*R*), provoquant l'activation d'une mort cellulaire semblable à l'apoptose, considérée comme une réponse d'hypersensibilité. De plus, les espèces réactives de l'oxygène (ROS) agissent comme une épée à deux tranchants: ce sont, chez les végétaux, soit des molécules toxiques ou des molécules de signalisation polyvalentes. La formation de ROS est une partie intégrante de la régulation et de la fonction hormonale dans les mécanismes de défense des

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végétaux. Les phytohormones sont également impliquées dans les voies de signalisation de la défense des végétaux: l'acide salicylique, l'acide jasmonique et l'éthylène ont été de plus en plus étudiés relativement à la réaction des végétaux aux agents pathogènes. Ces composés naturels du système immunitaire interagissent pour offrir une protection contre les agents pathogènes envahissants. Nous passons en revue les avancées relatives à la compréhension des aspects moléculaires des mécanismes de défense chez les végétaux et décrivons le rôle des ROS, des cascades de signalisation de la protéine kinase activée par des agents mitogènes (MAPK) et des hormones dans la modulation des réponses immunitaires. Nous présentons également un aperçu de la façon dont ces composés de la défense des végétaux interagissent pour produire une réaction de défense équilibrée et adéquate.

Mots clés: Immunité déclenchée par des effecteurs, protéine kinase activée par des agents mitogènes, immunité déclenchée par les PAMP, phytohormones, espèces réactives de l'oxygène

Introduction

For the last 500 million years, since the beginning of plants' colonization of the Earth's land surface, plants have been exposed to a combination of biotic and abiotic stresses. Through evolution, plants have developed sophisticated mechanisms to combat these stresses. Generally, these mechanisms act in two ways: by pre-formed structures and chemicals (non-specific barriers) and by infection-induced responses of the immune system (specific barriers). The non-specific barriers consist of the plant's external structures, for instance, cell wall appositions known as papillae, rigid cell walls (lignification), a waxy cuticle on the leaf surface, and epidermal hairs on the surface of the plant (Fu and Dong 2013), and preformed chemicals, including unsaturated fatty acids, reactive species scavengers, hormones, molecular chaperones, compatible solutes, and antimicrobial metabolites (phytoalexins) (Freeman and Beattie 2008; He et al. 2018). While these non-specific barriers prevent many pathogens from invading before they can cause extensive damage, a few pathogens manage to evade these initial barriers, activating the plant's innate immune system (Dangl and McDowell 2006). Following successful pathogen recognition, rapid generation of reactive oxygen species (ROS) is one of the earliest cellular responses. ROS accumulation represents a typical plant response to different biotic and abiotic stresses and is critical for successfully activated immune responses against pathogen infection (Petrov and Van Breusegem 2012; Noctor et al. 2014; Xia et al. 2015; Lee et al. 2020). Reactive oxygen species can have toxic effects on pathogens (O'Brien et al. 2012) and trigger programmed cell death (PCD), referred to as the hypersensitive response (HR), at the site of infection to limit pathogen progression (Mur et al. 2008).

Pathogen recognition results in downregulation of growth mediated by phytohormones and upregulation of defense-related genes (Karasov et al. 2017). Phytohormones play pivotal regulatory roles in this

complex immune system. Three phytohormones, salicylic acid (SA), jasmonic acid (JA), and ethylene (ET), are known to play significant roles in regulating plant defense responses. However, growth-related phytohormones, such as auxins, cytokinins (CKs), brassinosteroids (BRs), abscisic acid (ABA), and gibberellins (GAs) have also been shown to modulate plant immune defense (Tsuda and Katagiri 2010; Pieterse et al. 2012; Berens et al. 2017) through a complex network of communication referred to as hormone crosstalk.

Since plants usually encounter multiple pathogens simultaneously, these sensing recognition, signal collection, and transduction mechanisms are critical to the perception and identification of pathogens (Rizhsky et al. 2004; Lamers et al. 2020). The interplay between these defense mechanisms is presumed to confer advantages to plants, for example, an increased ability to respond to different types of pathogens and changing developmental and environmental conditions.

Although most of these defense mechanisms are well understood and widely discussed (Cheng et al. 2012; Wang et al. 2019), there is still uncertainty about how and why different components of defense mechanisms positively or negatively interact with each other and finally converge during biotic stress responses. For instance, PTI and ETI may be spatiotemporally distinct but are intimately related to the ROS burst (Torres et al. 2006; Kadota et al. 2015), or SA, JA, and ET production are triggered upon PAMP perception (Bigeard et al. 2015). Therefore, it is necessary to describe how these components activate their pathways and whether these components can interact with each other. Hence, to sketch a general picture of signalling networks and to understand how plants use signalling transduction to coordinate their cellular activities and how they respond to pathogens, we reviewed the molecular mechanisms by which plants detect pathogens and outlined the signalling and functional roles of ROS molecules and hormonal crosstalk in post-perception signal transduction and immune responses.

Pathogen recognition

Pathogen-associated molecular pattern-triggered immunity

Pathogen recognition consists of two levels. The first level is triggered in plants by the perception of microbial or pathogen-associated molecular patterns (MAMPs or PAMPs), which is one of the crucial mechanisms boosted by the detection of extrinsic molecules (Henry et al. 2012; Kushalappa et al. 2016). PAMPs are slow-evolving compounds, ranging from carbohydrates to proteins, recognized by host plants. Compounds such as flagellin, elongation factor Tu, and chitin act as PAMPs (Jones and Dangl 2006; Anderson et al. 2010). PAMPs trigger basal disease resistance and result in PAMP-triggered immunity (PTI). At the molecular level, PAMPs and MAMPs are recognized by transmembrane pattern recognition receptors (PRRs) with an extracellular ligand-binding domain and an intracellular leucine-rich repeat domain (LRR) (Henry et al. 2012). PAMPs and MAMPs are generally triggered by the detection of molecules released by pathogens known as elicitors, for instance, chitin or lipopolysaccharides, which consist of significant components of pathogen structures (i.e. cell walls) and infectious factors (i.e. enzymes). The perception of the presence of a pathogen depends on the specific interactions between plants' cellular receptors and the pathogen elicitors.

A typical example of PAMP receptor recognition is the interaction between bacterial flagellin 22 (flg22) and *Arabidopsis* LRR receptor-kinase FLS2 (Flagellin Sensitive 2) (Jones and Dangl 2006). The binding of flg22 and FLS2 triggers the intracellular interaction between the C-terminus of FLS2 and BRASSINOSTEROID INSENSITIVE-associated kinase 1 (BAK1), which further helps to activate plant immunity (Belkhadir et al. 2012; Sun et al. 2013). Evidence has suggested that the activation of FLS2 protein triggers a series of cellular responses related to plant defense (Navarro et al. 2004; Anderson et al. 2010; Sun et al. 2013).

Other molecular patterns similar to PAMPs are damage-associated molecular patterns (DAMPs), which refer to the recognizable molecules related to plant damage, such as cell wall fragments, protein fragments, peptides, nucleotides, amino acids, and lytic enzymes (Albert 2013; Doughari 2015; Kushalappa et al. 2016). DAMPs are perceived as plasma membrane-localized receptors in surrounding cells that regulate immune responses against invading organisms and promote damage repair. DAMPs overlap with PTI signalling

components (Boller and Felix 2009). In general, PAMPs, MAMPs and DAMPs elicit a series of defense signalings to respond to potential threats from invaders.

Effector-triggered immunity

The second level of pathogen recognition encircles plant resistance (R) proteins, which identify specific receptors from a pathogen (Avr proteins) (Abdul Malik et al. 2020; Dangl and McDowell 2006; Gouveia et al. 2017) and results in effector-triggered immunity (ETI). Avr proteins, also known as effectors, are secreted by pathogens and recognized by host receptors (R proteins) during infection. R proteins are produced by R genes that convey plant disease resistance against pathogens. This interaction is known as a gene-for-gene interaction. Therefore, the race-specific defense caused by effector-host recognition induces a stronger defense response known as effector-triggered immunity (ETI) (Henry et al. 2012; Kushalappa et al. 2016). Although there is no fundamental difference in signalling between ETI and PTI, ETI is considered a more rapid and vigorous version of PTI. ETI reinstates and amplifies PTI in cellular signalling (Cui et al. 2015). The defense following the recognition is known as the hypersensitive response (HR). HR is a mechanism to prevent the spread of infection. The rapid death of cells characterizes HR in the local region surrounding infection, and it serves to restrict the growth and spread of pathogens to other parts of the plant. Physiologically, the HR-based defense features a series of locally expressed resistance reactions at attempted penetration points. Localized tissue death occurs followed by nutrient exploitation of the living cells, which hinders the further proliferation of pathogens (Van Loon 1997; Thakur and Sohal 2013). For example, in some bacteria, when the pathogen penetrates the intercellular spaces and then the cell membrane, Type III Secretion System (T3SS) effectors are injected (Knepper and Day 2010). R proteins from the host plant then recognize and bind the effectors to induce HR, which subsequently halts the further invasion of the pathogen (Dangl and McDowell 2006). Findings suggest that HR causes DNA fragmentation, nuclear lobing, plasma membrane shrinkage, and condensation of the cytoplasm, which are the symptoms of localized cell death (LCD) (Li et al. 2008). However, HR-elicited PCD is not the only mechanism that slows down pathogen proliferation in host tissue. A study on *Arabidopsis* mutant lines of *dnd1* and *dnd2* (defective in HR cell death) revealed that HR was not entirely abolished.

Other defensive mechanisms, such as SA accumulation and induction of pathogenesis-related genes (*PRs*) compensated for defective HR cell death (Yu et al. 1998; Jurkowski et al. 2004).

Plant defense strategies can be divided into incompatible and compatible interactions; ETI causes the incompatible interaction, while the compatible interaction is the defense without ETI. The general profile of defense signalling from compatible and incompatible interactions can be very similar; however, gene expression at specific time points differed between these two interactions. ETI activates some expressions from PTI that is stronger and longer (Tao et al. 2003; Cui et al. 2015).

Besides PTI and ETI, another general mechanism named effector-triggered defense (ETD) is postulated, which lies between PTI and ETI (Stotz et al. 2014). ETD is characteristic of microbes that move into the intercellular matrix or apoplastic spaces of the host. ETD is initiated by the interaction of apoplastic effectors with cell surface-localized receptors, from which this type of defense has both ETI and PTI characteristics (Stotz et al. 2014). The receptor-like proteins (RLPs) interact with a receptor-like kinase SOBIR1 (Suppressor of Bir-1), and this interaction is associated with another factor, BAK1 (BRASSINOSTEROID INSENSITIVE 1-ASSOCIATED RECEPTOR KINASE 1), to promote cell death and defense responses (Liu et al. 2016). Moreover, Ma and Borhan (2015) found a *Brassica napus* homolog of AtSOBIR1, which interacts with *B. napus* RLP LepR3. This BnSOBIR1 was found to elicit HR in the case of the *AvrLm1-LepR3* interaction.

R and Avr proteins

In *Arabidopsis*, about 200 *R* genes are found with conserved domains (Meyers et al. 2003). Conserved domains can be used for *R* gene identification and classification. Nucleotide-binding site-leucine-rich repeat (NLR), receptor like kinase (RLK), and protein (RLP) genes are the main types of *R* genes. *R* genes duplicate in the genome so that more *R* proteins will be encoded. This could be advantageous for plants since the regulation of more *R* proteins is beneficial because it leads to a broader spectrum of disease resistance (Yi and Richards 2007).

The largest class of *R* proteins are nucleotide-binding site-leucine-rich repeat (NB-LRR) receptors. LRRs consist of 2–45 motifs of 20–30 amino acids in length. Each motif is considered as one repeat, and LRR proteins can have many repeats, forming the

LRR domain. LRR is involved in specific ligand-receptor interactions (Chisholm et al. 2006). In contrast, the NBS domain in the N-terminus binds ATP and GTP molecules. This interaction causes conformational changes to trigger downstream signalling (De Young and Innes 2006; McHale et al. 2006). NB-LRR domains can be subdivided further based on the presence or absence of an N-terminal Toll/interleukin1-like receptor (TIR) homology region or a CC motif in the N-terminal region (McHale et al. 2006; Knepper and Day 2010) into the functionally distinct TIR-domain-containing (TNL), CC-domain-containing (CNL), and RPW8 domain-containing (RNL) subfamilies. N-terminal motifs inhibit ligand-binding in the LRR domain to keep the *R* protein persistently inactive.

The structure and function of effector proteins vary among different pathogens. Effector proteins are generally short peptides, and many are cysteine-rich and harbour N-terminal signal peptides. Secretory proteins carry a short signal peptide in their N-termini that assists with their secretion into the cytosol or host apoplastic spaces (Owji et al. 2018).

Cysteine residues form a disulphide bridge, stabilizing the protein structure (Chisholm et al. 2006). Effectors can have multiple bridges for folding conformational, and functional stability; this seems more important in the hostile apoplastic space. Avr proteins are a subset of effector proteins and are genetically identified as triggering HR, due to recognition by *R* genes.

The stability of the Avr protein is essential for host recognition. For example, the mutated proteins of Avr4 in *Cladosporium fulvum* can avoid the interaction with the *R* protein Cf-4 in tomatoes (Joosten et al. 1997). The mutated derivatives of Avr4 have a substitution of Cys to Tyr, which causes unstable cysteine–cysteine disulphide bonds to affect the protein structure. The failed interaction produced more severe disease symptoms in tomato leaves (Joosten et al. 1997).

Studies have suggested that Avr proteins may have specific biological roles in infection and colonization. For example, in *C. fulvum*, Avr2 inhibits tomato cysteine protease Rcr3 activity (Chisholm et al. 2006) and changes the structure of Rcr3, which triggers the HR initiated by *R* protein Cf-2. Furthermore, some Avr proteins have been implicated in activating plant transcription (Chisholm et al. 2006). For instance, the AvrBs3 protein family found in *Xanthomonas* has a nuclear localization domain (Zhu et al. 1998), and AvrXa7 in *Xanthomonas oryzae* binds DNA with a preference for dA- and dT-rich fragments (Yang et al. 2000). The

interaction between Avr proteins and host nuclear content probably intervenes in the host transcriptional activation of defense genes.

R proteins can interact with Avr proteins directly and indirectly. For example, AvrPita from *Magnaporthe grisea* and Pita from *Arabidopsis thaliana* physically interacts with each other in the LRR domain (De Young and Innes 2006). Indirect interactions between R and Avr proteins may be described by the guard hypothesis. This hypothesis postulates that a host R protein (the product of an R gene) guards a protein, the guardee, that is the target of the Avr effector protein. Binding, deactivation, or cleavage of the target protein by the Avr effector protein is sensed by the R protein, sometimes through a conformational change, which in turn triggers the resistance function of the R protein (De Young and Innes 2006; Knepper and Day 2010). The guard model was first suggested explaining the mechanism of *Pseudomonas syringae* AvrPto perception by the tomato proteins Pto and Prf (Van der Biezen and Jones 1998). One well-known example is the interaction between the effector AvrRpt2 (*Pseudomonas syringae*) and R protein RPS2 (*Arabidopsis thaliana*) mediated by the RPM1-interacting protein 4 (RIN4). The interaction between AvrRpt2 and RIN4 disrupts the RIN4/RPS2 complex to switch RPS2 into active formation (Mackey et al. 2003; De Young and Innes 2006). R protein-mediated defense also occurs by detecting the biological activity of Avr protein. For example, AvrPphB acts as a protease, which cleaves a protein kinase, and the R protein RPS5 in *Arabidopsis* can detect the cleavage from the Avr protein and elicits subsequent defense (Shao 2003).

Moreover, results about additional targets of AvrPto and AvrBs3 provoked suggestions of the concept that some host targets of effectors act as decoys (antagonistic interactions between hosts and pathogens). Decoys mimic effector targets to trap the pathogen into a recognition event to detect pathogen effectors via R proteins (Zhou and Chai 2008; Zipfel and Rathjen 2008).

Plant defense molecular signalling

Oxidative burst

Reactive oxygen species are highly reactive chemical molecules formed via oxygen consumption in a so-called oxidative burst. ROS act as signal molecules in various biological processes in plants, including photorespiration, stomatal movement, and photosynthesis (Baxter et al. 2014; Das and Roychoudhury 2014). ROS signalling acts as an early response in plants

when combating biotic or abiotic stresses. Signalling itself controls a broad spectrum of biological processes. Common ROS molecules, such as superoxide ($\cdot\text{O}_2^-$), hydroxyl radical ($\cdot\text{OH}$), singlet oxygen ($^1\text{O}_2$), and nitric oxide (NO) are generated in plant cells by the electron transport chain (ETC), NADPH oxidase, and peroxisomes (Baxter et al. 2014; Liu and He 2016). Generally, ROS exists in ionic (hydroxyl radicals and superoxide anions) and molecular states (hydrogen peroxide and singlet oxygen) and can be produced by extracellular (environmental pollutants, radiation exposure, microbial infection, and exposure to engineered nanoparticles) and intracellular (mitochondria, the endoplasmic reticulum (ER), peroxisomes, microsomes, and NOX complexes) sources (Abdal Dayem et al. 2017).

Local and systemic ROS generation and signalling appear in biotic and abiotic stresses, such as high light, drought, pathogenic attack, and plant-arbuscular mycorrhizal interactions (O'Brien et al. 2012; Baxter et al. 2014). Cellular activities such as stomatal closure programmed cell death, and Ca^{2+} leakage during stress tolerance involve the modulation of ROS-derived signalling (Baxter et al. 2014). ROS generation also elicits extremely diverse signalling events from which an extensive and complicated genetic network is involved.

ROS molecules

Superoxide radicals ($\cdot\text{O}_2^-$) are the earliest ROS molecules produced from oxidative bursts, and are generally formed by adding electrons to an oxygen molecule (O_2) (Wojtaszek 1997; Sharma et al. 2012). They form in various locations inside plant cells, where electrons are available from ETC in chloroplasts and mitochondria (Elstner 1991; Das and Roychoudhury 2014). They are short-lived and are not frequently involved in biochemical reactions. They can be further converted to hydrogen peroxide (H_2O_2), a relatively stable molecule, by superoxide dismutase (SOD). Hydrogen peroxide is not a reactive molecule and can travel across a long distance through the apoplastic spaces and achieve long-distance signalling (Wojtaszek 1997; Sharma et al. 2012). Hydrogen peroxide production mainly occurs during ETC in the chloroplast, mitochondria, endoplasmic reticulum, and cell membrane, and during the β -oxidation of fatty acids and photorespiration (Das and Roychoudhury 2014). Hydrogen peroxide can induce cytological changes and gene activation, playing various roles in resistance to multiple stresses. For example, the over-accumulation of hydrogen peroxide can induce localized basic PR expressions such as that of *PRI* and *PR2* to defend against infection (Chamnongpol et al. 1998). The

accumulation of reactive oxygen species or hydrogen peroxide initiates PCD by causing membrane damage when the pathogen is established in the host cells (Bestwick et al. 1997). Hydrogen peroxide accumulates during papillae formation. Peroxidases can be used to promote cross-linking of proteins and phenolics to reinforce cell wall appositions (Brown et al. 1998). The apoplastic generation of superoxide or hydrogen peroxide has been documented following the recognition of various pathogens (Grant et al. 2000).

Hydrogen peroxide is a pivotal molecule for eliciting diverse downstream responses in various events, including cell cycle, senescence, lignification, electrolyte leakage, the MAPK cascade, SA, JA, ABA, or ET signalling, and stomatal closure (Quan et al. 2008). The formation of superoxide and hydrogen peroxide is catalysed by membrane-bound NADPH-oxidases (RBOHs) and cell wall-bound peroxidases (Lamb and Dixon 1997). The reduced ROS production has been reported to block the expression or function of these two types of genes in transgenic plants (Lamb and Dixon 1997; Torres et al. 2002; Morales et al. 2016).

In *Arabidopsis*, *RBOH-D* and *-F* are the two most well-studied NADPH-oxidase genes, which play crucial roles in cell death and basal defense by modulating hydrogen peroxide accumulation (Torres et al. 2002; Torres and Dangl 2005; Morales et al. 2016). Disruption of Daudi enzymes by mutation, knockdown, or chemical treatment can reduce or diminish plant resistance by attenuating the hydrogen peroxide-related defense such as cell death (Torres et al. 2002; Morales et al. 2016). For example, a diphenylene iodonium elicitor from *Phytophthora* spp. (or *C. lindemuthianum*) significantly inhibited hydrogen peroxide production in rose cells by targeting RBOH proteins (Bolwell et al. 1998). Reduced cell death, peroxide production, and electrolyte leakage were observed in *Arabidopsis* lines with *RBOH-D* and *-F* mutations when the plants were inoculated with *Pseudomonas syringae* DC3000 (Torres et al. 2002). Transgenic lines of antisense *NtRBOH-D* in tobacco showed reduced ROS and hydrogen peroxide production when the leaves were elicited by cryptogein (Simon-Plas et al. 2002).

The hydroxyl radical ($\cdot\text{OH}$) is the neutral form of the hydroxide ion (OH^-). The O-O double bonds can be formed when hydrogen peroxide cleaves. It is active and usually acts very near its production site. Therefore, it is the most reactive of the ROS and can react with all biological molecules. Cell wall polysaccharides can oxidize, resulting in cell wall loosening (Karkonen and

Kuchitsu 2015), and can also induce DNA single-strand breakage (Hiramoto et al. 1996).

Singlet oxygen (${}^1\text{O}_2$) is another ROS generated via energy transfer from excited chlorophyll to molecular oxygen during photosynthesis, mainly in photosystem II (Das and Roychoudhury 2014). Singlet oxygen has a short half-life but is highly reactive and destructive, damaging photosystems I and II, along with other essential plant components, such as proteins and nucleic acids (Das and Roychoudhury 2014). Singlet oxygen is moderately reactive and can be protonated at lower pH to form a highly reactive hydroperoxyl radical ($\text{HO}_2\cdot$). The hydroperoxyl radical is more hydrophobic and able to move through the cell membranes (Wojtaszek 1997).

Nitric oxide (NO) is also known as an important signalling and regulatory molecule in plants that regulates multiple processes during growth, development, reproduction, responses to the external environment and biotic interactions. It has been noted that cellular levels of NO facilitate the early establishment of the pathogen and restrict further pathogenic infections (Martínez-Medina et al. 2019). The interaction between NO and ROS is essential to initiation of cell death mechanisms in response to certain types of pathogens (Sadhu et al. 2019). Furthermore, the crosstalk of NO with other defense components, such as hormones (Mur et al. 2013) has been documented by Sami et al. (2018).

ROS scavenging

In plants, ROS molecules can either promote early signals to trigger various molecular events to respond to different conditions or impair tissues and cells when the amounts are excessive. Therefore, besides the signal network attributed to ROS molecules, plants have a series of enzymatic (SOD, catalase (CAT), glutathione peroxidase (GPX), and glutathione-S-transferase (GST)) and non-enzymatic (tocopherols, carotenoids, and flavonoids as a lipid phase; ascorbate, urate, glutathione, and other thiols as a liquid phase) protective antioxidant mechanisms; acting together, they protect the cells from oxidative damage and prevent the formation of radicals (Young 2001). These mechanisms constitute the ROS scavenging system. The first group of ROS scavengers belongs to the catalase family (CATs), which are the haem proteins catalysing the decomposition of hydrogen peroxide into water and dioxygen gas. The antioxidative activity of CATs mainly occurs in the peroxisomes, which are hotspots for superoxide radical and hydrogen peroxide production (Das and Roychoudhury 2014).

Catalase enzymes show a high affinity towards hydrogen peroxide and have a high turnover rate. Catalases can be highly expressed in plant tissues where antioxidative activity is needed (Mhamdi et al. 2010).

Superoxide dismutase is an enzyme that catalyses the conversion of superoxide radicals to hydrogen peroxide in cells (Das and Roychoudhury 2014). Superoxide dismutase enzymes are also regarded as metalloenzymes because they have metal ions and co-factors for achieving specific reactions. Superoxide dismutase enzymes can be classified into SODs associated with manganese (Mn), iron (Fe), or copper/zinc (Cu/Zn) by the ions with which they interact (Das and Roychoudhury 2014). These enzymes can induce multiple-stress tolerances and defense against pathogenic attacks. For example, Cu/Zn-SOD, Fe-SOD, and Mn-SOD activities were increased under mild and high drought stress conditions (Sharma and Dubey 2005). The overexpression of Cu/Zn-SOD can relieve oxidative stress by metabolizing superoxide radicals, reducing potential damage to the chloroplasts (Gupta et al. 1993). Superoxide dismutase activity is induced in defense against fungal pathogens in the genus *Cercospora* since the pathogen-derived toxin cercosporin can produce singlet oxygen and superoxide molecules. Superoxide dismutase in mitochondria also plays a role in incompatible interactions between *N. plumbaginifolia* and *P. syringae* (Bowler et al. 1992).

Ascorbate peroxidases (APXs) are another critical group of enzymes adjusting ROS levels in the cells. Ascorbate (AsA), with a low molecular weight, is a highly abundant antioxidant, which donates electrons to various enzymes for their reactions, including APXs (Sharma et al. 2012). Ascorbate molecules are mainly located in the cytosol and mediated by APXs. ROS scavenging reaction involving AsA and APXs can relieve oxidative damage and protect crucial macromolecules and organelles (Caverzan et al. 2012; Pandey et al. 2017).

In ROS scavenging pathways, ascorbate (AsA) is associated with glutathione (GSH) to form an ascorbate-glutathione (AsA-GSH) cycle (Fig. 1). The AsA-GSH cycle operates in the cytosol, mitochondria, plastids and peroxisomes. The AsA-GSH cycle starts the conversion of hydrogen peroxide to water by ascorbate peroxide (APX) with ascorbate (AsA) as the electron donor. The oxidized ascorbate (monodehydroascorbate, MDHA) is regenerated by monodehydroascorbate reductase (Wells and Xu 1994). However, monodehydroascorbate is a radical and if not rapidly reduced, disintegrates into ascorbate and dehydroascorbate (DHA). Dehydroascorbate is reduced to ascorbate by dehydroascorbate reductase (DHAR) at the expense of GSH, yielding oxidized glutathione (GSSG).

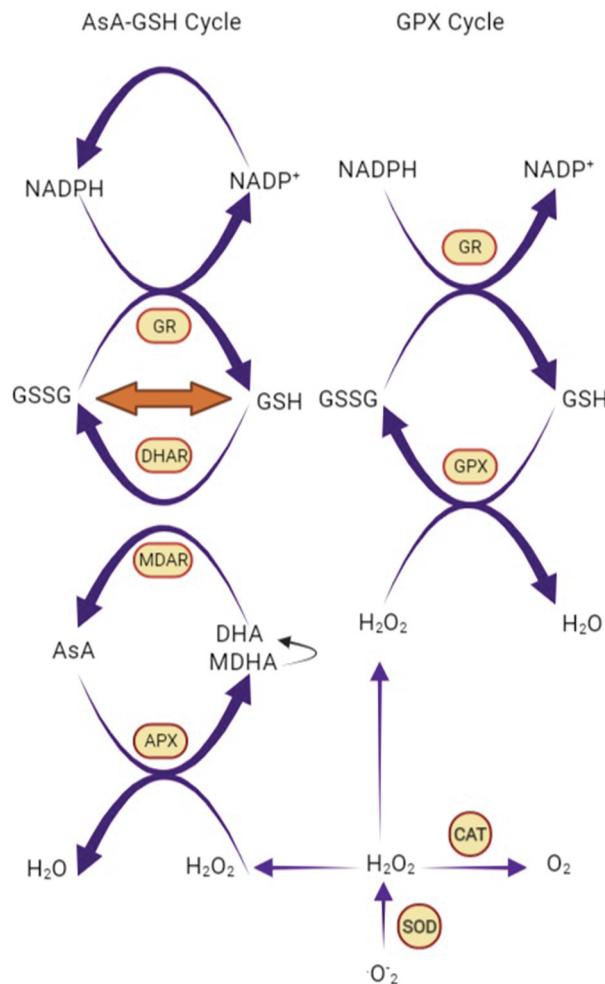


Fig. 1 (Colour online) The ascorbate glutathione (AsA-GSH) and glutathione peroxidase (GPX) cycles. GSSG: oxidized glutathione (glutathione disulphite); GSH: glutathione; GR: glutathione reductase; DHAR: dehydroascorbate reductase; MDAR: monodehydroascorbate reductase; AsA: ascorbate; DHA: dehydroascorbate; MDHA: monodehydroascorbate; APX: ascorbate peroxidase; GPX: glutathione peroxidase.

Finally, GSSG is reduced by glutathione reductase (GR) using NADPH as an electron donor (Noctor and Foyer 1998; Pandey et al. 2017). Therefore, the AsA-GSH cycle plays a crucial role in hydrogen peroxide detoxification.

Mitogen-activated protein kinase cascades

Mitogen-activated protein kinase (MAPK) cascades represent a group of signalling pathways that are highly conserved among eukaryotes. This signalling module plays diverse roles, including the regulation of growth and development, programmed cell death

and responses to biotic and abiotic stresses (Bigeard and Hirt 2018). Reactive oxygen species signalling induces MAPK cascades, electrolyte leakage, hormone secretion, programmed cell death and transcriptional reprogramming. Reactive oxygen species induce Ca^{2+} leakage and cause LCD by MAPK cascades starting with mitogen-activated protein (MAP)/extracellular signal-related kinases (ERK) (MEKs) (Zhang and Klessig 2001). SA, JA, and ET may create a homoeostatic network under oxidative stress; SA and ET promote cell death and lesion development, and JA attenuates those processes (Overmyer et al. 2000; Rao et al. 2002). Due to the importance of this biological section, the activation and timing of ROS signalling play important roles in effective plant defense.

The cascade consists of MAPKK kinase (MEKK), MAPK kinase (MEK), and MAPK (MPK). There are specific combinations among different MEKKs, MEK, and MPK factors. For example, MEKK1-MEK1/2-MPK4 in *Arabidopsis* negatively regulates signal transduction against biotrophic pathogens, but positively regulates it against necrotrophic pathogens (Ichimura et al. 2006; Petersen et al. 2010). Hydrogen peroxide regulates MEKK1 to attain ROS homoeostasis (Nakagami et al. 2006), and it is found to negatively regulate the ROS signalling factors, including MPK3/6 (Ichimura et al. 2006). In tobacco (*Nicotiana tabacum*), the module of NPK1 (a MEKK1)-MEK1-NTF6 (an MPK) is crucial for *N*-gene (an *R* gene in tobacco) expression to defend against tobacco mosaic virus (TMV). The activation of defenses also involves the expression of *WRKY* and *MYB* genes (transcription factors) and JA responsive factor *COII* (Liu et al. 2004).

The ROS production activates MAPK cascades, such as *MPK3/6*, which regulate hormonal signals such as *ERF1* (as an ET transcription factor) (Moon et al. 2003). Wang et al. (2009) suggested that *MPK4* suppresses ROS production and activates the ET-JA-responsive factor *PDF1.2* in canola (*Brassica napus*). The overexpression of *MPK4* in transgenic canola plants makes them more resistant to necrotrophic pathogens such as *Sclerotinia*. MPK4 in ET-JA binds a nuclear substrate called MAPK kinase substrate 1 (MKS1) to regulate *WRKY33*, which is a WRKY factor promoting ET-JA signalling (Petersen et al. 2010). In summary, MAPK cascades induce diverse mechanisms combatting various biotic and abiotic stresses. Since there are numerous plant MAPK factors, the genetic network of MAPK cascades can be diverse and fine-tuned to respond to various stresses.

Phytohormones

Plants activate other defensive responses to cope with pathogens, which are modulated by the induced production of a wide variety of hormones (Vos et al. 2015), including auxins, gibberellins (GA), abscisic acid (ABA), cytokinins (CK), salicylic acid (SA), ethylene (ET), jasmonates (JA), brassinosteroids (BR) and peptide hormones (Bari and Jones 2009). Classical defense phytohormones SA, JA and ET are known to play major roles in regulating plant defense responses (Kunkel and Brooks 2002).

Salicylic acid is a group of phenolic compounds containing an aromatic ring and a hydroxyl group. Previous studies have shown that SA plays various roles in plant defense and growth (Vlot et al. 2009; Rivas-San Vicente and Plasencia 2011). In plants, the biosynthesis of SA starts with shikimic acid and chorismic acid, and the pathway divides into two routes: the route of isochorismic acid (catalysed by isochorismate synthase (ICS)) and the route of cinnamic acid (catalysed by phenylalanine ammonia-lyase (PAL)) (Dempsey et al. 2011) (Fig. 2).

Since SA represents similar molecules, it has many derivatives that play different functions under various conditions. Salicyloyl glucose ester (SGE), SA O - β -glucoside (SAG), methyl salicylate (MeSA), and methyl salicylate O - β -glucoside (MeSAG) are four of them. MeSA is a methylated type of SA and a phloem-mobile signalling molecule. MeSA is involved in systemic acquired resistance (SAR), and crosstalk occurs between SA and JA signalling (Dempsey et al. 2011). SAG is a glycosylated form of SA and is produced in the cytosol and actively transported from the cytosol to the vacuole as storage for inactive SA (Dempsey et al. 2011; Rivas-San Vicente and Plasencia 2011). Both MeSA and SAG are inactive; they are converted into free SA when the SA signalling is needed (Vlot et al. 2009).

SA plays a wide range of biological roles in plants. For example, the role of SA in seed germination has been controversial as contradictory reports suggest that it can either inhibit or increase seed germination. It has been reported that SA inhibits seed germination in *Arabidopsis* (Rajjou et al. 2006), maize (Guan and Scandalios 1995), and barley (Xie et al. 2007), which might be due to SA-induced oxidative stress (Rivas-San Vicente and Plasencia 2011). In contrast, during seed maturation, SA promotes the synthesis of proteins for germination (Rivas-San Vicente and Plasencia 2011).

Previous studies have revealed that SA effectively defends against biotrophic pathogens (Bari and Jones 2009). SA-mediated immune responses are essential components of both PTI and ETI (Tsuda et al. 2009)

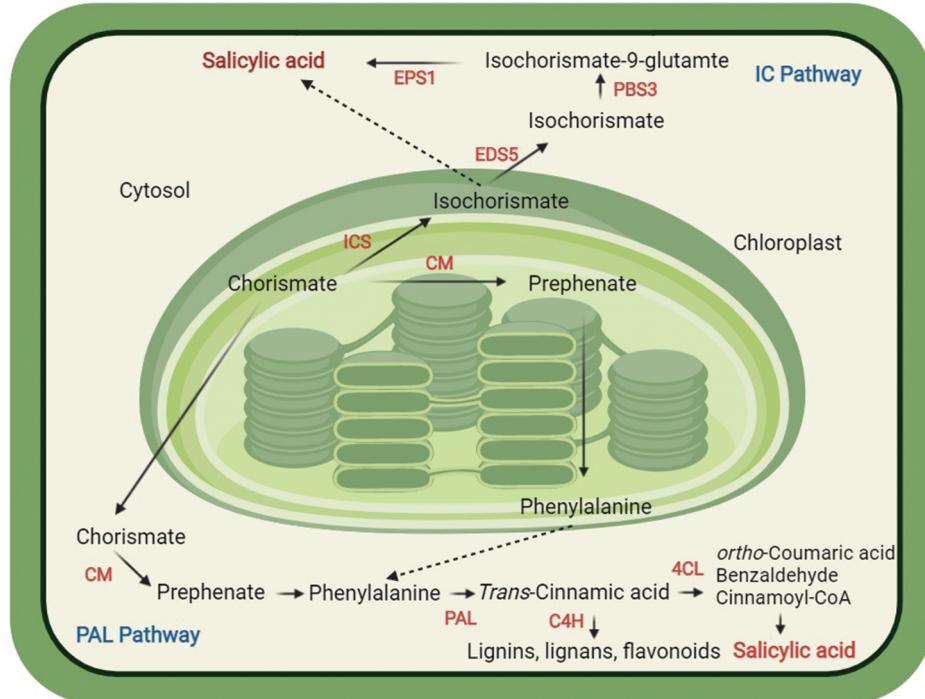


Fig. 2 (Colour online) Salicylic acid biosynthesis pathways. The pathway is divided into phenylalanine ammonia-lyase (PAL) and isochorismate (IC) routes, mediated by isochorismate synthase (ICS). Chorismate is converted to isochorismate. IC is moved from plastid to cytosol, and then IC is converted into isochorismate-9-glutamate (IC-9-Glu) mediated by *avrPphB SUSCEPTIBLE3* (PBS3), and then finally, IC-9-Glu is spontaneously converted to salicylic acid. The PAL route involves the *trans*-cinnamic acid (made from phenylalanine by PAL) to lignins, lignans, and flavonoids (mediated by cinnamate 4-hydroxylase, C4H), and precursors of salicylic acid (involving 4-coumarate: CoA ligase: 4CL).

and important for SAR activation (Durrant and Dong 2004). Furthermore, one of the well-known roles of SA in plants is to provoke oxidative bursts. The role of SA related to ROS signalling is complicated. Salicylic acid regulates both provocative and inhibitive roles upon oxidative bursting. As a critical mechanism in treating biotic and abiotic stresses, the modulation of ROS by SA can adjust multiple defensive activities, including stomatal closure, gene expression, PCD, and SAR. The initial defense and the subsequent SAR occur in different parts of the tissue with different SA levels (Vlot et al. 2009). Salicylic acid promotes ROS signalling via the ETC in early responses and growth-promoting defense priming in late response (Dong et al. 2016). Salicylic acid also has its feedback loop in the signalling pathway (Brodersen et al. 2005; Vlot et al. 2009). For example, SA triggers hydrogen peroxide signalling and causes cell death.

On the other hand, the ectopic expression of *nahG* (salicylate hydroxylase, a SA metabolizing enzyme) is found to block spontaneous lesion formation, which balances the effects of SA signalling (Vlot et al. 2009).

Rao et al. (2002) also depicted a model that increases oxidative status (increased amounts of superoxide and hydrogen peroxide molecules) and activates SA secretion, which further upregulates ET secretion and signalling and induces cell death and leaf lesion. RBOH-D suppresses the induction of oxidative bursts and cell death by SA and ET in *Arabidopsis*. RBOH-D plays a dual role in ROS signalling; it promotes hydrogen peroxide accumulation and attenuates SA and ET secretion. The *AtrobohD* mutant showed an excessive accumulation of free SA and ET and macroscopic cell death, while wild-type *Arabidopsis* induced cell death in distinct single cells (Pogány et al. 2009). These findings suggest that SA-induced oxidative bursts and cell death has a homoeostatic feedback loop to focus these processes more on pathogen-damaged tissues. Xu and Brosché (2014) found that the accumulation of SA in *Arabidopsis* attenuated the apoplastic ROS burst, while other defense mechanisms were induced. AtRBOH-D, as a factor producing apoplastic hydrogen peroxide, plays a role in suppressing SA accumulation and macroscopic cell death (Pogány et al. 2009). Collectively, this

suggests that there is a homoeostatic network between SA and ROS in plant defense. First, the SA accumulation supports ROS signalling for specific cell defense against pathogenic infection. Second, ROS signalling also restricts the extent of SA signalling, preventing unnecessary damage to the plant.

NON-EXPRESSOR of PR1 genes (NPRI) and *WRKY70* are the two pivotal regulators in SA signalling (Li et al. 2004; Vlot et al. 2009). The *NPRI* gene encodes a nuclear localization factor (a novel protein containing an ankyrin repeat domain involved in protein—protein interactions) induced by SA, which correlates with the expression of the genes in SAR such as *PR1*. *PR1* is also considered as one of the components in *R*-gene-mediated defense. *WRKY70* is another regulator lying on the node between SA and JA signalling. The overexpression of *WRKY70* supports SA signalling and suppresses JA signalling. Moreover, microarray data reveal that *WRKY70* upregulates genes in oxidative stress responses, cell death, and cell wall modification. When regulating JA, on the other hand, *WRKY70* down-regulates the JA-related signals, such as vegetative storage protein 1 (*VSP1*) and -2 (Li et al. 2004). The accumulation and signalling of SA are also dependent on the activity of *PHYTOALEXIN DEFICIENT 4 (PAD4)* and *ENHANCED DISEASE SUSCEPTIBILITY (EDS1)* (Kunkel and Brooks 2002; Vlot et al. 2009). *PAD4* and *EDS1* regulate glycerol metabolism and play roles in basal resistance and *R*-gene mediated ETI (triggered by infection of biotrophic pathogens). The *SIZ1*-mediated sumoylation of *EDS1* and *PAD4* inhibits glycerol metabolism as one way of attenuating SA accumulation (Vlot et al. 2009). The signalling activated by these factors lead to the activation of genes encoding antimicrobial proteins, including *PATHOGENESIS-RELATED PROTEINS (PR's)*. *PR1* and *PR2* are the two crucial *PR* genes regulated by SA. *PR1* includes a group of proteins found in plants with antifungal activity at the micromolar level (Stintzi et al. 1993; Borad and Sriram 2008). The expression of *PR1* proteins is positively regulated by *WRKY70* (Kunkel and Brooks 2002; Li et al. 2004). The *PR1* gene is also found to be one of the basal resistance QTLs in *Arabidopsis* against *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst* DC3000) (Ahmad et al. 2011). The *PR1* gene is also involved in PAMP-induced callose formation (Ahmad et al. 2011). *PR2* (also known as *BGL2*) encodes beta 1, 3-glucanase 2 that degrade the fungal cell wall. It cleaves the 1, 3-D-glucosidic linkage in a 1, 3-glucan, an essential part of the fungal cell wall (Stintzi et al. 1993; Borad and Sriram 2008). *PR2* is activated by SA

accumulation and is essential for plant defense against fungi (Thibaud et al. 2004). Another important SA-induced *PR* is *PR3*, a chitinase cleaving chitin polymers from the fungal cell wall (Stintzi et al. 1993; Borad and Sriram 2008).

Jasmonic acid includes a group of fatty acid-derived compounds (linolenic acid, which is oxygenated by lipoxygenase (13-LOX), forming a peroxide) playing roles in various plant development processes, including seed and pollen development, root growth, flower development, tuber formation, and senescence (Bari and Jones 2009; Kazan and Manners 2008; Wasternack and Hause 2013). The octadecanoid pathway follows the biosynthesis of JA. The pathway starts with the oxygenation of α -linolenic acid (α -LeA, 18:3) by 13-lipoxygenases (13-LOXs) in the chloroplast. Mediated by allene oxide cyclase (AOC) and allene oxide synthase (AOS), 13-HPOT is converted to *cis*-(+)-oxo-phytodienoic acid (OPDA), and OPDA is transported to the peroxisome. The final step of JA biosynthesis is β -oxidation, mediated by acyl-CoA-oxidase 1 (ACX1), converting OPC8 to (+)-7-iso-JA, which is further added to with one isoleucine residue by JA-amino acid synthetase 1 (JAR1) to become (+)-7-iso-JA-Ile (Fig. 3). Attachment of this amino acid to JA results in nuclear localization where it can induce the expression of multiple JA-related genes, such as *JAZ* and *MYC2* (Wasternack and Hause 2013).

Jasmonic acid is associated with ET and light response to inhibit root growth mediated by JA responsive factor *COI1*. Jasmonic acid also achieves this goal by regulating the synthesis and transport of auxin (Wasternack and Hause 2013). The inhibitive role of JA towards auxins also causes reduced lateral and adventitious root formation since auxins play essential roles in root growth and development (Wasternack and Hause 2013). One of the JA-responsive factors, *MYC2*, promotes root elongation by inhibiting auxin transport (Dombrecht et al. 2007). Jasmonic acid is also involved in leaf senescence in conjunction with ET, *EIN3*, *ETR1*, *EIN2*, *EIN1*, and *CTR1*, which are essential components of senescence regulation. The ET-related factors *EIN3* and *EIL1* positively regulate the JA-mediated gene *HDA6* during leaf senescence. When considering JA-responsive signalling solely, factors, such as *COII* and *AOS* are found to regulate the timing of leaf senescence, while JA regulates ET-factor *EIN2* in leaf senescence (Kim et al. 2015).

Jasmonic acid is involved in wounding, insect herbivory responses, and pathogen defense (Kunkel and Brooks 2002; Kazan and Manners 2008; Wasternack

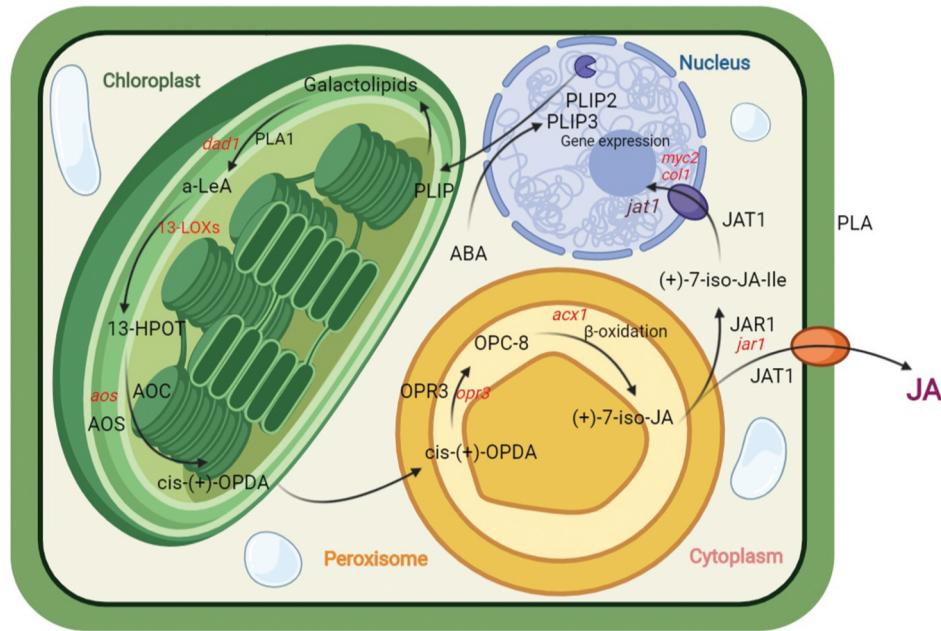


Fig. 3 (Colour online) Jasmonic acid biosynthesis pathway. The pathway starts with α -LeA in the chloroplast and moves to the peroxisome at the point of *cis*-(+)-oxo-phytodienoic acid (OPDA). The final product is (+)-7- iso-jasmonate conjugated with isoleucine, which is involved in JA-responsive signalling. A-LeA: α -linolenic acid; AOS: allen oxide synthase; AOC: allene oxide cyclase; 13-LOX: 13-lipoxygenase; 13-HPOT: (13-*S*)-hydroperoxy-octadecatrienoic; OPC-8: 3-oxo-2-(2-pentenyl)-cyclopentane-1-octanoic acid; *cis*-(+)-OPDA: *cis*-(+)-12-oxophytodienoic acid; (+)-7-iso-JA: (+)-7-iso-jasmonic acid; (+)-7-iso-JA-Ile: (+)-7-iso-jasmonoyl-L-isoleucine.

and Hause 2013). Among phytopathogens, JA is more specific for defense against necrotrophic pathogens so that JA signalling can enhance resistance to necrotrophic pathogens and herbivorous insects (Kazan and Manners 2008; Bari and Jones 2009). JA is also known to play a negative role in PCD and lesion development and reduced lesion development is seen following JA signalling (Overmyer et al. 2000; Rao et al. 2002). However, other evidence suggests that incompatible interactions may also involve the cooperation between SA and JA signalling (Spoel et al. 2007; Becker et al. 2017), making the signalling network more complicated. Spoel et al. (2007) showed that SA- and JA-responsive genes are co-expressed to achieve localized and systemic resistances, which confers a new model of plant defense.

The JA signalling in plant defense against biotic stresses starts early through MAPK cascades. There is an MSK1-MPK4-WRKY33 module when *A. thaliana* is inoculated with *P. syringae*. This pathway can induce antimicrobial camalexin (Qiu et al. 2008). Overexpression of *MPK4* in *B. napus* is also found to induce higher JA-responsive defensin *PDF1.2*, enhancing the resistance against the necrotrophic fungal

pathogens *Sclerotinia sclerotiorum* and *Botrytis cinerea* (Wang et al. 2009). The JA-related WRKY factor *WRKY33* enhances the resistance against two fungal pathogens, *B. cinerea* and *Alternaria brassicicola* in *A. thaliana*. They also upregulate the JA-responsive defense genes *PDF1.2* and *PR3* while downregulating the SA-related defense genes *PR1*, -2, and -5 (Zheng et al. 2006). The overexpression of two other JA-related WRKY genes, *WRKY28* and *WRKY 75*, enhanced resistance to *S. sclerotiorum* and delayed disease symptom in *A. thaliana*, where the ET-JA-related defense genes *PDF1.2*, *VSP2*, and *LOX2* are upregulated (Chen et al. 2013). For more downstream transcription factors (TFs) related to JA, a basic helix-loop-helix zip TF (bHLHzip), *MYC2* activates JA-related defense genes *VSP2* and *MYC2* to elicit defense against herbivores by inducing *VSP2* (Dombrecht et al. 2007; Wasternack and Hause 2013). Another important JA-related TF COI1, an F-box protein with Leu repeats, also assists *MYC2* signalling. *MYC2* protein is physically associated with and repressed by the JAZ proteins. COI1 binds both JAZs and SCFCOI, which activates the ubiquitination and 26S proteasome degradation of JAZs to release the function

of MYC2 (Kazan and Manners 2008; Wasternack and Hause 2013). This feature makes COI1 an essential factor activating JA signalling.

Ethylene (C_2H_4) is a gaseous hormone and signal molecule. ET plays diverse roles in plants, including plant defense, leaf development, senescence, flowering, and fruit ripening. This hormone is also considered an efficient molecular signal in cell-to-cell communication because it is the smallest plant hormone, which is also capable of plant–plant communication. The biosynthesis of ET starts with methionine, which is converted to S-adenosyl methionine (SAM) by ACCPage synthase (ACS). SAM is then changed to ACC (1-aminocyclopropane-1-carboxyl acid), which is in turn converted to C_2H_4 by ACC oxidase (ACO) (Dubois et al. 2018).

Exposure to ET can cause leaf yellowing, abscission, desiccation, and necrosis, which suggests its positive role in leaf senescence. Exposure of rocket salad (*Eruca sativa*) to ET results in chlorophyll reduction and a shorter shelf life (Iqbal et al. 2017). The activation of ET signalling is associated with the expression of a group of genes called *Ethylene Responsive Factors* (*ERFs*). Like SA- and JA-responsive TFs, *ERFs* interact with MAPK factors and activate ET signalling. The first cloned ethylene signalling component, CTR1, encodes a kinase with homology into mammalian Raf MAPK kinase kinase (MAPKKK) (Kieber et al. 1993). Based on genetic data, CTR1 is a negative regulator and is inactivated after ethylene sensing, which then leads to the activation of downstream components including ethylene-insensitive 2 and 3 (*EIN2*, *EIN3*), ethylene-insensitive like (*EIL*), and *ERF* transcription factors (Zhao and Guo 2011). The MAPK factor MPK6 physically interacts with an ERF (ERF104) to regulate downstream genes in basal resistance (Bethke et al. 2009). ERF6 can be phosphorylated by the MPK3/6 cascade to induce *PDF1.1* and *PDF1.2* in *Arabidopsis*, enhancing its defense against *B. cinerea* (Meng et al. 2013). The *ERFs* activate multiple processes, including defense against phytopathogens. The ectopic expression of *ERF1* enhances the resistance by upregulating defense genes such as *PR3* and *PDF1.2* in *Arabidopsis* (Adie et al. 2007). ET signalling is reported to enhance resistance to necrotrophic pathogens and to herbivorous insects (Bari and Jones 2009).

The signal transduction of SA has an antagonistic relationship with ET and JA (Kunkel and Brooks 2002; Li et al. 2004; Bari and Jones 2009). There are specific signalling pathways and factors attributed to each phytohormone. Simultaneously, these sets of pathways also modulate each other to build an extensive genetic

network to adapt to various situations during a pathogenic infection, such as the lifestyle of the pathogen, environmental factors, and the location or onset patterns of infection. Brodersen et al. (2005) found that the genes evoking accelerated PCD (*ACD11* and *SID2*) modulate SA biosynthesis. The secretion of SA and ET also enhances lesion development and tissue death following an oxidative burst in plants (Chamnongpol et al. 1998; Overmyer et al. 2000; Rao et al. 2002). The potential cooperation between SA and ET in plant defense was demonstrated by the co-expression of SA- and ET-responsive genes following the infection of *B. napus* by *Leptosphaeria maculans* during an incompatible interaction (Sašek et al. 2012).

In general, ET is associated with JA in plant defense, and ET-JA signalling shows an antagonistic relationship with SA responsive signalling (Kunkel and Brooks 2002; Berens et al. 2017; Li et al. 2019). For instance, the JA factor ORA59 and the ET factor ERF1 induce the expression of plant defensins in *PDF1.2* (Dubois et al. 2018). The cooperation between *EIN2* and JA signalling exerts defense gene expression, such as *PDF1.2*, *THI2.1*, *PR4* (*HEL*), and *CHIB* (Kunkel and Brooks 2002; Li et al. 2019). However, some studies also indicated that ET and JA also have an antagonistic relationship. For example, ERF1 induces defense genes against plant pathogens while suppressing genes involved in wound responses (Adie et al. 2007). Moreover, the overexpression of SA-responsive *WRKY70* suppresses JA-signal vegetative storage proteins (*VSPs*), and the suppression of *WRKY70* activates JA/COI1 responsive genes (Li et al. 2004), suggesting an antagonistic relationship between SA and ET-JA. COI1 is the transcription factor for JA signalling, and is also involved in the antagonistic interactions between SA and JA. The overexpression of the master SA regulator *WRKY70* can suppress the expression of *COI1* (Li et al. 2004). Although there is a general theory implicating the antagonistic relationship between SA and ET-JA signalling, SA-ET cooperation suggests that the interactions among hormones are not simple and straightforward. ET potentiates the SA-induced expression of *PR1* and the co-expression of SA- and ET-induced defense genes is also found in the *B. napus-L. maculans* interaction (Adie et al. 2007; Sašek et al. 2012). ET has also been found to modulate SA and JA signalling by regulating *NPR1*, suggesting that ET (Leon-Reyes et al. 2009) adjusts the antagonism between SA and JA. Additionally, other hormones may also have an interplay in plant defense, including SA, ET, and JA. For example, SA and ABA work together in stomata-related plant defense; as a negative factor in

plant defense, auxin signalling is repressed by SA; cytokinins are known to support the defense against biotrophs and hemi-biotrophs, and there is a synergetic relationship between CKs and SA (Bari and Jones 2009; Berens et al. 2017).

Brassinosteroids (BRs) are well known for their influence on seed germination, cell division and elongation, and flowering (Bari and Jones 2009). The function of BRs in plant defense is well known for its responsive factor BRI1-associated kinase 1 (BAK1), which is an essential protein in PAMP-triggered signalling. BAK1 is also involved in ETI (Bari and Jones 2009). BR also has an antagonistic relationship with GA, stabilizes DELLA proteins (a key negative regulator of gibberellin (GA) signalling), inhibits GA biosynthesis, and activates GA inhibitors (De Bruyne et al. 2014).

Auxins comprise a group of signalling molecules that play numerous pivotal roles in plant development, including lateral root growth and photo- and gravitropism. Auxins also controls cell division, elongation, and differentiation (Teale et al. 2006). Auxin signalling has two crucial factors: auxin responsive factors (*ARFs*) and their downstream *GH3* genes. Auxins affect basal defense positively and negatively (Bari and Jones 2009; Fu and Wang 2011). Auxins cause cell wall loosening by inducing expansions that can lead to susceptibility to some pathogens. They are also involved in stomatal opening and inhibition of SA signalling, which weakens the plant's defense against many phytopathogens (Fu and Wang 2011). Conversely, inhibition of auxin signalling can benefit plant defense. For example, the overexpression of micro-RNA miR393, which silences the gene for auxin receptors, can enhance the resistance against *Pst* DC3000 in *Arabidopsis* (Bari and Jones 2009). However, auxin signalling also contributes to plant resistance. For example, *GH3.5*, a member of the *GH3* family of early auxin-responsive genes in *Arabidopsis*, encodes a protein possessing *in vitro* adenylation activity on both indole-3-acetic acid (IAA) and SA during pathogen infection, and *GH3.8* in rice enhances host resistance against *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) (Bari and Jones 2009). Moreover, there are potential pathways for biosynthesis of IAA, indole glucosinolate (IG) and camalexin. Camalexin (3-thiazol-2'-yl-indole), which is toxic to necrotrophic fungi, and IGs, which are broad-spectrum defense compounds, are indole derivatives that share overlapping biosynthesis steps with tryptophan (Trp) dependent IAA synthesis pathways in plants.

The auxin precursor Trp is applied to produce IGs by *CYP79B2* and *CYP79B*. *ARF1* and *AFR9* inhibit IG production, and *AFR9* supports camalexin accumulation (Fu and Wang 2011).

Cytokinins (CKs) are crucial for shoot and root growth, inflorescence branching, seed development, and stress tolerance (Bari and Jones 2009). Cytokinin plays a positive role in plant defense, inducing SA-dependent genes, such as *NPRI* and *WRKY45* in rice (Akagi et al. 2014). However, CK can also cause more severe pathogenic infections because low to moderate amounts of CK promote the growth of some pathogens, such as powdery mildew on wheat leaves (Albrecht and Argueso 2017).

Gibberellins (GAs) belong to a large family of tetracyclic diterpenoids. Gibberellin was first identified in an extract from a culture of the fungus *Gibberella fujikuroi*, which causes the 'foolish seedling' Bakanae disease in rice (Navarro et al. 2008). Gibberellins regulates a wide range of plant physiological processes, including seed germination, root, leaf, stem, fruit growth, and flower and seed development (Hartweck 2008; Hauvermale et al. 2012). Gibberellins stimulate plant growth by promoting the degradation of DELLA proteins, which act as negative regulators of growth. It has been reported that DELLA proteins promote resistance to necrotrophic pathogens by activating JA-ET-dependent defense responses, but also susceptibility to biotrophic pathogens by repressing SA-dependent defense responses in *Arabidopsis* (Bari and Jones 2009).

By contrast, GA likely promotes resistance to biotrophy and susceptibility to necrotrophy as GA stimulates the degradation of DELLA proteins. This might be because DELLA proteins regulate immunity by modulating the balance between SA and JA in favour of JA. At the same time, GA antagonizes JA action and promotes SA signalling perception. Another scenario is where GA antagonizes JA and SA signalling pathways and where the rice DELLA protein SLR1 integrates and strengthens both signalling pathways (De Vleesschauwer et al. 2016). Although the role of DELLA proteins in controlling plant immune responses by modulating SA- and JA-dependent defense responses is well acknowledged (Navarro et al. 2008), its role in hosts undergoing pathogen attack remains subject to debate.

In one study, GA application enhanced *Arabidopsis* resistance to the (hemi) biotrophic bacterial pathogen *Pst* DC3000 and compromised resistance to *A. brassicola*, a necrotrophic fungus (Navarro et al. 2008). Similarly, in rice, the *gid1* mutant (defective in the GA receptor) had higher GA levels. It also showed enhanced resistance to the blast fungus *Magnaporthe grisea* compared to wild-type plants, suggesting that GA signalling components play roles in defense signalling in rice (Tanaka et al. 2006). In contrast, GA treatment enhanced susceptibility to (hemi) biotrophic pathogens *M. oryzae* and

Xanthomonas oryzae pv. *oryza* (*Xoo*) in rice (De Vleesschauwer et al. 2016). These findings suggest that the role of GA in plant immunity depends on the host and the pathogen (De Bruyne et al. 2014).

Abscisic acid (ABA) is a plant hormone involved in various development and stress responses, including seed germination and embryo maturation (Bari and Jones 2009). ABA plays an essential role in stress tolerance to heavy metals, heat, drought, radiation, and salinity (Vishwakarma et al. 2017). Generally, ABA plays opposing roles in plant defense. Several mutants conferring ABA deficiency gain more resistance against various diseases (Bari and Jones 2009). For example, *aba2-1* from *Arabidopsis* showed stronger resistance against *Fusarium oxysporum* (Anderson et al. 2004). However, ABA could play positive roles in plant defense, such as defense against tobacco mosaic virus (TMV) in tobacco (plants); TMV infection increases the amount of ABA production of the host plant (Bari and Jones 2009). Abscisic acid and SA induce resistance against the fungus in the *B. napus* and *S. sclerotiorum* pathosystem (Nováková et al. 2014). Transcripts of the two ABA factors NCED3 and RD26 are induced during fungal infection. Previous studies suggest that the defensive roles from ABA come from its ability in cell wall modifications (such as callose deposition), and its involvement in ROS signalling could contribute to plant defense (Bari and Jones 2009).

Interaction among the various signalling compounds

Plants have evolved sophisticated and efficient defense mechanisms to cope with biotic stresses and to mount effective defense mechanisms. Although these defense mechanisms are separately well understood, the interaction between these defense components is poorly evaluated. Here, we outline the mechanisms underlying plant immunity and the emerging role for immune regulators in biotic stress tolerance. The plant immune system is regarded as consisting of two levels of defense, PTI and ETI, defined by the recognition mechanisms detecting invading pathogens. However, this distinction appears less pronounced than originally believed. Indeed, both PTI and ETI are associated with the activation of defense in the infected tissue, including the generation of ROS, increases in intracellular Ca^{2+} concentrations, the activation of MAPKs, the increased expression of various defense-associated genes, the synthesis of antimicrobial compounds, and the accumulation of SA. This recognition also results in the downregulation of growth, mediated by phytohormones. The components and

events occurring following the detection of the pathogen by the host are depicted in Fig. 4.

ROS is involved in intra-organelar communication to trigger the immune response and are induced in both PTI and ETI. ROS play a central role in PTI responses towards attacking pathogens by a homologous NADPH oxidase. ROS accumulation is detected via different redox-based mechanisms. The perception of PAMPs and MAMPs induces weak ROS bursts and leads to PTI-dependent basal defense responses. In response, pathogens exude effector proteins to suppress the ROS burst and PTI, resulting in effector-triggered susceptibility (ETS). Effectors interact with intracellular nucleotide-binding domain leucine-rich repeat containing receptor (NLR) proteins, leading to a strong ROS burst and HR cell death response. PTI induces a fast and transient ROS burst, while ETI is associated with a biphasic ROS burst with the second peak usually much stronger and more sustained than during PTI (Chandra et al. 1996).

In addition, the accumulation of ROS activates MAPK signalling cascades, which trigger various downstream pathways, including redox-modulated SA signalling, with NPR1 being the master redox sensor for SA-mediated gene expression in the defense response (Fig. 4). PTI is dependent on the activation of MAPK cascades, while a ROS burst is independent of these factors. The rapid influx of Ca^{2+} into the cytosol, immediately after the activation of PRR signalling and PAMP recognition is known to be a major hallmark of early PTI responses. The subsequent change in cytosolic Ca^{2+} levels is then thought to play a role in triggering downstream responses. Changes in cytosolic Ca^{2+} are known to be ubiquitous events in signalling networks and are believed to be linked to many cellular functions and immune responses, including ROS production, stomatal closure, the expression of immunity genes and the synthesis of Ca-dependent protein kinases (Thor et al. 2020) (Fig. 4). Nonetheless, how Ca^{2+} influx is regulated during ETI remains unclear.

Upon pathogen detection, ETI is also activated following recognition of effector proteins or their actions by resistance (R) protein receptors and results in HR, a specialized form of PCD, which usually leads to or is linked to resistance associated with NBS-LRR domain R-proteins. The activation of PTI and ETI enhances plant disease resistance and restricts pathogen growth. The detection of effectors or their actions reflects an evolutionary arm race between the host and pathogen to recognize pathogens and initiation of the defense mechanisms and to defeat host defenses and establish

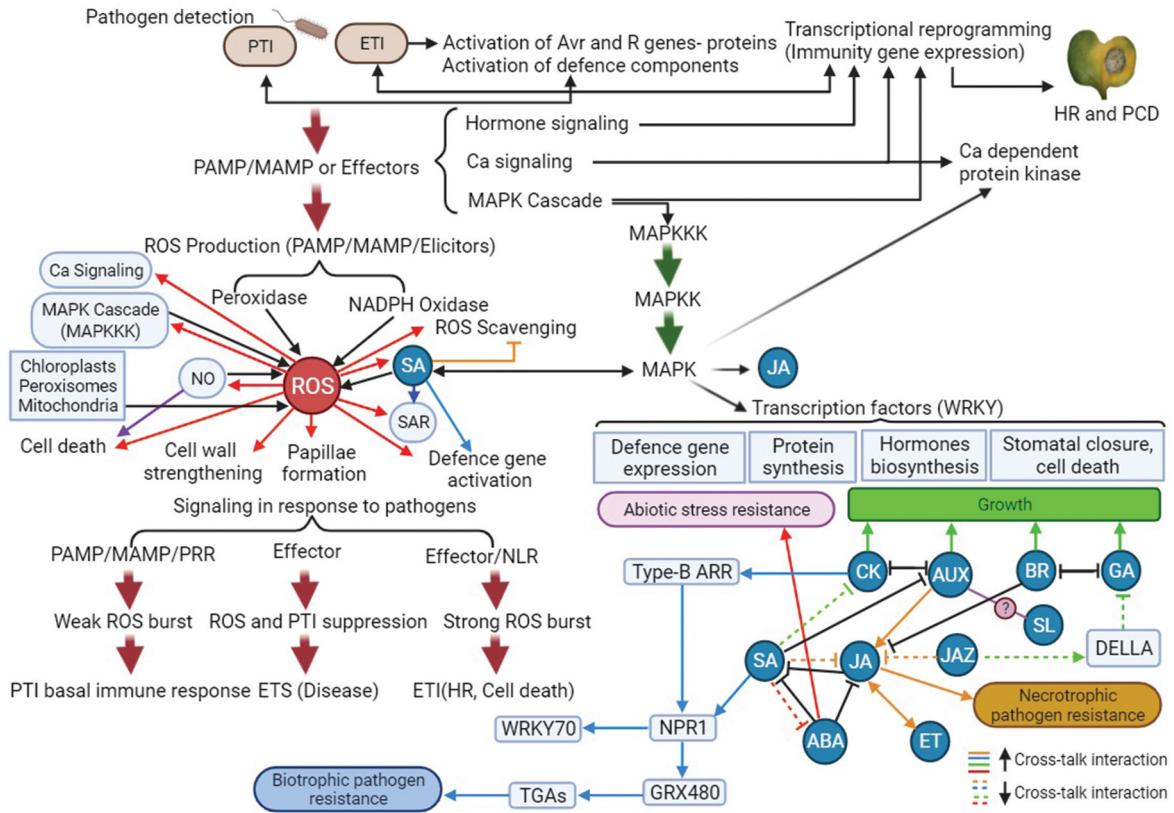


Fig. 4 (Colour online) Proposed model depicting the components and events occurring following a host's detection of a pathogen. The network represents relationships between PTI, ETI, ROS, MAPK cascade, and phytohormones.

compatibility with the pathogen, respectively. This recognition triggers transcriptional reprogramming in plant and pathogen cells.

Rapid activation of the MAPK cascade is a well-known characteristic of PRR signalling. MAPK cascades involve both PTI and ETI. The activation of NLR signalling triggers a slower but longer-lasting MAPK activation (Su et al. 2018). MAPK cascades also involve ROS generation, HR, and signalling of plant defense hormones (Fig. 4). MAPKs are involved in SA and JA signalling pathways as both positive and negative regulators. MAPKs regulate JA biosynthesis and the expression of JA-dependent genes (Fig. 4). However, downstream MAPK targets are involved in SA- and JA-dependent processes and the crosstalk between JA and MAPK signalling is not clearly understood.

SA, JA, and ET play roles in plant defense mechanisms. SA triggers the expression of antimicrobial proteins *PRI* and *PR2* and the activation of SAR. The non-expressor of PR genes 1 (NPR1) is the master regulator in the SA pathway, and is required for the full activation of both PTI and ETI,

and especially cell death as triggered by ETI (Zhang et al. 2018). SA is generally involved in the activation of defense responses against biotrophic and hemibiotrophic pathogens, while JA and ET are usually associated with defense against necrotrophic pathogens. In most cases, JA and SA defense signalling pathways are mutually antagonistic. Furthermore, JA and ET are associated by activating their responsive signalling factors and mainly play antagonistic roles against SA. Significant JA accumulation occurs when ETI is evoked. According to Rao et al. (2002), SA and ET have cooperative roles during oxidative bursts, causing cell death signals, and JA usually suppresses the related signals.

Prospects

Most of the findings of the plant-pathogen interactions described above are well documented in the literature. However, there are still some conflicts among the previous results regarding the various roles of components of the defense responses. Furthermore, there are challenges in understanding the unknown aspects of these defense responses, such as their dynamic and spatial regulation

and their interaction with other signalling pathways and cellular functions. Therefore, more effort should be placed on understanding the interaction between the different defense mechanisms. More signalling pathways and factors need to be explored to create a more comprehensive map of plant defense mechanisms. To this end, there is a need to develop molecular studies on how defense responses and immunity functions operate in plants. Further investigations into the mechanisms underlying signal collaboration between PRR-initiated and NLR-initiated immunity will enable a more complete understanding of the plant immune system. It is clear that many of the questions revolving around plant defense mechanisms remain to be answered.

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