Hormonal Modulation of Plant Immunity

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Abstract

Plant hormones have pivotal roles in the regulation of plant growth, development, and reproduction. Additionally, they emerged as cellular signal molecules with key functions in the regulation of immune responses to microbial pathogens, insect herbivores, and beneficial microbes. Their signaling pathways are interconnected in a complex network, which provides plants with an enormous regulatory potential to rapidly adapt to their biotic environment and to utilize their limited resources for growth and survival in a cost-efficient manner. Plants activate their immune system to counteract attack by pathogens or herbivorous insects. Intriguingly, successful plant enemies evolved ingenious mechanisms to rewire the plant's hormone signaling circuitry to suppress or evade host immunity. Evidence is emerging that beneficial root-inhabiting microbes also hijack the hormone-regulated immune signaling network to establish a prolonged mutualistic association, highlighting the central role of plant hormones in the regulation of plant growth and survival.

Contents

INTRODUCTION

Hosting the Good, the Bad, and the Ugly

Plants play a vital role in the sustainability of life on Earth, as they fix the solar energy that drives nearly all living organisms. Plants are exploited by a plethora of parasites, including viruses, bacteria, fungi, oomycetes, nematodes, insects, and even other plants. To cope with their enemies, plants possess a highly sophisticated defense system that, similar to the animal innate immune system, recognizes nonself molecules or signals from their own injured cells and responds by activating an effective immune response against the invader encountered (Howe & Jander 2008, Jones & Dangl 2006). Successful pathogens and insects can actively interfere with the plant immune system to establish a prolonged interaction with the plant. Beneficial associations between plants and microbes are frequent in nature as well. They often reside in the roots or the rhizosphere and significantly improve plant growth or help the plant to overcome biotic or abiotic stress. Because beneficial microbes are initially recognized as potential invaders, active interference with the plant immune system is fundamental for the establishment of an intimate mutualistic relationship with the plant (Zamioudis & Pieterse 2012).

Rhizosphere: narrow zone of soil immediately surrounding the root system that is influenced by root secretions and associated microbes

Innate Immunity to Plant Pathogens

According to their lifestyles, plant pathogens are generally divided into necrotrophs and biotrophs (Glazebrook 2005). Necrotrophic pathogens first destroy host cells, often through the production of phytotoxins and cell-wall-degrading enzymes, and then feed on the contents. Biotrophic pathogens derive nutrients from living host tissues, commonly through specialized feeding structures. Some plant pathogens display both lifestyles, depending on the stage of their life cycle, and are called hemi-biotrophs.

In recent years, exciting new discoveries have greatly advanced our understanding of how the coevolutionary arms race between plants and pathogens has shaped the plant immune system into a refined defensive shield capable of warding off the majority of harmful organisms (Boller & Felix 2009, Thomma et al. 2011, Zipfel 2009). Currently, the evolutionary development of the plant immune system is represented as a zig-zag model (Jones & Dangl 2006). Pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs), such as flagellin, chitin, glycoproteins, and lipopolysaccharides, or endogenous plant-derived signals that arise from damage caused by pathogen infection, called damage-associated molecular patterns (DAMPs), are recognized by pattern-recognition receptors. This results in the activation of PAMP-triggered immunity (PTI). Successful pathogens acquired so-called effector molecules to breach this first line of defense, either by preventing detection of their PAMPs by the host (Bardoel et al. 2011, De Jonge et al. 2010) or by suppressing PTI signaling. In an ongoing arms race, plants acquired a second line of defense in which resistance (R) proteins mediate recognition of these attacker-specific effectors, resulting in effector-triggered immunity (ETI).

Plant Defenses Against Insect Herbivores

Herbivorous insect species can be roughly divided into two categories, tissue-chewing and piercing-sucking, depending on their feeding strategy (Schoonhoven et al. 2005). To fend off insect herbivores, plants use two distinct strategies: induced direct defense, which targets the attacker, and induced indirect defense, which is aimed at recruiting the natural enemies of the attacker (Dicke & Baldwin 2010, Howe & Jander 2008, Wu & Baldwin 2010). Direct defense includes the production of secondary chemicals or enzymes that act as toxins or feeding deterrents, whereas indirect defense involves the production of a blend of volatiles that attracts predatory or parasitic enemies of the herbivores. Relatively little is known about the molecular recognition events that trigger plant immunity to insect herbivores. In response to tissue damage, endogenous plant signals (DAMPs) are produced that play an important role in the perception of herbivory. Moreover, plants can recognize specific insects via the perception of herbivore-associated molecular patterns (HAMPs) from insect secretions or plant compounds that are modified by the insect while feeding (Hogenhout & Bos 2011, Howe & Jander 2008, Wu & Baldwin 2010).

Host Immune Responses to Beneficial Microbes

In nature, plant roots abundantly form beneficial associations with soil-borne microbes that are important for plant growth and survival. Among the best-studied mutualistic microbes are mycorrhizal fungi, *Rhizobium* bacteria, and plant-growth-promoting rhizobacteria (PGPR) and fungi (PGPF). Mycorrhizal fungi can form a symbiosis with most terrestrial plant species (Harrison 2005). They acquire mineral nutrients from niches in the soil that are unreachable for plant roots and deliver these to the plants. Symbiotic *Rhizobium* bacteria induce the formation of symbiotic structures (nodules) in the roots of leguminous plants, where they fix atmospheric nitrogen for the plant (Spaink 2000). Beneficial PGPR and PGPF of diverse genera also live in close associations with plant roots. They can stimulate plant growth by producing phytostimulators or by suppressing

PAMPs: pathogen-associated molecular patterns

MAMPs: microbe-associated molecular patterns

ETI: effector-triggered immunity

PTI: PAMP-triggered immunity

Effector: molecule of microbe or insect that binds to a host protein, commonly to suppress host immunity

PGPR: plant-growth-promoting rhizobacteria

plant diseases and pests in below- and aboveground plant parts (Lugtenberg & Kamilova 2009, Pineda et al. 2010, Shoresh et al. 2010, Van Wees et al. 2008). The establishment of beneficial plant-microbe associations requires mutual recognition and a high degree of coordination of plant immune responses (Harrison 2005, Zamioudis & Pieterse 2012).

Salicylic acid (SA): plant hormone essential for the immune response against biotrophic pathogens

Jasmonic acid (JA): plant hormone essential for the immune response against necrotrophic pathogens and herbivorous insects

ET: ethylene

ABA: abscisic acid

GAs: gibberellins

CKs: cytokinins

Hormone cross talk: interactions of hormone signal transduction pathways, via shared signaling components or downstream of signal transduction at the gene expression level

Modulation of Plant Immunity: A Matter of Hormones

Downstream of PTI or ETI activation, or other early molecular recognition events of microbes and insects, diverse plant hormones act as central players in triggering the plant immune signaling network (Bari & Jones 2009, Howe & Jander 2008, Katagiri & Tsuda 2010, Pieterse et al. 2009). Analogous to animal hormones, plant hormones were originally recognized as regulators of growth and development (Santner & Estelle 2009). Salicylic acid (SA) and jasmonic acid (JA) with its derivatives (collectively called jasmonates) are recognized as major defense hormones (Browse 2009, Vlot et al. 2009). However, the hormones ethylene (ET) (Van Loon et al. 2006a), abscisic acid (ABA) (Ton et al. 2009), gibberellins (GAs) (Navarro et al. 2008), auxins (Kazan & Manners 2009), cytokinins (CKs) (Walters & McRoberts 2006), brassinosteroids (Nakashita et al. 2003), and nitric oxide (NO) (Moreau et al. 2010) function as modulators of the plant immune signaling network as well. Changes in hormone concentration or sensitivity triggered during parasitic interactions mediate a whole range of adaptive plant responses, often at the cost of growth and development (Walters & Heil 2007). The composition and timing of the hormonal blend produced can determine whether plant tissues become more susceptible or resistant to the invading organism (Verhage et al. 2010).

Antagonistic and synergistic interactions between diverse hormone signal transduction pathways add yet another layer of regulation. This so-called hormone cross talk (Jaillais & Chory 2010, Mundy et al. 2006) provides the plant with a powerful capacity to finely regulate its immune response to the invader encountered and to utilize its resources in a cost-efficient manner. Hormone cross talk is a rapidly developing theme in plant immune signaling research (Pieterse et al. 2009, Robert-Seilaniantz et al. 2011a, Spoel & Dong 2008). Here, we review recent advances in our understanding of hormone cross talk in immune signaling network interactions between plants and pathogens, pests, and beneficial microbes. Most of what we discuss is based on work with the model *Arabidopsis thaliana*, but where appropriate, we include examples from other species as well. First, we provide an overview of current knowledge on the signal transduction pathways of the two major defense hormones, SA and JA, followed by progress in our understanding of the molecular players in SA-JA cross talk. Second, we review how other plant hormones modulate the SA-JA backbone of the plant immune signaling network. Third, we discuss the role of hormone cross talk in the suppression of plant defenses by microbial pathogens and insect herbivores. Finally, we highlight how beneficial soil-borne microbes hijack plant hormone signaling pathways to suppress host defenses to establish a beneficial association with the host.

THE SALICYLIC ACID–JASMONIC ACID BACKBONE OF THE PLANT IMMUNE SIGNALING NETWORK

Salicylic Acid Pathway

The plant hormone SA plays a major role in disease resistance signaling (Vlot et al. 2009). The SA response pathway is typically (but not exclusively) effective against microbial biotrophic pathogens (Glazebrook 2005). SA is a phenolic compound that can be synthesized from the primary metabolite chorismate via two distinct enzymatic pathways, one involving PHENYLALANINE AMMONIA LYASE (PAL) and the other ISOCHORISMATE SYNTHASE (ICS/SID2) (Garcion & Métraux 2006) (**Figure 1*a***). SA biosynthesis is triggered during PTI and ETI upon recognition

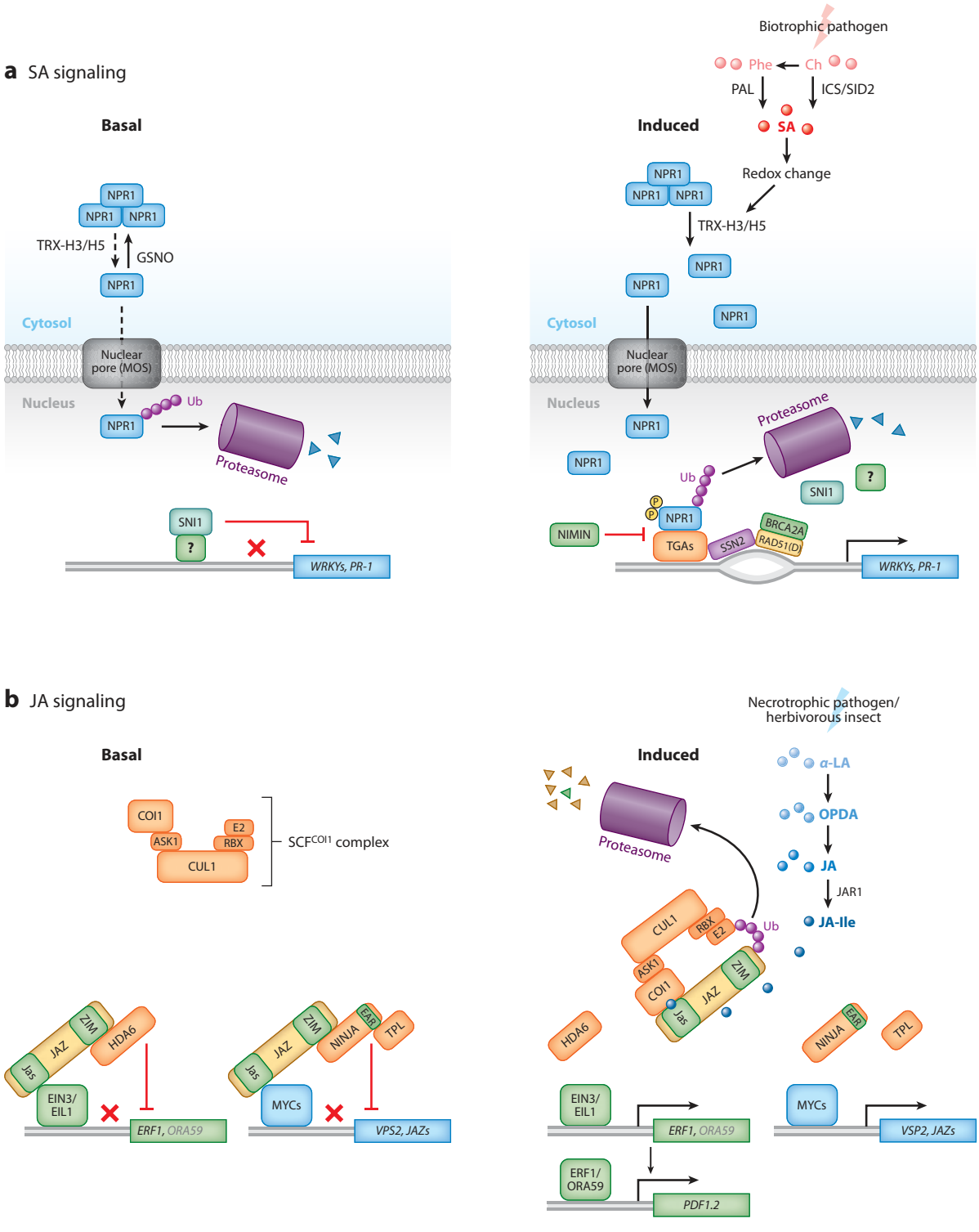
of PAMPs or effectors of pathogens (Mishina & Zeier 2007). Transient microbe-induced effects on Ca^{2+} levels are important early signaling events upstream of SA biosynthesis (Du et al. 2009). Subsequently, the lipase-like proteins ENHANCED DISEASE SUSCEPTIBILITY1 (EDS1) and PHYTOALEXIN DEFICIENT4 (PAD4) act in the onset of SA biosynthesis during PTI. When ETI is initiated by TIR-NBS-LRR-type R proteins, SA biosynthesis is mediated by EDS1 and PAD4 (Wiermer et al. 2005), but when CC-NBS-LRR-type R proteins trigger ETI, NON-RACE-SPECIFIC DISEASE RESISTANCE1 (NDR1) functions in the onset of SA production (Bernoux et al. 2011).

Signaling downstream of SA is largely controlled by the regulatory protein NONEXPRESSOR OF *PR* GENES1 (NPR1), which upon activation by SA acts as a transcriptional coactivator of a large set of defense-related genes (Dong 2004, Moore et al. 2011) (**Figure 1*a***). These *PR* (*PATHOGENESIS-RELATED*) genes are a diverse group, but several encode proteins with antimicrobial activity (Van Loon et al. 2006b). Among the best-characterized *PR* genes is *PR-1*, which is often used as a robust marker for SA-responsive gene expression. In addition, many WRKY transcription factor genes are SA inducible. WRKY transcription factors activate or repress SA responses, which highlights their role in both SA-mediated resistance and feedback control of the SA signaling pathway (Rushton et al. 2010, Wang et al. 2006).

Nuclear translocation of NPR1 is an important regulatory step in SA signaling. In resting cells, the majority of NPR1 is sequestered in the cytoplasm as an oligomer through intermolecular disulfide bonds that are facilitated by S-nitrosylation of NPR1 via *S*-nitrosoglutathione (Tada et al. 2008), a process in which NO is covalently attached to a reactive cysteine thiol to form an *S*-nitrosothiol (Lindermayr et al. 2005). The relatively small amount of NPR1 monomers that constitutively translocate to the nucleus are ubiquitinylated and targeted to the proteasome to prevent untimely activation of NPR1 target genes (Spoel et al. 2009). SA-induced changes in the cellular redox state accommodate monomerization of NPR1 by the activity of the thioredoxins TRX-H3 and TRX-H5 (Tada et al. 2008). In SA-induced cells, large amounts of monomeric NPR1 translocate to the nucleus via nuclear pore proteins, such as MODIFIER OF *snc1* (MOS) 3, 6, and 7 (Cheng et al. 2009, Monaghan et al. 2010). In the nucleus, NPR1 monomers interact with members of the TGA subclass of the basic leucine zipper (bZIP) family of transcription factors that bind to the promoters of SA-responsive genes, such as *PR-1*, resulting in their activation (Després et al. 2000, Fan & Dong 2002). During this process, NPR1 becomes phosphorylated and subsequently ubiquitinylated by an E3 ubiquitin ligase with high affinity for phosphorylated NPR1, after which it is targeted for degradation by the proteasome. This clearance of phosphorylated NPR1 from the target gene promoter is required for full induction of the SA-responsive target genes, probably because it allows new NPR1 monomers to reinitiate the transcription cycle (Spoel et al. 2009).

Several negative regulators, such as the NPR1-interacting proteins NIM1-INTERACTING1 (NIMIN1), 2, and 3, and SUPPRESSOR OF *npr1* INDUCIBLE1 (SNI1), keep SA- and NPR1-regulated genes in check (Li et al. 1999, Pape et al. 2010, Weigel et al. 2005), possibly to prevent untimely activation. NIMINs inhibit promoter activity of defense genes likely by targeting TGA transcription factors (Weigel et al. 2005), whereas SNI1 exerts its negative effect through association with defense gene promoters, possibly via interaction with an unknown DNA-binding protein (Song et al. 2011). Upon activation of SA signaling, SNI1 is removed from the promoter, likely through its physical interaction with DNA damage repair proteins SUPPRESSOR OF *sni1* 2 (SSN2) and RAS ASSOCIATED WITH DIABETES51D (RAD51D). A complex of RAD51 (a paralog of RAD51D) and BRCA2A (BREAST CANCER2A) is also recruited to the *PR-1* promoter, which together with

NONEXPRESSOR OF *PR* GENES1 (NPR1): redox-sensitive transcriptional regulator of SA responses and mediator of SA-JA cross talk



SSN2 and RAD51D positively regulates plant immune gene expression, likely through a direct effect on DNA accessibility (Durrant et al. 2007, Song et al. 2011, Wang et al. 2010).

Once the SA pathway is activated at the site of infection, a similar response is often triggered in distal plant parts to protect undamaged tissues against subsequent pathogen invasion. This long-lasting and broad-spectrum induced resistance is referred to as systemic acquired resistance (SAR) (Vlot et al. 2009).

Jasmonic Acid Pathway

JA and its structurally related metabolites are lipid-derived compounds that are synthesized rapidly via the oxylipin biosynthesis pathway upon pathogen or insect attack (Gfeller et al. 2010). JA biosynthesis starts with the release of α-linolenic acid (α-LA) from membrane lipids (**Figure 1*b***). The subsequent enzymatic pathway reactions and their subcellular localization are well documented (Browse 2009, Wasternack 2007). Upon synthesis, JA can be readily metabolized to methyl jasmonate (MeJA) through the activity of JA CARBOXYL METHYLTRANSFERASE (JMT) (Seo et al. 2001) or conjugated to amino acids such as isoleucine via the JA conjugate synthase JAR1 (Staswick & Tiryaki 2004), which results in a biologically highly active enantiomer of jasmonoyl-isoleucine (JA-Ile) (Fonseca et al. 2009).

The F-box protein CORONATINE INSENSITIVE1 (COI1) is a key regulator of the JA signaling pathway. Together with JASMONATE ZIM (JAZ) domain transcriptional repressor proteins, COI1 functions as a JA-Ile receptor in the E3 ubiquitin-ligase SKP1-Cullin-F-box complex SCF^{COI1} (Sheard et al. 2010, Yang et al. 2009). Binding of JA-Ile to COI1 leads to ubiquitinylation and subsequent degradation of JAZ repressor proteins via the proteasome (Pauwels & Goossens 2011). In resting cells, JAZ proteins act as transcriptional repressors of JA signaling by binding to positive transcriptional regulators, such as the basic helix-loop-helix leucine zipper proteins MYC2, 3, and 4 (Fernandez-Calvo et al. 2011, Niu et al. 2011). The adaptor protein NOVEL INTERACTOR OF JAZ (NINJA) interacts with the ZIM domain of most JAZ proteins (Pauwels et al. 2010). Through its ERF-ASSOCIATED AMPHIPHILIC REPRESSION (EAR) motif (Kazan 2006), NINJA recruits the corepressor TOPLESS (TPL), thereby preventing untimely activation of the JA pathway (Pauwels et al. 2010). In JA-stimulated cells, the physical interaction between JAZ proteins and transcriptional activators is broken, which results in derepression of the JA signaling pathway and activation of a large number of JA-responsive genes (Memelink 2009).

In *Arabidopsis*, two major branches of the JA signaling pathway are recognized: the MYC branch and the ERF branch. The MYC branch is controlled by MYC-type transcription factors as described above and includes the JA-responsive marker gene *VEGETATIVE STORAGE PROTEIN2* (*VSP2*). The ERF branch is regulated by members of the APETALA2/ETHYLENE RESPONSE FACTOR (AP2/ERF) family of transcription factors, such as ERF1 and OCTADECANOID-RESPONSIVE ARABIDOPSIS59 (ORA59) (Dombrecht et al. 2007, Lorenzo et al. 2003, McGrath et al. 2005, Pré et al. 2008), and includes the JA-responsive marker gene *PLANT DEFENSIN1.2* (*PDF1.2*). Activation of the ERF branch of the JA pathway

Systemic acquired resistance (SAR): SA-dependent enhanced defensive capacity of the entire plant, acquired after a primary, local pathogen infection

JASMONATE ZIM (JAZ): transcriptional repressor protein with a central role in JA signaling and target of different hormone pathways

Figure 1

Schematic overview of the (*a*) salicylic acid (SA) and (*b*) jasmonic acid (JA) signaling pathways, as summarized in the text. (*a*, *b*, *left panels*) Basal SA and JA signaling in uninduced cells is depicted. (*a*, *b*, *right panels)* SA and JA signaling in induced cells is shown. Solid arrows indicate established activities or accumulation of compounds; dashed arrows represent relatively low activities; and red inhibition lines and crosses indicate repression of transcription. *ORA59* (*gray text*) is a hypothesized target of EIN3/EIL1. Abbreviations: Ch, chorismate; P, phosphorylated protein; Phe, phenylalanine; Ub, ubiquitinylated protein.

requires both JA and ET signaling, but the molecular basis of the role of COI1/JAZ in the regulation of this branch, in contrast to the MYC branch, is not well understood. Recently, Zhu et al. (2011) showed that the ET-stabilized transcription factors ETHYLENE INSENSITIVE3 (EIN3) and EIN3-LIKE1 (EIL1) interact directly with JAZ proteins and recruit HISTONE DEACETYLASE6 (HDA6) as a corepressor to inhibit the transcriptional activity of EIN3/EIL1 in uninduced cells. In JA- and ET-stimulated cells, COI1-dependent degradation of JAZ proteins enhances the transcriptional activity of EIN3/EIL1. This results in the activation of *ERF1* (and possibly also *ORA59*) and its downstream target genes, such as the ERF branch marker gene *PDF1.2*. In general, the ERF branch of the JA pathway is associated with enhanced resistance to necrotrophic pathogens (Berrocal-Lobo et al. 2002, Lorenzo et al. 2003), whereas the MYC branch of the JA pathway is associated with the wound response and defense against insect herbivores (Kazan & Manners 2012, Lorenzo et al. 2004), although MYC2 also plays a role in priming for enhanced pathogen defense (Pozo et al. 2008, Van der Ent et al. 2009a). Once the JA pathway is activated, e.g., at the site of wounding or herbivory, a similar JA-dependent response can be triggered in distal, undamaged plant parts. This wound-induced resistance involves chemical defenses such as the production of repellent, antinutritive, or toxic compounds, which help the plant to protect itself against future invasion by insect herbivores (Howe & Jander 2008).

ASPIRIN-PROSTAGLANDIN ANTAGONISM

The antagonism between the SA and JA signaling pathways in plants shows a striking resemblance to the effect of the anti-inflammatory drug aspirin, the acetylated form of plant aspirin SA, on prostaglandins in animal cells. Prostaglandins are hormonal pain messengers structurally related to JAs and play a role in inflammation at sites of infection or tissue injury (Funk 2001). Both JAs and prostaglandins are synthesized via the oxylipin biosynthesis pathway, in which the enzymatic reactions leading to JA and prostaglandin formation are similar (Pan et al. 1998). In animal cells, aspirin antagonizes prostaglandin formation by targeting enzyme activity and gene expression of CYCLOOXYGENASE (COX) (Funk 2001), the counterpart of the key JA biosynthesis enzyme ALLENE OXIDE SYNTHASE (AOS) in plants. However, no inhibitory effect of SA on AOS enzyme activity has been observed in plants (Laudert & Weiler 1998). Moreover, the antagonistic effect of SA on pathogen-induced JA signaling acts downstream of AOS (Leon-Reyes et al. 2010b), indicating that the molecular mechanism underlying SA-JA cross talk differs from the phenomenologically similar interaction between aspirin and prostaglandins.

Cross Talk Between the Salicylic Acid and Jasmonic Acid Pathways

Transcriptome analyses of wild-type and mutant *Arabidopsis* plants challenged by different attackers revealed complex regulatory relationships between hormone signaling sectors of the plant immune signaling network (De Vos et al. 2005, Glazebrook et al. 2003, Sato et al. 2010, Tsuda et al. 2009, Van Verk et al. 2011). This hormonal cross talk is thought to equip the plant with a powerful regulatory capacity to finely tune its immune response to the attacker encountered (Reymond & Farmer 1998). The first indications for SA-JA cross talk came from studies in tomato, which revealed that SA and its acetylated form aspirin are potent suppressors of the JA-dependent wound response (Doherty et al. 1988, Peña-Cortés et al. 1993). Since its discovery in tomato, antagonism between the SA and JA pathways was demonstrated in many plant species, including *Arabidopsis* (Spoel et al. 2003, Van Wees et al. 1999). The phenomenon of SA-JA cross talk shows striking similarities with the inhibitory effect of aspirin on prostaglandins in animal cells that are produced via the same biosynthetic pathway as JAs. However, the molecular bases of these negative signal interactions seem to differ (see sidebar, Aspirin-Prostaglandin Antagonism).

Interplay between SA and JA optimizes the immune response against single attackers, such as virulent *Pseudomonas syringae*, that initially stimulate both the SA and JA pathways (Spoel

et al. 2003). However, in nature, plants are simultaneously or sequentially attacked by multiple enemies with often different strategies and lifestyles. Hence, SA-JA cross talk can also be a powerful mechanism to prioritize one pathway over the other, depending on the sequence and type of attackers encountered. Indeed, trade-offs between SA-dependent resistance to biotrophs and JA-dependent defense against insect herbivores or necrotrophs have been reported repeatedly (Bostock 2005, Kunkel & Brooks 2002, Verhage et al. 2010). For example, induction of the SA pathway by avirulent *P. syringae* suppressed JA signaling and rendered infected *Arabidopsis* leaves more susceptible to the necrotrophic fungus *Alternaria brassicicola* (Spoel et al. 2007). Similarly, prior inoculation with the SA-inducing biotrophic pathogen *Hyaloperonospora arabidopsidis* suppressed JA-mediated defenses that were activated upon feeding by caterpillars of imported cabbageworm, *Pieris rapae* (Koornneef et al. 2008a).

In nature, plants often deal with simultaneous or subsequent invasion by multiple pathogens and insects. In a field study with *Brassica oleracea* plants, early season herbivory was shown to significantly affect plant defense responses to secondary herbivores and the development of their populations (Poelman et al. 2008a). Gene expression analyses implicated a dominant role for plant hormones in the regulation of this process. In lima bean, SA-inducing, phloem-feeding sweetpotato whitefly (*Bemisia tabaci*) negatively affected JA biosynthesis and JA-dependent indirect plant defenses that were triggered by the twospotted spider mite (*Tetranychus urticae*) on the same plant (Zhang et al. 2009). In the absence of whitefly, spider mite–infested plants produce a volatile blend that attracts predatory mites that will kill the spider mites. However, in whitefly-infested plants this induced indirect defense was suppressed, which resulted in reduced attractiveness to predatory mites. This antagonistic effect could be mimicked by SA, which indicates that the effect of SA-JA cross talk extends to plant immune responses against organisms from different trophic levels.

SA-JA cross talk has also been implicated in adaptive responses to abiotic stresses, such as thermotolerance (Clarke et al. 2009) and shade avoidance (Ballaré 2011, Cerrudo et al. 2012, Ritsema et al. 2010). Hence, in addition to its regulatory role in prioritizing one induced pathway over the other upon perceiving specific stresses, SA-JA cross talk may help integrate the ecological context and stress-related life history to prepare a plant for future environmental conditions.

COR: coronatine

MOLECULAR BASIS OF SALICYLIC ACID–JASMONIC ACID CROSS TALK

In *Arabidopsis*, the JA-responsive genes *PDF1.2* (marker of the ERF branch of the JA pathway) and *VSP2* (marker of the MYC branch of the JA pathway) are highly sensitive to suppression by SA. This suppression by SA occurs irrespective of whether these JA responsive genes are activated by necrotrophic pathogens, by insect herbivores, or by JA, JA-Ile, or its precursors α-LA and 12-oxo-phytodienoic acid (OPDA) (Koornneef et al. 2008a, Leon-Reyes et al. 2010b). Antagonism between the SA and JA response pathways was observed in a large number of *Arabidopsis* accessions collected from different geographic origins (Koornneef et al. 2008a) and was even reported to remain active in a next generation (Luna et al. 2012), highlighting the potential significance of SA-JA cross talk in nature.

Reciprocally, JA signaling can suppress the SA pathway as well. The antagonistic effect of JA signaling on SA-dependent defenses has been studied predominantly in the context of the interaction between plants and the pathogen *P. syringae* (Brooks et al. 2005, Nomura et al. 2005). *P. syringae* produces the virulence factor coronatine (COR), which is a phytotoxin that functions as a mimic of JA-Ile and suppresses SA-dependent defenses to promote susceptibility of the host (see also Rewiring of the Hormone Signaling Network by Plant Enemies, below). However, relatively little is known about the molecular

details involved in the antagonistic effect of JA signaling on the SA pathway.

Although many reports describe an antagonistic interaction between the SA and JA pathways with corresponding trade-offs in disease and pest resistance, neutral and synergistic interactions have been described as well (Mur et al. 2006, Schenk et al. 2000, Van Wees et al. 2000). For example, treatment of *Arabidopsis* with low concentrations of JA and SA resulted in a synergistic effect on the JA- and SA-responsive genes *PDF1.2* and *PR-1*, respectively. At higher concentrations the effects were antagonistic, demonstrating that the outcome of the SA-JA interaction is dependent upon the relative concentration of each hormone (Mur et al. 2006). Timing and sequence of initiation of SA and JA signaling are also important (Koornneef et al. 2008a, Leon-Reyes et al. 2010a), indicating that the kinetics of hormone biosynthesis and signaling during the interaction between a plant and its attacker(s) is crucial for the final defense output of the immune signaling network.

Molecular Players in Salicylic Acid–Jasmonic Acid Cross Talk

Although interactions between the SA and JA response pathways can be either antagonistic, synergistic, or neutral, antagonistic interactions seem to prevail (Pieterse et al. 2009, Tsuda et al. 2009). Here we describe our current understanding of proteins that play a role in regulating SA-mediated suppression of the JA pathway (**Figure 2**). The effects of other hormones on the balance between the SA and JA response pathways are discussed below.

Mitogen-activated protein kinases. Mitogen-activated protein (MAP) kinases transfer information from sensors to cellular responses in all eukaryotes and thus play a central role in plant immune signaling (Rodriguez et al. 2010). In *Arabidopsis*, MAP KINASE4 (MPK4) was identified as a negative regulator of SA signaling and a positive regulator of JA signaling, as mutant *mpk4* plants displayed elevated SA levels and constitutive expression of SA-responsive *PR* genes but failed to induce JA defense marker genes (Petersen et al. 2000). EDS1 and PAD4, which act early in the SA pathway and stimulate SA biosynthesis, were identified as downstream components of MPK4 function (Brodersen et al. 2006). Another target of MPK4 is its substrate MPK4 SUBSTRATE1 (MKS1). RNAi-mediated knockdown of *MKS1* partially rescued the *PR-1*-overexpressing phenotype of *mpk4*, suggesting that phosphorylation of MKS1 leads to repression of SA signaling (Andreasson et al. 2005). However, JA signaling was not affected by *MKS1* overexpression or silencing, suggesting that alternative substrates of MPK4 target JA signaling.

Redox regulators. Changes in the cellular reductive and oxidative states play an important role in regulating many plant processes, including plant immunity (Foyer & Noctor 2011, Spoel & Loake 2011). Glutaredoxins (GRXs) and thioredoxins (TRXs) are central players in mediating redox regulation of protein activity because of their capacity to catalyze disulfide transitions. Both SA and JA affect the cellular redox buffer glutathione. SA increases both the cellular amount and the ratio between reduced and oxidized glutathione, whereas JA decreases the glutathione pool (Spoel & Loake 2011). In *Arabidopsis*, the specific time frame in which SA suppresses JA-responsive gene expression coincides with a transient increase in the level of glutathione (Koornneef et al. 2008a). The glutathione biosynthesis inhibitor L-buthionine-sulfoximine (BSO) impacts this suppressive effect of SA, suggesting that SA-mediated modulation of the cellular redox state is an important trigger for the attenuation of the JA pathway (Koornneef et al. 2008a).

The implication of GRX480 in SA-JA cross talk confirmed the role for redox regulation in SA-JA cross talk (Ndamukong et al. 2007). GRX480 was identified in a two-hybrid screen for interactors with TGAs. Overexpression of *GRX480* in *Arabidopsis*

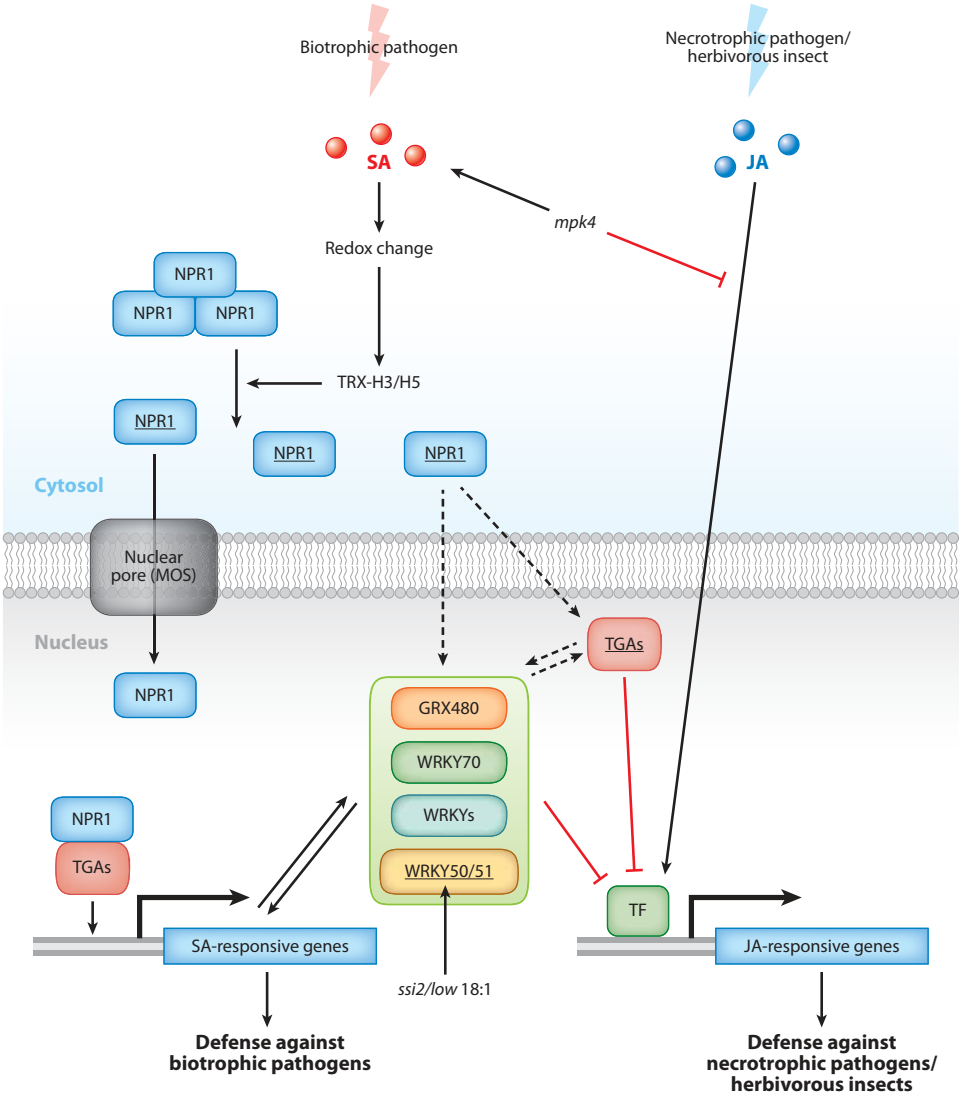


Figure 2

Schematic representation of molecular components involved in salicylic acid (SA)–mediated suppression of jasmonic acid (JA)–regulated gene expression (see text for details). Components that have been shown by mutational analysis to be essential for SA-JA cross talk are underlined. The green frame highlights components for which the expression was shown to be SA-responsive. Solid lines indicate established interactions; dashed lines indicate hypothesized interactions.

did not affect SA-dependent responses, but it strongly antagonized the transcription of *PDF1.2*. A *grx480* knockout mutant, however, showed wild-type levels of SA-mediated suppression of the JA pathway, indicating that GRX480 is not required for SA-JA cross talk. Recently, Zander et al. (2012) demonstrated that in addition to GRX480, several other TGA-interacting members of the ROXY class of GRXs are able to suppress transcription

of the ERF-branch transcription factor gene *ORA59*. Hence, it is plausible that SA-activated ROXY class GRXs act redundantly in SA-JA cross talk.

NPR1. The regulatory protein NPR1 is an important transducer of SA-induced redox changes and a crucial transcriptional coactivator of many SA-responsive genes (Wang et al. 2006). *Arabidopsis npr1* mutants are not only impaired in SA signaling, they are also blocked in SA-mediated suppression of JA-regulated genes (Leon-Reyes et al. 2009, Spoel et al. 2003). Nuclear localization of NPR1 is essential for SA-responsive defense gene expression, but not for SA-mediated suppression of the JA pathway (Spoel et al. 2003). Stimulation of the SA pathway in *Arabidopsis* plants overexpressing a fusion protein of NPR1 that was retained in the cytosol resulted in wild-type levels of suppression of JA responses, indicating that SA-JA cross talk is mediated by cytosolic NPR1 (Spoel et al. 2003). The role of cytosolic NPR1 in SA-JA cross talk was confirmed in rice (*Oryza sativa*), where overexpression of cytosolic OsNPR1 suppressed JA-responsive gene transcription, whereas no antagonistic effect on the JA response was recorded when OsNPR1 was constitutively targeted to the nucleus (Yuan et al. 2007). Additional evidence is accumulating for a differential role of nuclear and cytoplasmic NPR1 in the regulation of SA- and JA-dependent signaling (Glazebrook et al. 2003, Johansson et al. 2006, Leon-Reyes et al. 2009, Mao et al. 2007, Ramirez et al. 2010, Stein et al. 2008). However, the molecular details involved in the differential regulation of nuclear versus cytosolic NPR1-mediated responses need to be elucidated.

Although cytosolic NPR1 seems to be sufficient for SA-mediated suppression of the JA pathway, nuclear NPR1 regulates several SA-responsive transcriptional (co)factors with a direct or indirect role in suppressing JA-responsive gene expression. These (co)factors include GRX480, TGAs, and WRKYs. Their role in SA-JA cross talk is discussed elsewhere in this section.

TGA transcription factors. TGAs are important regulators of SA-induced expression of *PR* genes (Zhang et al. 2003). In *Arabidopsis*, seven TGAs interact with NPR1 (Kesarwani et al. 2007), while TGA2 and TGA6 interact with GRX480 (Ndamukong et al. 2007). Because both NPR1 and GRX480 have been implicated in SA-mediated suppression of the JA pathway, the role of TGAs in SA-JA cross talk has been tested. Interestingly, the *tga256* triple and *tga2356* quadruple mutants, which are impaired in SA-responsive gene expression, are also blocked in SA-mediated suppression of the JA pathway (Leon-Reyes et al. 2010a, Ndamukong et al. 2007, Zander et al. 2009), indicating that TGAs are essential for SA-JA cross talk.

TGAs bind to the core motif TGACG in SA-responsive promoters (Lebel et al. 1998). The JA- and ET-responsive promoter of *PDF1.2* contains a TGACG motif to which TGA2 can bind, which suggests that TGAs may directly inhibit promoter activity of JA-responsive genes (Spoel et al. 2003). However, deletion of the TGACG motif from the *PDF1.2* promoter affected neither JA inducibility nor SA-mediated suppression of the promoter (Spoel et al. 2003, Zander et al. 2009). Hence, it is likely that TGAs play an indirect role in SA-JA cross talk, e.g., in the activation of a negative regulator or in the suppression of a positive regulator of the JA response pathway.

In addition to their role in SA signaling, TGAs are important for the activation of JA- and ET-dependent defense genes in the absence of an SA stimulus (Zander et al. 2009). Because of their regulatory role in transcription, it is plausible that in the absence of an SA stimulus certain TGAs may function as positive regulators of JA- and ET-responsive gene expression. However, upon induction of the SA pathway their negative regulatory role in the JA pathway dominates (Zander et al. 2009).

SSI2. SUPPRESSOR OF SA INSENSITIVITY2 (SSI2) was identified in a screen for SA signaling components that are associated with NPR1-independent defense signaling

(Kachroo et al. 2001). *SSI2* encodes a protein that desaturates stearic acid to oleic acid (18:1) in plant cells. Mutant *ssi2* plants have a reduced 18:1 level, which simultaneously signals upregulation of the SA pathway and downregulation of the JA pathway (Kachroo et al. 2003). This phenotype was independent of whether *NPR1* was active. Moreover, lowering the SA levels in *ssi2* by ectopic expression of the SA hydroxylase gene *nahG* did not relieve the suppressive effect on the JA pathway, suggesting that *ssi2*/low 18:1–mediated suppression of JA signaling is regulated by a component downstream of SA in the SA pathway (Kachroo et al. 2001). Genome-wide transcriptional profiling of *ssi2* plants revealed that several *WRKY* transcription factor genes potentially have a role in *ssi2*/low 18:1–induced SA-JA cross talk. Mutations in *WRKY50* and *WRKY51* reduced the *ssi2*/18:1-mediated enhanced SA levels and restored JA-responsive gene expression in the *ssi2* background, indicating that WRKY50 and WRKY51 function together as both positive regulators of the SA pathway and negative regulators of the JA pathway (Gao et al. 2011).

WRKY transcription factors. WRKY transcription factors are important regulators of SA-dependent defense responses, and many of them are upregulated themselves by SA (Rushton et al. 2010). Several WRKY transcription factors have been implicated in SA-JA cross talk. In addition to their role in *ssi2*/low 18:1-mediated suppression of JA signaling, WRKY50 and WRKY51 were implicated in SA-induced suppression of the JA pathway in wild-type plants. Exogenous application of SA suppressed JA-inducible gene expression in wild type but not in *wrky50* or *wrky51* mutant plants (Gao et al. 2011). Hence, WRKY50 and WRKY51 seem to be essential for SA-mediated suppression of JA signaling.

Arabidopsis WRKY70 is an important node of convergence between SA and JA signaling (Li et al. 2004, Li et al. 2006). Overexpression of *WRKY70* in *Arabidopsis* enhanced the expression of SA-responsive *PR* genes, whereas it suppressed JA-responsive gene expression (Li et al. 2004, Ren et al. 2008). However, mutant *wrky70* was not affected in the responsiveness to SA and JA, or in the antagonistic effect of SA on the JA pathway (Leon-Reyes et al. 2010a, Ren et al. 2008). Hence, similar to GRX480, WRKY70 is sufficient but not essential for SA-mediated suppression of the JA pathway. Because *WRKY70* is induced in an SA- and partly NPR1-dependent manner (Li et al. 2004), it is conceivable that SA-induced WRKY70 negatively affects transcription of JA-responsive genes, which is supported by microarray data (Li et al. 2004).

Another WRKY factor associated with SA-JA cross talk is WRKY62 (Mao et al. 2007). *WRKY62* is synergistically induced by SA and JA in wild-type *Arabidopsis* but not in mutant *npr1* plants. Mutant *wrky62* plants have enhanced JA-responsive gene expression, whereas overexpression of *WRKY62* suppresses the JA pathway. Hence, analogous to WRKY70, these findings point to a SA- and NPR1-inducible negative regulatory role for WRKY62 in the JA response pathway. On the basis of results with overexpression or knockout lines, WRKY8 (Chen et al. 2010); WRKY11 and WRKY17 (Journot-Catalino et al. 2006); WRKY18, WRKY40, and WRKY60 (Xu et al. 2006); and WRKY41 (Higashi et al. 2008) also have been connected to SA-JA cross talk, but whether or not they play a redundant role in this process is unknown.

Targets of Salicylic Acid Antagonism in the Jasmonic Acid Signaling Pathway

The list of molecular players in SA-JA cross talk grows steadily, but relatively little is known about their target(s) in the JA signaling pathway. JA signaling is under the control of a positive-feedback regulatory system, as many JA biosynthesis genes are themselves induced by JA (Wasternack 2007). In *Arabidopsis*, several genes encoding key enzymes in the JA biosynthesis pathway can be repressed by SA, suggesting that SA-mediated antagonism depends possibly on repression of de novo JA

biosynthesis (Leon-Reyes et al. 2010b). However, in mutant *aos/dde2*, which is completely blocked in JA synthesis because of a mutation in the *ALLENE OXIDE SYNTHASE* (*AOS*) gene, SA suppresses MeJA-induced gene expression to the same level as in wild-type plants (Leon-Reyes et al. 2010b). Thus, the antagonistic effect of SA on JA signaling must act at a target in the JA signaling pathway downstream of JA biosynthesis. Nevertheless, it is likely that suppression of JA biosynthesis genes by SA may contribute to the attenuation of the JA response during plant-attacker interactions.

Downstream of JA biosynthesis, SCF^{COI1} complex and JAZ repressor proteins are central components in signal transduction. Interference of SA by either one of these components could result in suppression of JA responses, but this needs to be investigated. Because the antagonistic effect of SA on the JA pathway is often clearly expressed at the level of gene transcription, it is plausible that the JA transcription machinery is targeted by SA. Indeed, several transcriptional (co)activators, such as NPR1, TGA, and WRKY, play a role in SA-mediated suppression of JA-responsive genes (**Figure 2**). Upon induction of the SA pathway, they may act as negative regulators. However, the exact mechanism by which these transcriptional (co)activators target the JA response pathway needs to be resolved.

Both SA- and JA-responsive gene expression involve alterations in the chromatin configuration by covalent modifications of the histone tails in the nucleosome to allow or prevent access of the transcription machinery (Moore et al. 2011). Hence, SA-mediated chromatin remodeling may also play a role in SA-JA cross talk. Histone deacetylation, mediated by histone deacetylases, is generally correlated with transcriptional repression (Pfluger & Wagner 2007). However, chromatin immunoprecipitation analysis using an antibody directed against acetylated histone H3 revealed that SA does not affect this histone modification at the JA-responsive promoter of *PDF1.2* (Koornneef et al. 2008b). This finding suggests that chromatin remodeling does not play a major role in SA-JA cross talk, but this also needs further investigation.

HORMONAL MODULATORS OF THE SALICYLIC ACID–JASMONIC ACID BACKBONE

Several other plant hormones antagonistically or synergistically interact with the SA-JA backbone of the plant immune signaling network. In addition, plant hormones can have SA- and JA-independent effects on plant immunity, but this is outside the scope of this review and is described elsewhere (Bari & Jones 2009, Robert-Seilaniantz et al. 2011a). Here we focus on recent developments that have elaborated our understanding of how other plant hormones modulate the SA-JA backbone of the plant immune signaling network.

Ethylene

The gaseous hormone ET is a major constituent of the blend of defense signals that is produced during many plant-attacker interactions and functions as an important modulator of plant immunity (Broekaert et al. 2006, Van Loon et al. 2006a, Von Dahl & Baldwin 2007). Analyses of global gene expression profiles of pathogen-infected wild-type and hormone-signaling-defective mutant plants revealed extensive cross talk between ET and the SA and JA signaling sectors of the immune signaling network (Glazebrook et al. 2003, Sato et al. 2010). ET can act both positively and negatively on plant immunity. For instance, in *Arabidopsis*, ET potentiates SA-responsive *PR-1* expression (De Vos et al. 2006, Lawton et al. 1994), and in tobacco it is essential for the onset of SAR (Verberne et al. 2003). Conversely, the ET-responsive transcription factors EIN3 and EIL1 were implicated in global repression of PAMP-responsive genes in *Arabidopsis*, including the SA biosynthesis gene *ICS/SID2*, resulting in reduced accumulation of SA (Chen et al. 2009).

ET also greatly affects the outcome of the JA response. When produced in combination

with JA, such as upon infection by necrotrophic pathogens, ET acts synergistically on the expression of the ERF branch of the JA pathway, whereas it antagonizes the MYC branch, resulting in prioritization of the immune signaling network toward JA- and ET-dependent defense signaling associated with resistance to necrotrophs (**Figure 3**) (Anderson et al. 2004, Lorenzo et al. 2003, Lorenzo et al. 2004, Pré et al. 2008). Moreover, when the ERF branch was activated and the MYC branch suppressed by *ORA59* overexpression, plants became more attractive to *P. rapae* larvae (Verhage et al. 2011). Hence, modulation of the JA response by ET signaling can negatively affect the plant's chance to survive insect attack.

Also during SA-JA signal interaction, ET can play a critical role. ET applied exogenously or produced during pathogen infection bypassed the need for NPR1 in the suppression of the JA response by SA (Leon-Reyes et al. 2009). Consequently, SA-mediated suppression of resistance to the JA- and ET-inducing necrotrophic fungus *Alternaria brassicicola* became uncoupled from NPR1, but not the antagonistic effect of SA on JA-dependent resistance against the ET-noninducing insect herbivore *Frankliniella occidentalis* (western flower thrips). Hence, the final outcome of the SA-JA signal interaction during the complex interactions between plants and their attackers can be shaped by ET present in the signal signature produced upon attack. The molecular events through which ET modulates the role of NPR1 in SA-JA cross talk are unknown.

Additionally, ET signaling makes plant tissues immune to future SA-mediated suppression of the JA pathway (Leon-Reyes et al. 2010a). When the JA and ET signaling pathways are activated during or after the onset of the SA response, SA is capable of exerting a strong suppressive effect on JA-responsive gene expression. However, when the JA and ET pathways are fully induced prior to SA induction, the antagonistic effect of SA on the JA pathway is completely abolished. This effect could be attributed to ET because it was not apparent when the ET signaling inhibitor

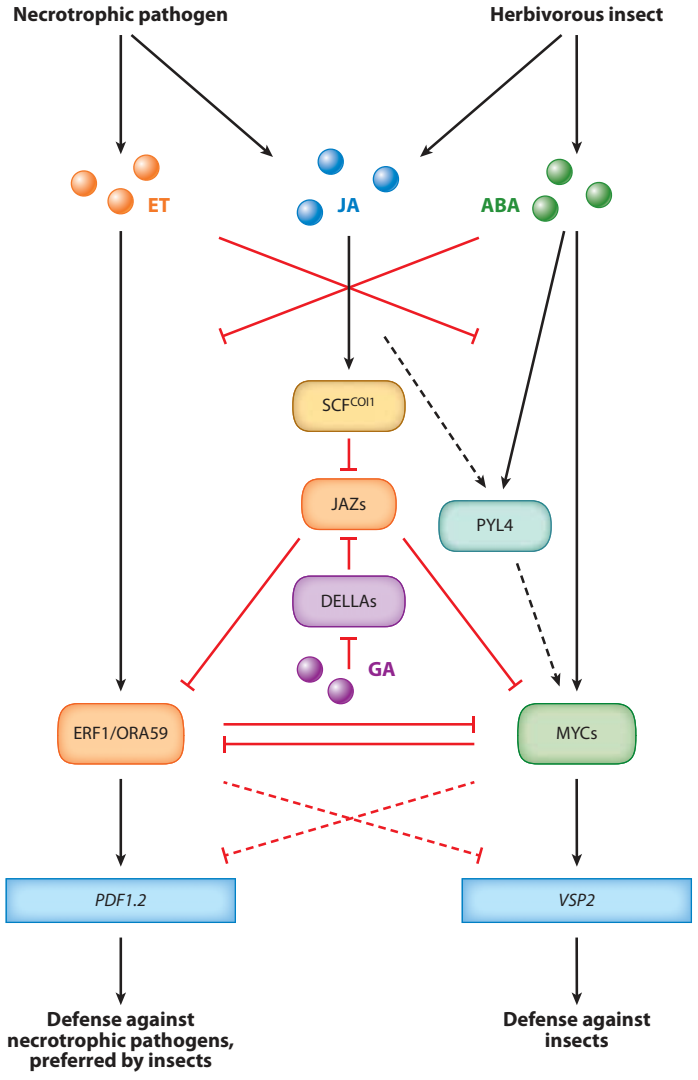


Figure 3

Modulation of the JA signaling pathway by ET, ABA, and GA (see text for details). Necrotrophic pathogens induce JA- and ET-dependent signaling pathways; herbivorous insects induce JA- and ABA-dependent signaling pathways. The ET- and ABA-regulated branches of the JA pathway are mutually antagonistic. Solid lines indicate established interactions, dashed lines represent hypothesized interactions, arrows indicate positive effects, and red inhibition lines represent negative effects. Abbreviations: ABA, abscisic acid; ET, ethylene; GA, gibberellin; JA, jasmonic acid.

1-methylcyclopropene (1-MCP) was included. Simultaneous induction of the JA and ET pathways through infection by a necrotrophic pathogen, or constitutively in mutant *cev1* (*constitutive expression of VSP1*) and transgenic

35S:*ORA59* plants, similarly rendered leaf tissues unresponsive to SA-mediated suppression of the JA pathway. This acquired insensitivity to SA antagonism may reflect a mechanism by which plants prioritize the JA and ET pathways over the SA pathway, which may be important for plant survival during multi-attacker interactions.

Abscisic Acid

Recent discoveries have greatly expanded our understanding of ABA perception and signaling (Cutler et al. 2010). In addition to its role in development and adaptation to abiotic stress, in particular drought and salinity stress, ABA emerged as an important modulator of the plant immune signaling network (Asselbergh et al. 2008, Cao et al. 2011, Ton et al. 2009). ABA signaling antagonizes plant immunity by suppressing SA-dependent defenses (Cao et al. 2011, De Torres-Zabala et al. 2009, Jiang et al. 2010, Yasuda et al. 2008). In *Arabidopsis*, ABA and SA response mechanisms affect each other at multiple steps, from the level of biosynthesis to intermediate components of the signal transduction pathways (Yasuda et al. 2008). Hence, plants seem to balance ABA-mediated abiotic stress tolerance and SA-mediated biotic stress resistance through ABA-SA cross talk.

When produced in combination with JA, such as upon wounding or herbivory, ABA acts synergistically on the expression of the MYC branch of the JA response pathway, while it antagonizes the ERF branch (Abe et al. 2003, Anderson et al. 2004) (**Figure 3**). This results in prioritization of the immune signaling network toward the MYC branch of the JA pathway, which is associated with resistance to herbivory (Anderson et al. 2004, Dombrecht et al. 2007, Fernandez-Calvo et al. 2011), while resistance to necrotrophs is compromised (Anderson et al. 2004). Conversely, JA signaling can function positively on ABA signaling by inducing genes, such as *PYL4* (Lackman et al. 2011), that encode proteins of the ABA receptor family. This way certain JA-inducible responses depend on ABA and vice versa. Transcription factors from the R2R3-MYB and NAC families are implicated in ABA-JA interactions as well and as such function as important modulators of plant responses to abiotic and biotic stress (AbuQamar et al. 2009, Nakashima et al. 2007, Wu et al. 2009).

Because ABA negatively affects SA signaling and promotes the MYC branch of the JA response pathway, it is likely to affect SA-JA cross talk. Indeed, interactions between ABA, SA, and JA play a role in the regulation of basal and β-aminobutyric acid (BABA)-induced defenses (Flors et al. 2008), but the general biological significance and molecular details of this tripartite hormone interaction are still poorly understood.

Auxin

Auxins play a role in virtually every stage of plant development (Benjamins & Scheres 2008). Many microbes can produce auxins themselves or manipulate auxin signaling in the host to interfere with normal developmental processes (Kazan & Manners 2009, Robert-Seilaniantz et al. 2011a). Auxin signaling can repress SA levels and signaling (Robert-Seilaniantz et al. 2011b), so it is not surprising that certain biotrophic pathogens evolved ways to exploit auxin-mediated suppression of SA to enhance susceptibility of the host (Chen et al. 2007). On the contrary, transcript profiling showed that SA signaling impedes auxin responses through global repression of auxin-related genes (Wang et al. 2007). During PTI, induction of the microRNA miR393 by the bacterial PAMP flagellin targets auxin receptors and suppresses auxin signaling, thereby preventing auxin from antagonizing SA signaling (Navarro et al. 2006, Robert-Seilaniantz et al. 2011b). This suppression of auxin responses resulted in enhanced resistance to *P. syringae* and *H. arabidopsidis*, suggesting that antagonism of auxin signaling is an intrinsic part of SA-dependent defenses against biotrophs. Although overexpression of miR393 rendered plants more resistant to biotrophs, it caused enhanced susceptibility to necrotrophs, suggesting that suppression of auxin signaling

also affects SA-JA cross talk. In addition, suppression of auxin signaling by miR393 redirects the metabolic flow of the tryptophan metabolic pathway by which auxins and antimicrobial indole glucosinolates and camalexin are synthesized. As a result, auxin-suppressed plants produce more indole glucosinolates, which are implicated in biotroph resistance, whereas production of camalexin, which is more effective against necrotrophic fungi, is reduced (Robert-Seilaniantz et al. 2011b).

In *Arabidopsis*, the JA signaling suppressor *JAZ1* was expressed in early phases of the auxin response, suggesting that JAZ1 acts as an integrator of auxin and JA responses (Grunewald et al. 2009). However, the role of the JA-auxin interaction in the regulation of the plant immune signaling network remains to be elucidated.

Gibberellins

GAs are hormones that control plant growth by regulating the degradation of growth-repressing DELLA proteins (Sun 2011). GAs were firmly implicated in plant immune signaling when degradation of DELLA proteins was shown to promote susceptibility to necrotrophs and resistance to biotrophs through modulation of JA and SA signaling (Navarro et al. 2008). DELLA mutant plants showed reduced sensitivity to JA, whereas constitutive DELLA activation in a GA-insensitive mutant resulted in enhanced sensitivity to JA, indicating that DELLA proteins positively interact with the JA pathway (**Figure 3**). Interestingly, DELLA proteins sequester the JA signaling repressor JAZ1 by binding to it, thereby reducing JAZ/MYC2 interactions and allowing MYC2 to activate JA-responsive target genes (Hou et al. 2010). GA-mediated degradation of DELLA proteins accordingly enhanced JAZ-mediated suppression of JA-responsive gene expression. Thus, GAs suppress the cellular competence to respond to JAs and consequently shift the balance between JA and SA signaling, resulting in enhanced SA signaling and biotroph resistance. Because DELLA proteins integrate plant responses to various hormonal signals and environmental conditions, they are central players in the plant's capacity to maximize growth and protection.

DELLA: growth-repressing GA signal mediator that acts positively on JA signaling by sequestering JAZ repressor proteins

Cytokinins

CKs are classic growth hormones that also emerged as modulators of plant immunity (Choi et al. 2011, Robert-Seilaniantz et al. 2011a). CKs are often linked to a plant's response to biotrophic pathogens that alter the host's physiology (Walters & McRoberts 2006). Choi et al. (2010) showed that CKs modulate SA signaling. The CK-activated transcription factor ARR2, which regulates CK-responsive genes, can bind to the SA response transcription factor TGA3 and positively regulates *PR-1* gene expression and resistance against *P. syringae*. Thus, CKs can act synergistically on the SA signaling sector of the plant immune signaling network.

REWIRING OF THE HORMONE SIGNALING NETWORK BY PLANT ENEMIES

Although hormone cross talk may provide the plant with a powerful regulatory potential to finely tune its defenses, it is also a possible target, such that plant attackers can manipulate the plant immune signaling network for their own benefit. For instance, the necrotrophic fungus *Botrytis cinerea* produces an exopolysaccharide that acts as an elicitor of the SA/NPR1 pathway and consequently suppresses effective JA-dependent defenses in its host, the tomato plant (*Solanum lycopersicum*) (El Oirdi et al. 2011). In recent years, numerous examples of plant pathogens that hijack specific hormone-regulated signaling pathways, e.g., by producing plant hormones, hormone mimics, or effectors that target hormone signaling components (Robert-Seilaniantz et al. 2011a), have been described. Here we focus on the bacterial model pathogen *P. syringae*, which is exceptionally well-equipped to hijack the immune signaling network of its host to promote

virulence. In addition, we provide an overview of recent developments of hormonal modulation of host immunity by insect herbivores.

Hormonal Modulation of Host Immunity by the Model Pathogen *Pseudomonas syringae*

Infection of *Arabidopsis* by virulent *P. syringae* results in PAMP-triggered stomatal closure and the activation of SA-dependent basal defenses that limit pathogen entry and growth (Melotto et al. 2008, Nomura et al. 2005). Basal SA-dependent defenses can be promoted by bacterial flagellin, e.g., via CK-activated ARR2 transcription factors, which through interaction with TGA3 promote SA-responsive gene expression (Choi et al. 2010), or by the induction of miR393, which suppresses auxin signaling and concomitantly relieves the inhibitory effect of auxin on the SA response pathway. As a countermeasure, virulent *P. syringae* suppresses SA-dependent immune responses by bacterial effector proteins, which are injected into the plant cell through the type III secretion system, and by the bacterial toxin COR, which functions as a molecular mimic of JA-Ile (Nomura et al. 2005). In many cases, *P. syringae* utilizes the hormone-regulated defense signaling network of the host to suppress host immunity (**Figure 4**).

COR binds directly to the JA receptor COI1 and is much more active in stimulating the JA pathway than JA-Ile is (Katsir et al. 2008, Yang et al. 2009). COR-mediated activation of the JA pathway antagonizes SA-dependent defenses (Brooks et al. 2005, Ishiga et al. 2010) and inhibits PAMP-triggered stomatal closure (Melotto et al. 2008), resulting in enhanced susceptibility of the host. Several type III effectors of virulent *P. syringae* target the SA pathway as well to promote pathogenesis. The effector HopI1 localizes to the chloroplasts where it suppresses SA accumulation (Jelenska et al. 2007). The defense-suppressive activity of HopI1 depends on its interaction with the plant stress chaperone HEAT SHOCK PROTEIN 70 (HSP70), which is thought to possess a defense-promoting function (Jelenska et al. 2010). In addition, AvrPtoB stimulates ABA biosynthesis and ABA responses that antagonize SA biosynthesis and SA-mediated defenses (De Torres-Zabala et al. 2007, 2009). Similarly, AvrRpt2 alters the auxin physiology, which antagonizes the SA pathway and consequently promotes host susceptibility (Chen et al. 2007). Hence, manipulation of plant hormone homeostasis, which leads to suppression of host immunity, is a major virulence strategy of *P. syringae*.

The stabilization of DELLA proteins and the ET-mediated activation of EIN3 and EIL1 also suppress the SA response pathway and promote susceptibility to *P. syringae* (Chen et al. 2009, Navarro et al. 2008). However, there is no evidence that *P. syringae* recruits these mechanisms to promote virulence.

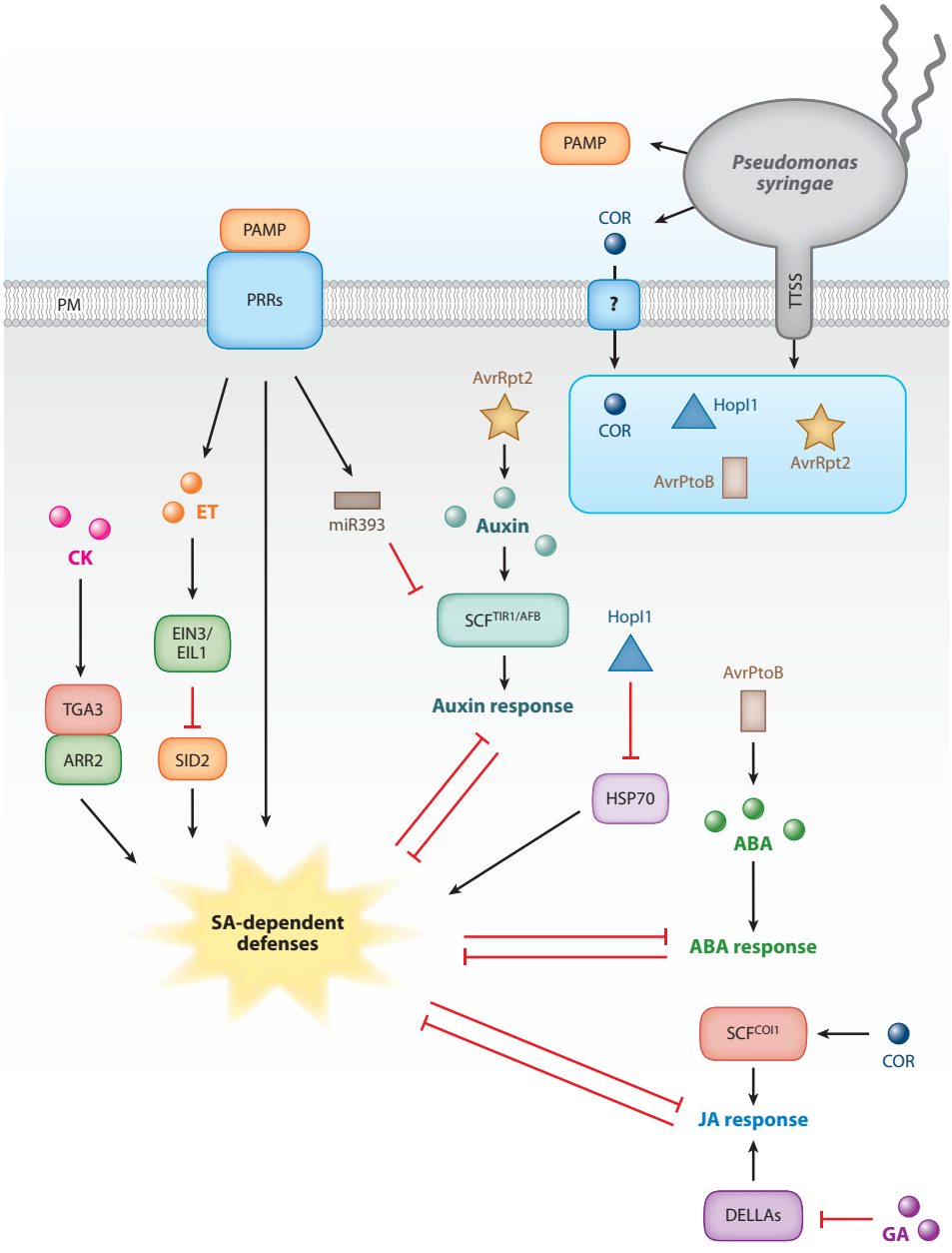
Hijacking Host Hormone Integration by Insect Herbivores

Similar to virulent pathogens, insect herbivores have also leveraged the molecular

Figure 4

Rewiring of the hormone-regulated immune signaling network. *Pseudomonas syringae*–derived PAMPs are recognized by the host's PRRs, leading to activation of SA-dependent defenses. *P. syringae* delivers the phytotoxin COR and effectors such as AvrRpt2, AvrPtoB, and HopI1 (*indicated in the blue frame*) into the host cell, which suppress the SA pathway via activation of JA, auxin, or ABA signaling pathways, or via a direct suppressive effect on SA biosynthesis. Cross talk between SA signaling and the other hormone signaling pathways is commonly mutually antagonistic, which could help the plant to counteract the effector-triggered susceptibility. ET-stabilized EIN3/EIL1 transcription factors suppress SA-regulated genes such as the SA biosynthesis gene *SID2*. The plant hormones GA and CK can contribute positively to SA-dependent defenses. Arrows indicate positive effects; red inhibition lines represent negative effects. See text for details. Abbreviations: ABA, abscisic acid; CK, cytokinin; COR, coronatine; ET, ethylene; GA, gibberellin; JA, jasmonic acid; PAMP, pathogen-associated molecular pattern; PM, plasma membrane; PRR, pattern-recognition receptor; SA, salicylic acid; TTSS, type III secretion system.

communication within the host immune signaling network to enhance their success on host plants (Hogenhout & Bos 2011, Walling 2008). For instance, the invasive spider mite *Tetranychus evansi* suppresses SA- and JA-dependent defenses in tomato to levels even lower than those in herbivore-free plants, resulting in a much better performance on previously attacked plants than on non-attacked plants (Sarmento et al. 2011). Also, nymphs of



the phloem-feeding silverleaf whitefly (*Bemisia tabaci*) are able to manipulate hormone-regulated host defenses to their own benefit. On *Arabidopsis*, they activate the SA signaling pathway, which concomitantly suppresses effective JA-dependent defenses, resulting in increased plant susceptibility and enhanced insect performance (Zarate et al. 2007). Some tissue-chewing insects appear to have adopted this strategy as well. Elicitors from salivary excretions of the beet armyworm (*Spodoptera exigua*) suppressed effective JA-regulated defenses through the activation of the SA pathway (Diezel et al. 2009, Weech et al. 2008). Interestingly, elicitors from insect eggs activated the SA pathway (Bruessow et al. 2010). Consequently, JA-dependent defenses were suppressed at the site of oviposition, resulting in enhanced growth of freshly hatched larvae of the generalist herbivore *Spodoptera littoralis* (cotton leafworm) that fed from the undefended tissue. Hence, recruiting the SA pathway to suppress effective JA-dependent defenses seems to be an effective strategy employed by different insect herbivores to counteract host defense.

Alternative strategies have been described as well. For instance, caterpillars of the herbivore *P. rapae* attempt to rewire different branches of the JA response pathway for their own benefit. Elicitors in their oral secretions activate the insect-preferred ERF branch of the JA pathway in *Arabidopsis* (Verhage et al. 2011), possibly to guide the JA pathway away from the MYC branch, which regulates herbivore resistance (Fernandez-Calvo et al. 2011) (**Figure 3**). However, despite the initial attempt of *P. rapae* to stimulate the ERF branch of the JA pathway, the MYC/ERF balance shifts toward the MYC branch, suggesting that the arms race between plant and attacker during this interaction is decidedly in favor of the plant.

HORMONAL MODULATION OF HOST IMMUNITY BY BENEFICIAL MICROBES

Like leaf tissues, roots are capable of responding to a variety of defense elicitors, such as MAMPs produced by soil-borne microbes (Jacobs et al. 2011, Millet et al. 2010). Because of the plethora of soil microbes that reside in the rhizosphere (each gram of soil typically contains over a billion microbes), immune signaling in plant roots must be under tight control (Zamioudis & Pieterse 2012). Hormone-regulated defenses can influence the composition of the indigenous microflora in the rhizosphere (Doornbos et al. 2011; Berendsen et al. 2012). Evidence is emerging that beneficial soil microbes have evolved decoy strategies to short-circuit hormone-regulated immune responses that are triggered in the roots upon initial recognition, which paves the way for a prolonged mutualistic association with their host. For instance, the beneficial PGPF *Piriformospora indica* recruits the JA pathway to suppress both early and late defenses, including SA-mediated defenses (Jacobs et al. 2011) (**Figure 5*a***). Moreover, in both mycorrhizal and root-nodule symbioses, JA transiently accumulates in the roots of host plants at the early stages of infection, which suggests a role for JA signaling in counterbalancing SA-triggered responses (Gutjahr & Paszkowski 2009). In addition, many free-living PGPR and PGPF produce substantial amounts of plant hormones, such as auxins and GAs (Lugtenberg & Kamilova 2009, Sirrenberg et al. 2007), that potentially attenuate SA signaling via hormonal cross talk mechanisms.

The recently discovered MiSSP7 effector of the ectomycorrhizal fungus *Laccaria bicolor* and the SP7 effector of the arbuscular mycorrhizal fungus *Glomus intraradices* are two examples of symbiotic effectors that promote a biotrophic interaction by affecting hormonal signaling pathways (Kloppholz et al. 2011, Plett et al. 2011). MiSSP7 is imported into the plant cell through lipid raft–mediated endocytosis, after which it is translocated into the nucleus of host cells, where it promotes the expression of auxin-responsive genes (Plett et al. 2011) (**Figure 5*b***). SP7 is the first symbiotic effector described so far to possess immune-suppressive function by targeting the ET signaling pathway, which is an important component of PTI

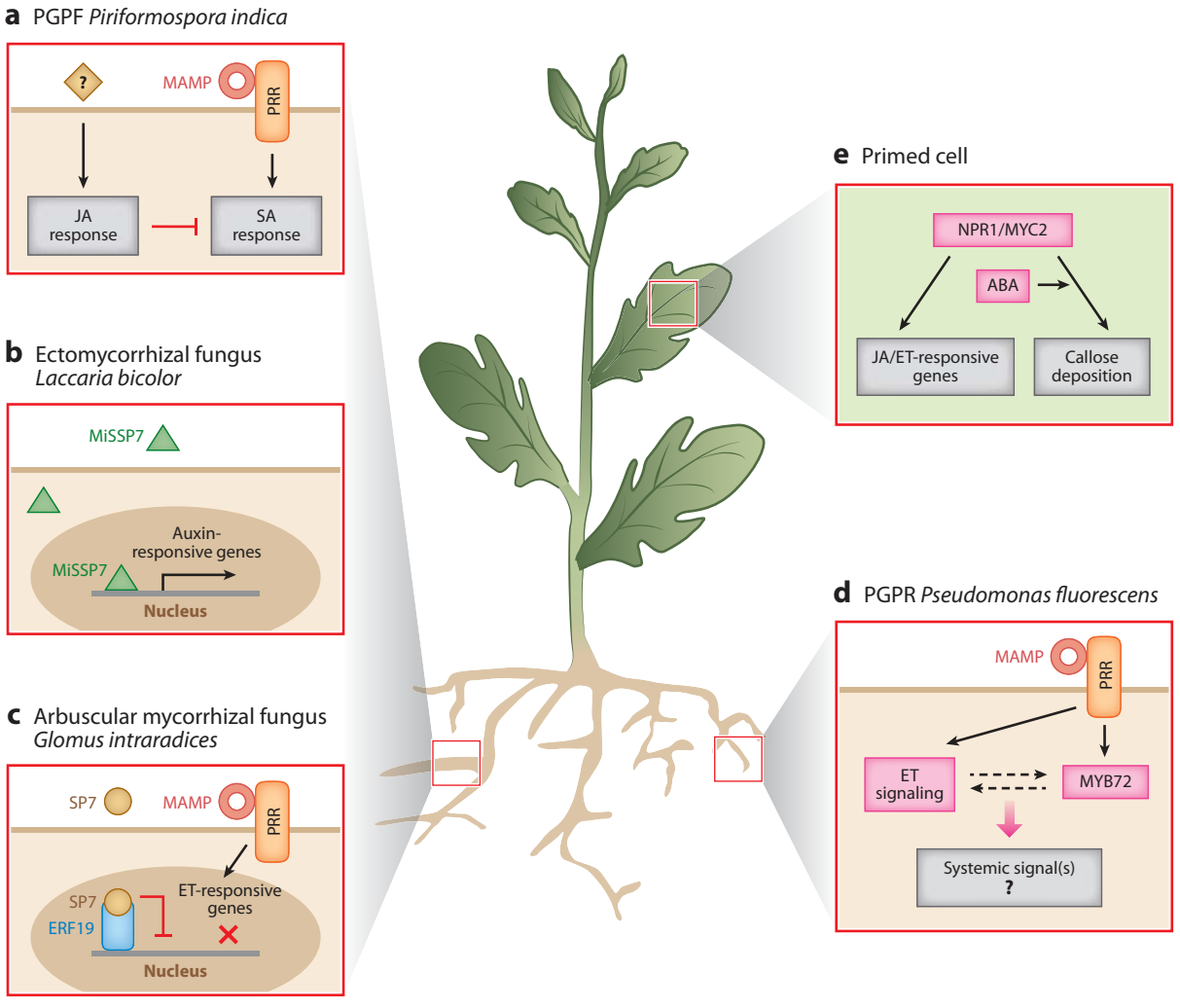


Figure 5

Soil-borne mutualists utilize effector molecules that interfere with hormone-regulated signaling pathways to facilitate root colonization. (*a*) The beneficial fungus *Piriformospora indica* recruits the JA signaling pathway to suppress MAMP-triggered SA-dependent defenses. (*b*) The symbiotic effector MiSSP7 of the ectomycorrhizal fungus *Laccaria bicolor* is targeted to the nucleus to promote the expression of auxin-responsive genes. (*c*) The symbiotic effector SP7 of the arbuscular mycorrhizal fungus *Glomus intraradices* interacts with the ET-responsive transcription factor ERF19 to suppress ET-mediated defenses. Root colonization by beneficial microbes commonly results in the onset of a systemic immune response. (*d*) Colonization of roots by selected strains of the PGPR *Pseudomonas fluorescens* is associated with an enhanced defensive capacity in the aerial parts of the plant. Initiation of ISR is regulated by the root-specific transcription factor MYB72 and components of the ET signaling pathway that locally act to generate a so far unknown systemic signal(s). (*e*) In systemic tissues, the onset of ISR depends on functional JA/ET and ABA signaling pathways and further requires the transcriptional regulators NPR1 and MYC2. ISR-expressing plants are primed for accelerated JA- and ET-responsive gene expression and increased callose deposition at the sites of pathogen or insect attack. Dashed arrows represent hypothesized interactions, solid arrows indicate positive effects, and red inhibition lines represent negative effects or repression of transcription. Abbreviations: ABA, abscisic acid; ET, ethylene; ISR, induced systemic resistance; JA, jasmonic acid; MAMP, microbe-associated molecular pattern; PGPF, plant-growth-promoting fungi; PGPR, plant-growth-promoting rhizobacteria; PRR, pattern-recognition receptor; SA, salicylic acid.

Induced systemic resistance (ISR): JA-/ET-dependent enhanced defensive capacity of the entire plant, acquired upon colonization of the roots by specific mutualistic microbes

in the roots (Boutrot et al. 2010, Mersmann et al. 2010, Millet et al. 2010). SP7 is translocated into the nucleus of host cells, where it interacts with the defense-related transcription factor ERF19 and blocks its transcriptional program (Kloppholz et al. 2011) (**Figure 5*c***). Considering the delicate symbiotic interactions between plant roots and soil mutualists, many more symbiotic effectors that manipulate the hormone-regulated defense signaling network of the host are likely to be discovered.

Once established, interactions between plant roots and mutualistic microbes are often associated with an enhanced defensive capacity in above-ground plant parts, a phenomenon known as induced systemic resistance (ISR) (Van Wees et al. 2008). Induction of ISR in *Arabidopsis* by the rhizosphere-colonizing PGPR *Pseudomonas fluorescens* WCS417 is well studied. WCS417 benefits from the plant by utilizing nutrients that are exuded by the roots. WCS417 suppresses local flagellin-triggered PTI responses in the roots via apoplastic secretion of one or more low-molecular-weight molecule(s) (Millet et al. 2010). Whereas PTI is suppressed locally, an immune signaling cascade is initiated systemically that confers resistance against a broad spectrum of pathogens and even insects (Pineda et al. 2010, Van der Ent et al. 2009b, Van Oosten et al. 2008). Initiation of ISR in the roots is regulated by the root-specific transcription factor MYB72 and components of the ET pathway that act locally to generate or translocate one or more unknown systemic signal(s) (Knoester et al. 1999, Van der Ent et al. 2008). The ISR response is associated not with direct defense activation, but with priming for accelerated JA- and ET-dependent gene expression and increased deposition of callose at the site of pathogen entry (Van der Ent et al. 2009b, Van Wees et al. 2008) (**Figure 5*d*,*e***). Systemic establishment of WCS417-ISR in leaf tissues depends on the JA/ET and ABA signaling pathways and requires NPR1 and MYC2 (Pozo et al. 2008, Van der Ent et al. 2009a). Priming of systemic hormone-regulated immune responses by beneficial microbes is suggested to be part of an autoregulatory mechanism that keeps colonization by mutualists in check. One of its outcomes is the ISR phenomenon, which provides broad-spectrum systemic protection of roots and shoots (Zamioudis & Pieterse 2012).

CONCLUDING REMARKS

We now have a wealth of information on the molecular details of hormone perception, derepression of hormone signaling pathways, and activation/degradation of hormone-specific transcription factors (Santner & Estelle 2009). Also, the central role of plant hormones in the regulation of immune signaling is firmly established. Not only SA and JA, but also nearly all other hormones, which were discovered originally because of their effects on growth or development, have been implicated in defense or pathogenesis. Manipulation of hormone homeostasis and signal cross talk appear to be dominant features in the regulation of the defense signaling network, initiated either by the plant to fine-tune or prioritize its defenses to maximize growth and protection, or by pathogens, insects, or beneficial microbes to rewire the immune signaling circuitry for their own benefit. However, an integrated view on the spatial and temporal dynamics of hormone production and signaling during the interaction of plants with other organisms is still lacking, especially in relation to how hormone interplay steers the final outcome of the plant immune response. Also, our understanding of the molecular events that foster hormonal cross talk is still in its infancy.

That several important mediators of hormone cross talk are transcriptional (co)factors suggests that cross talk predominantly takes place downstream of signal transduction, at the level of gene transcription. Hence, future research on hormone interactions will benefit greatly from next-generation deep sequencing technologies, such as RNA-seq and ChIP-seq. These technologies will allow high-resolution, whole-genome expression profiling to infer

core gene regulatory networks and to identify the transcriptional regulators involved. Computational modeling approaches will subsequently be essential to identify key regulatory nodes in the cross talk gene regulatory network model. To this end, experimental biologists should join forces with bioinformaticians and mathematicians and engage in the systems biology cycle of predictive, quantitative modeling and biological experimentation.

Repressors of transcriptional activators of hormone responses, such as JAZ and DELLA, emerged as important nodes of convergence in the hormone signaling network. As they are crucial for suppression of their core signaling pathway and function in complex signalosomes, they are theoretically ideal targets for hormone cross talk. Novel tandem affinity purification and proteomics approaches allow the isolation and identification of core signaling modules and interactors of key nodal proteins (Pauwels et al. 2010). Hence, this technology will be highly instrumental in identifying and functionally characterizing important molecular players in hormone cross talk.

At the other end of the spectrum, challenges for future research lie in understanding how complex signal interactions are functional in an ecological context. In nature, plants interact simultaneously or sequentially with multiple beneficial and harmful organisms. Community ecology studies show that the invasion history of a plant influences the response to secondary attackers and that plant hormones can play a decisive role in this process (Kessler et al. 2004, Poelman et al. 2008b). By placing research on molecular mechanisms of hormone cross talk in an ecological perspective, we will be able to achieve a more complete understanding of the role of this process in plant survival.

SUMMARY POINTS

1. Plants utilize hormone cross talk to optimize defenses, whereas pathogens, insects, and mutualists can rewire the hormone-regulated signaling circuitry to evade or suppress host immunity.
2. Transcriptional (co)regulators, such as NPR1, TGAs, and WRKYs, emerged as molecular players in SA-JA antagonism.
3. ET is an important modulator of SA-JA cross talk, as it bypasses the NPR1 dependency of SA-JA cross talk, and can render plant tissues unresponsive to subsequent SA-mediated suppression of the JA pathway.
4. ABA, auxins, GA, and CK affect the SA-JA backbone of the plant immune signaling network, resulting in positive or negative effects on biotroph and necrotroph resistance.
5. In general, opposing effects of other hormones on SA and JA signaling are found: ET, auxin, and ABA antagonize SA signaling but synergize JA signaling, whereas GA antagonizes JA signaling but synergizes SA signaling.
6. *P. syringae* exploits the JA mimic COR and several type III secreted effectors to activate the JA, ABA, and auxin signaling pathways and consequently suppress SA responses and promote pathogen virulence.
7. Plant hormone signaling pathways are rewired by symbiotic effectors of beneficial microbes to suppress host immunity and enable a prolonged mutualistic interaction.

FUTURE ISSUES

1. Components of core hormone signaling pathways that are targeted by other hormone signaling pathways need to be identified to fully understand the molecular basis of hormone cross talk.
2. Large-scale transcript profiling and subsequent computational modeling approaches are required to identify novel key regulatory nodes of pathway cross talk.
3. Analysis of hormone cross talk during multiorganism and multistress interactions would provide new insights into how the hormone-regulated plant defense signaling network functions.
4. The identification of effectors of mutualistic microbes that relay the plant's hormone-regulated signaling network to suppress host immunity is a challenging new field of research.
5. How conserved are the molecular mechanisms of hormone cross talk as identified in *Arabidopsis*, and what is their significance in an ecological and evolutionary context?

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