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Review Article

Systemic acquired resistance-associated transport and metabolic regulation of salicylic acid and glycerol-3-phosphate

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Systemic acquired resistance (SAR), a type of long-distance immunity in plants, provides long-lasting resistance to a broad spectrum of pathogens. SAR is thought to involve the rapid generation and systemic transport of a mobile signal that prepares systemic parts of the plant to better resist future infections. Exploration of the molecular mechanisms underlying SAR have identified multiple mobile regulators of SAR in the last few decades. Examination of the relationship among several of these seemingly unrelated molecules depicts a forked pathway comprising at least two branches of equal importance to SAR. One branch is regulated by the plant hormone salicylic acid (SA), and the other culminates (based on current knowledge) with the phosphorylated sugar derivative, glycerol-3-phosphate (G3P). This review summarizes the activities that contribute to pathogen-responsive generation of SA and G3P and the components that regulate their systemic transport during SAR.

The mammalian adaptive immune response is a type of 'learnt' immunity during which, previous exposure to pathogen results in the development of a 'memory'. This improves the host's ability to better resist the same pathogen in the future [1]. Adaptive immunity can be long-lasting and relies on the ability of the lymphocyte-secreted antibodies to traverse systemically through the bloodstream. Interestingly, despite the lack of a circulatory system, plants too can activate a type of long-lasting systemic immune response, termed systemic acquired resistance (SAR) [2]. Like adaptive immunity, SAR is induced in response to primary infection and provides protection against subsequent infections [3–7]. SAR efficacy can last up to several months, and booster inoculations with the primary infectious agent have been reported to extend the longevity of secondary protection [7–9]. Additionally, intergenerational inheritance of SAR has been reported in Arabidopsis, although the underlying processes are not comparable to parental transfer of antibodies in vertebrate progeny [10,11]. However, unlike the limited efficacy (antigen-specific) of adaptive immunity, SAR is broad-spectrum in nature, providing protection against organisms both related and unrelated to the primary infecting pathogen [12]. Additionally, plant-to-plant transfer of SAR signals has been reported [13].

Early studies defining the SAR phenomenon focused on the secondary systemic immune response activated through a classical gene-for-gene recognition of the primary immunizing challenger [2]. However, SAR has also been reported to be activated following exposure to nonpathogenic or virulent pathogens [14]. SAR can be both activated by, and is effective against, a variety of microorganisms including viruses, bacteria, fungi, and oomycetes [15–17]. Additionally, root exposure to incompatible rhizobacteria and foliar insect oviposition also activate SAR-like responses [18,19].

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Mobile inducers of SAR

During SAR, primary infection results in the generation and systemic transport of the SAR signal within 3–6 h, at least in cucumber and Arabidopsis [16,20]. The infected leaf continues to generate and transmit

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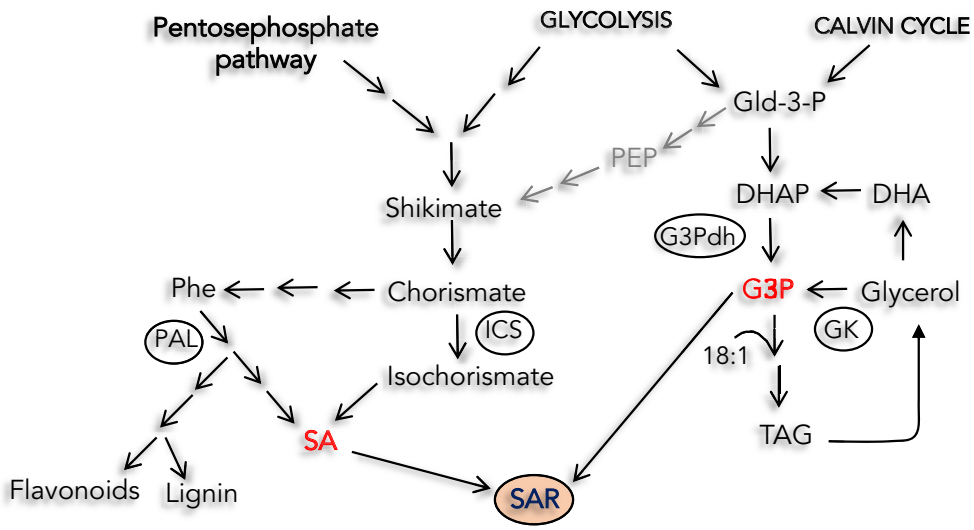

Figure 1. Biochemical reactions participating in G3P and SA metabolism

Abbreviations used are oleic acid (18:1), gycerol-3-phospate (G3P), glyceraldehyde-3-phosphate (Gld-3-P), dihydroxyacetone (DHA), DHA phosphate (DHAP), triacylglycerol (TAG), glycerol kinase (GK), G3P dehydrogenase (G3Pdh), phenylalanine (Phe), phenylalanine ammonia lyase (PAL), isochosrismate synthase (ICS). These pathways also contribute to the synthesis of aromatic amino acids, flavonoids and lignin. Single arrows indicate single step synthesis. Multiple arrows simply indicate that intermediate reactions required, number of arrows are not reflective of number of intermediate steps.

the graft transmissible signal(s) throughout the plant beyond this timeframe [15,21,22]. Systemic signal movement occurs in an acropetal manner and is therefore thought to be transported mainly via the phloem [8,23,24]. Chemically induced SAR has been shown to be effective against root pathogens and an important SAR inducer, glycerol-3-phosphate (G3P), is transported from the shoot to roots during restriction of genetically incompatible rhizobia [18,25]. While the identity of a specific mobile signal(s) that confers SAR remains unresolved, it appears to be conserved between highly diverse plants [18,26]. The mobile signal either comprises proteinaceous component(s) or requires them for movement/functionality [20]. To date, numerous SAR-inducing chemicals have been identified; they confer systemic resistance when applied exogenously and are required for pathogen-induced SAR. These include, salicylic acid (SA, [27]) and its derivative methyl SA (MeSA, [28]), azelaic acid (AzA, [29–31], G3P [20,30], dehydroabietinal (DA, [32]), the free radicals nitric oxide (NO) and reactive oxygen species (ROS) [33], pipecolic acid (Pip) [34–36] and its derivative *N*-hydroxy Pip (NHP) [37,38], pinene volatiles [13,39], and extracellular (e)NAD(P) [40]. Some of these exhibit systemic mobility or are considered mobile due to their volatile nature and operate in a bifurcate pathway, with SA regulating one branch and, Pip, NO, ROS, AzA, and G3P regulating the other [3,5,33,41]. These chemical signals also undergo additional nonlinear interactions among them [13,20,29,30,42,43]. Here, we restrict our discussion to the SAR-related synthesis and transport of G3P and SA.

G3P synthesis

G3P, a three-carbon phosphorylated sugar, is the obligatory precursor of all glycerolipid biosynthesis in most organisms. In plants, G3P is synthesized via the glycerol kinase (GK)-mediated phosphorylation of glycerol, or the G3P dehydrogenase (G3Pdh)-mediated reduction of dihydroxyacetone phosphate (DHAP, Figure 1). DHAP itself is derived from glycolysis and the Calvin cycle via glyceraldehyde-3-phosphate (Gld-3-P) and the activity of triosephosphate isomerase, or from the conversion of glycerol to dihydroxacetone by glycerol dehydrogenase, followed by phosphorylation of DHA to DHAP by DHA kinase. G3P is catabolized either upon its conversion to glycerol by G3P phosphatase or its utilization in the synthesis of membrane lipids (glycerolipids) and triacylglycerol (TAG). TAG can in turn be hydrolyzed to generate glycerol. Thus, G3P is an important node between plant carbohydrate and lipid metabolism. In Arabidopsis, G3P enzymatic activities comprise multiple isoforms in different subcellular locations; the total G3P pool in Arabidopsis is derived from five G3Pdh isoforms located in the cytoplasm, mitochondria or plastids, and a single cytosolic GK [20]. Three of these isoforms, two chloroplastic and one cytosolic, contribute nonredundantly to SAR. Additionally, the cytosolic GK is also a nonredundant contributor of SAR-associated G3P in Arabidopsis [20].

G3Pdh and GK also contribute nonredundantly to SAR in wheat and soybean [18,20,44]. This indicates that both the plastidal and cytoplasmic G3P pools contribute to SAR. Pathogen elicitor-induced increase in *GK* and *G3Pdh* expression, and G3P accumulation has also been reported in red algae, suggesting an evolutionarily conserved role for GK- and G3Pdh-derived G3P in pathogen defense [45].

During SAR, pathogen infection results in the rapid accumulation of Pip, which in turn promotes NO accumulation via an unknown mechanism [34,36,46]. NO functions in a feed-back loop with ROS, which hydrolyze 18 carbon unsaturated fatty acids (FA), present on the chloroplastic lipids monogalactosyldiacylglycerol (MGDG) and digalactosyldiacylglycerol (DGDG) to generate AzA [30,47,48]. AzA then induces the expression of *Gly1* and *GK*, which results in G3P accumulation [29]. Thus, the *noa1 nia1/2* double mutants, which are defective in the NO-generating NOA1 (NO associated 1) and NIA1/NIA2 (nitrate reductases), cannot accumulate normal levels of pathogen-responsive AzA or G3P and are SAR defective [33]. These mutants are competent in SA accumulation and response, and exogenously supplied G3P is sufficient to rescue their SAR defect [33]. Like NO generation, defects in the major chloroplastic lipids MGDG and DGDG also affect pathogen-responsive AzA and G3P accumulation [30]. Pathogen-responsive G3P accumulation also requires two lipid transfer-like proteins, DIR1 (Defective in induced resistance 1) and AZI1 (AzA-induced 1) [29,31,49]. Conversely, lack of G3P reduces *DIR1* and *AZI1* transcript levels, suggesting a feed-back regulatory loop between G3P, DIR1, and AZI1 [29].

G3P transport

G3P is systemically mobile in the presence of DIR1, although direct binding between the two has not been detected [50]. G3P is rapidly metabolized in the infected leaf and both G3P and its derivative are transported systemically. The thin-layer chromatography (TLC) separable G3P derivative(s) is bioactive, though its identity is yet unknown [50]. Notably, shoot to root mobility of G3P that is important for genetic incompatibility to rhizobacteria also involves its derivative, which exhibits similar mobility to the G3P-derivative induced during SAR [18]. It is not known whether G3P mobility during rhizobia incompatibility also requires DIR1-like protein(s) in soybean. Interestingly, DIR1 is also mobile during SAR and this requires G3P [50,51]. It is possible that protein aggregates comprising DIR1 contribute to the systemic mobility of G3P because DIR1 interacts with AZI1, which is also systemically mobile and required for G3P (as well as AzA [31])-induced SAR [29]. In fact, the plasmodesmata (PD), one of the subcellular locations of DIR1 and AZI1, is the preferred intercellular transport route of G3P (Figure 2) [29,42,50–52]. This symplastic transport of G3P involves specific isoforms of PD-localizing proteins (PDLP), which regulate PD gating. Interestingly, SAR is inhibited by a mutation in *PDLP5*, which increases PD opening, as well as by overexpression of *PDLP5*, which promotes PD closure. This indicates that tight regulation of PD aperture is key for SAR activation. The PDLP5 protein associates with PDLP1 and both proteins regulate the endoplasmic reticulum (ER), PD, and chloroplastic localization of AZI1. Normal transport of G3P in *pdlp1* and *pldp5* plants suggests that these proteins likely regulate SAR by altering the localization of AZI1. The function of chloroplast-localized AZI1 protein remains unknown at present.

SA synthesis

SA, a small phenolic phytohormone, regulates multiple biological processes in plants including SAR. SA is generated via the shikimic acid pathway that bifurcates into two branches after chorismic acid synthesis. In one branch, SA is generated via phenylalanine and cinnamic acid intermediates through the activity of phenylalanine ammonia lyase (PAL). In the other branch, SA is generated by isochorismate synthase (ICS), which converts chorismic acid to IC in the plastids (Figure 1) [53,54]. The multidrug and toxin extrusion transporter EDS5 (Enhanced disease susceptibility 5) exports IC to the cytosol [55–57], where it is conjugated to glutamate via the GH3 acyl adenylate-thioester-forming enzyme PBS3 (avrPphB susceptible 3), to form isochorismate-9-glutamate. SA is generated either by spontaneous decay of isochorismate-9-glutamate, or via the activity of EPS1 (enhanced Pseudomonas susceptibility 1), a BAHD (referring to the first four biochemically characterized enzymes of this group) acyltransferase [57,58]. These studies indicate that while the SA biosynthesis pathway is initiated in the chloroplast, SA itself is generated in the cytosol. Contrary to this inference, transgenic plants expressing a bacterial salicylate hydroxylase (nahG, converts SA to catechol) specifically in the chloroplast, are unable to accumulate pathogen-responsive SA [59]. One possibility is that chloroplastic overexpression of nahG interferes with the enzymatic activities that constitute the initial SA biosynthetic pathway. Another possibility is that other metabolic changes in the NahG-expressing plants feed-back regulate SA levels. For instance, NahG plants not only accumulate catechol, which can interfere with some defense responses, but also contain reduced levels of the phytoalexin, camalexin [60,61].

The Arabidopsis genome encodes two isoforms of ICS (ICS1 and ICS2) and four isoforms of PAL (PAL1–4) [62,63]. The *ics1* mutant (also referred to as *sid2* for SA induction deficient 2 [61]) accumulates 90–95% less SA than wild-type

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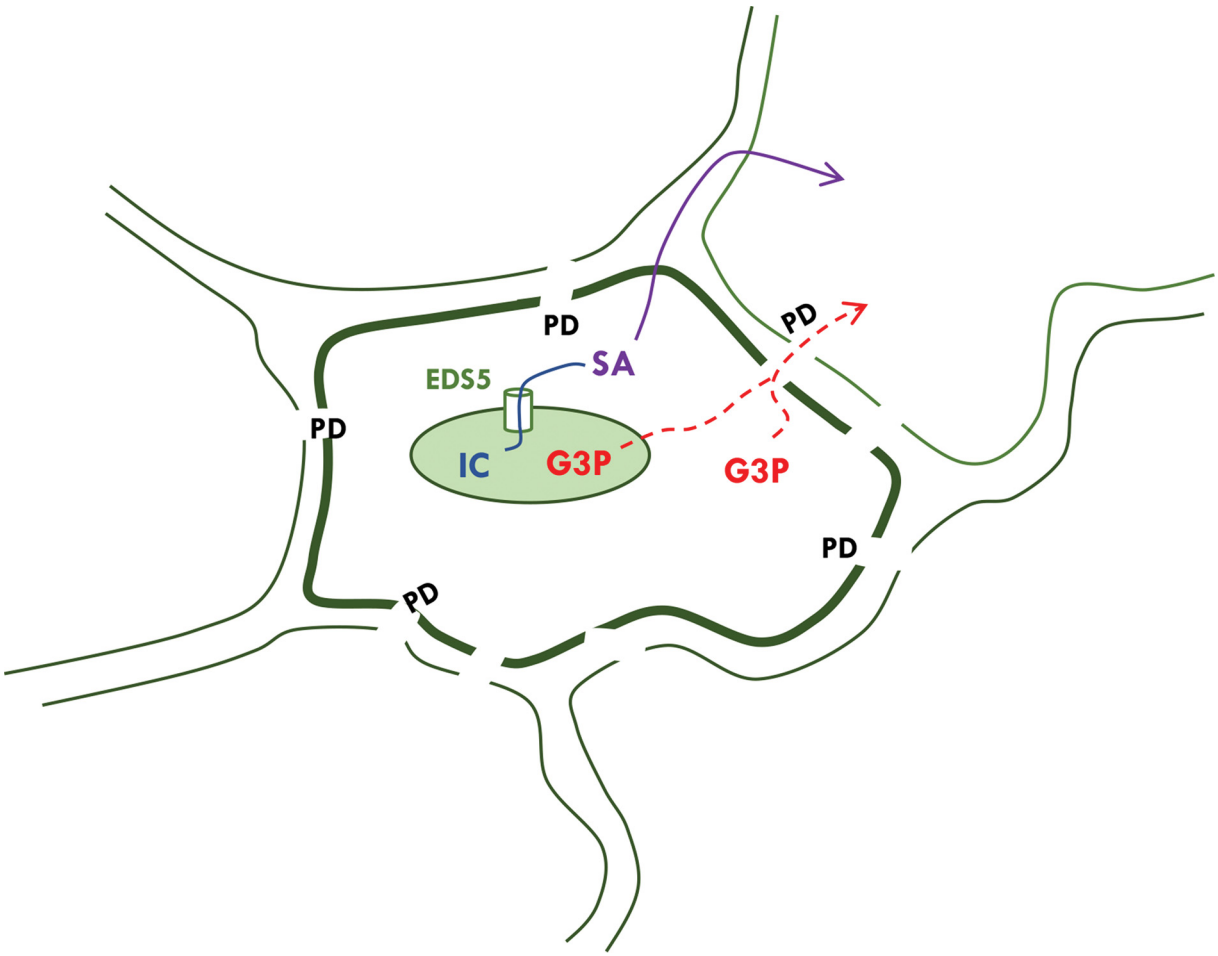

Figure 2. Intercellular transport of SA and G3P

SA biosynthesis begins in the chloroplast (green oval). Isochorismate (IC) is exported via EDS5 and converted to SA in the cytoplasm. SA traverses the plasma membrane (thicker green line) multiple times to move (purple arrow) preferentially through the apoplast. G3P synthesized in the chloroplast and cytoplasm contributes to SAR by moving preferentially through the PD. Cell size, organelles, transporters etc. are not to scale.

plants after pathogen infection, while the *ics1 ics2* double mutant accumulates 96% less SA than wild-type plants after exposure to ultraviolet light [63]. This indicates that ICS1 is the major functional ICS isoform and although both PAL and ICS activities contribute to stress-responsive SA generation in Arabidopsis, 96% of pathogen-responsive SA is derived from the ICS branch. Importantly, mutations in either *ICS1*, *PBS3*, or *EDS5* inhibit SA biosynthesis and abolish SAR in Arabidopsis [53,58]. Additionally, several transcription factors (TFs), including SARD1 (SAR-deficient 1) and CBP60g (Calmodulin Binding Protein 60g), CAMTA (Calmodulin-Binding Transcription Factor) 1 and 2, and CHE (Circadian Clock Associated 1 Hiking Expedition), regulate SAR-associated SA accumulation by regulating *ICS1* expression [64–66]. While SARD1, CBP60g, and CHE bind the ICS1 promoter and are positive regulators of *ICS1* expression and pathogen-responsive SA accumulation, the CAMTA TFs are negative regulators of SA synthesis and SAR [64–66]. Because the *che* mutant is only defective (lower than wild-type levels) in systemic SA accumulation, it was suggested that CHE is important for systemic SA synthesis. However, recent work demonstrating the importance of SA systemic transport (see Section on SA transport) [67] poses the possibility of SA transport defects in the *che* mutant.

Mutations in *PAL* also affect pathogen-responsive SA accumulation, *albeit* to a lesser extent; the quadruple *pal* mutant of Arabidopsis accumulates 50% less SA than wild-type plants after pathogen infection [62]. This suggests that PAL and ICS may have cooperative functions in stress-related SA biosynthesis. Indeed, soybean lines defective for either PAL or ICS are equally susceptible to pathogen infection and PAL-mediated SA biosynthesis is important

for nematode resistance in wheat [68,69]. On the other hand, PAL is likely the major contributor of defense-related SA in rice because knock-down of the *PAL6* isoform (total nine in rice) results in 60% reduction in SA content and increased pathogen susceptibility, despite up-regulation of *ICS* expression in these plants [70]. One possibility is that defects in downstream metabolites derived from the PAL pathway (like lignin) may affect the normal functioning of the ICS branch. Notably, silencing *PAL* attenuates SAR, whereas overexpression of *PAL* enhances SAR against tobacco mosaic virus in Arabidopsis [71]. Similarly, PAL is essential for both pathogen and incompatible rhizobia-induced SAR in soybean [18], indicating that SA-derived from both ICS and PAL branches contribute to SAR and SAR-like responses.

Several other SAR inducers, including DA, pinene volatiles, NHP, and (e)NADP, can affect SA levels suggesting that these function in the SA branch of the SAR signaling pathway [32,39]. NHP and eNAD(P) are expected to feed into the SA branch; NHP and NADP induce expression of the SA marker genes *PR* (pathogenesis related)-1, *PR-2* [38,72], though the specificity of these responses is unclear. In addition, similar to SA synthesis, the CAMTA TFs also suppress NHP accumulation via negative regulation of *SARD1* and *CBP60g* [73]. Interestingly, Pip, which serves as a precursor to NHP, does not induce SA [36,38].

Both SA and NHP are glycosylated by uridine diphosphate (UDP)-dependent glycosyltransferase (UGT76B1) [74–77]. A loss-of-function mutation in *UGT76B1* increases NHP and SA levels, and thereby enhanced pathogen resistance. In Arabidopsis, SA can also be glycosylated by UGT74F1, and the homologous UGT74F2 converts SA to SA-glucose esters [78,79]. Notably, ugt76b1, *ugt74f1* single and double mutant plants accumulate very similar levels of SA and SAG [78], suggesting that they might not differ significantly in their substrate preference. Overexpression of *UGT76B1* reduces free NHP and SA levels and attenuates the SAR response. Like SA, the SA derivative MeSA also undergoes glycosylation to form MeSA 2-O-β-d-glucoside, and this reaction is catalyzed by UGT71C3 [80]. UGT71C3 is specific to MeSA and does not act on SA. A mutation in *UGT71C3* enhances the SAR potency, while its overexpression compromises SAR. These results suggest an important role for MeSA in SAR. Likewise, mutations in, or chemical inhibition of the methyl esterase SABP2 (SA-binding protein 2), which converts MeSA to SA, inhibit SAR. Grafting studies indicate that SABP2 activity in the distal leaves is essential for SAR [28]. The possibility that MeSA has additional signaling roles in SAR warrants further investigation, especially given the fact that SA itself is systemically mobile (see below).

SA transport

Grafting studies between wild-type and transgenic *nahG*-expressing tobacco plants had resulted in the conclusion that although presence of SA in the distal tissue is essential for SAR, SA movement from infected to distal tissue is not [81]. This led to the widely accepted belief that SA is not a mobile signal during SAR. However, recent work demonstrating systemic mobility of SA in wild-type as well as NahG plants has discounted this notion [67]. Like G3P and AzA, only a small percentage of SA is transported to distal tissue [20,29,42,67]. However, despite being much smaller (138.12 Da) than the passive size exclusion limit of PD (800–1000 Da), and unlike the PD mobile and size comparable G3P (172.07 Da) or AzA (188.12 Da), cell-to-cell transfer of SA occurs preferentially via the apoplast (space between cell wall and plasma membrane, Figure 2) [42]. In fact, apoplastic transport of SA precedes its accumulation in the cytosol. Due to its low pKa (negative log of acid dissociation constant) value (2.98), the COOH group of SA predominantly exists in its deprotonated form (COO-) at the neutral to slightly alkaline pH (∼7–7.5) of the cytosol [67]. Therefore, it is possible that pathogen-induced SA is exported to the apoplast in a pH- and carrier-dependent manner to avoid a rapid increase in cytosolic pH from protons being released by the accumulating SA [67,82]. Indeed, protoplast uptake of SA is higher at acidic pH and can be inhibited by proton pump inhibitors [67]. Ca^{2+} may also be involved in SA transport because EGTA can inhibit export of SA from protoplasts and this is reversible by increasing exogenous Ca^{2+} concentration [83]. Notably, even though SA preferentially moves through the apoplast, it does regulate PD gating and thereby symplastic transport of molecules transported via PD [42,84]. This suggests the involvement of a plasma membrane-localized SA transporter that aides the exit and entry of SA into the cytosol.

Systemic SA transport also requires an intact cuticle because a portion of total SA is partitioned to cuticle wax [67]. Cuticle defective mutants exhibit impaired SA transport to distal tissue and are compromised in SAR [67,85]. Reducing water loss in such mutants by using high relative humidity growth conditions can restore systemic SA transport and SAR [67]. Thus, cuticle defects inhibit SA transport through the apoplast because increased transpiration in these mutants reduces apoplastic hydrostatic pressure and shunts SA into the cuticle. Notably, MeSA and SA differ in their abilities to rescue the SAR defect of different cuticle defective mutants [85,86]. Perhaps different cuticle wax components aid diffusion across the cuticle of exogenously applied SA [82] versus MeSA. Such components may also have different consequences on SA transport because cuticle defective mutants can differ in their abilities to generate

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or perceive the SAR signal [85,86]. For instance, mutations in ACP4 (Acyl carrier protein 4), a critical component of *de novo* FA biosynthesis and initiation of lipid synthesis, reduce levels of wax components (FA, alkanes, primary alcohols) as well as cutin aliphatic monomers [85]. The SAR defect of the cuticle defective *acp4* mutant, which can generate the SAR mobile signal but cannot perceive it, can be rescued by exogenous MeSA but not SA [85]. In contrast, mutations in some ACBP (acyl CoA-binding proteins) isoforms, which are involved in intracellular transport of FA/lipid precursors, increase cutin wax components but decrease cutin aliphatic monomers levels. The SAR defect of the cuticle defective *acbp* mutants, which perceive the SAR mobile signal but do not generate it, can be rescued by either MeSA or SA [86]. It is possible that specific cuticle wax components have additional yet unexplored functions in SAR, besides regulating SA transport through maintaining cuticle integrity.

Conclusions

Recent focus on understanding SAR has greatly advanced knowledge of the molecular mechanisms underlying SAR. Still, there is much we do know about this mode of immunity that was first recorded nearly a century ago. Many questions remain unanswered. For example, localized application of either SA or G3P activates systemic resistance in wild-type plants, without inducing accumulation of the reciprocal compound. This suggests that while SA and G3P do accumulate in response to pathogen infection, accumulation is not essential for SAR. This in turn raises the possibility that pathogen-responsive systemic transport of an existing molecule(s) may be sufficient for SAR, and both SA and G3P might facilitate transport and/or stability of this molecule. How does AzA induce G3P-synthesizing gene expression? How does chloroplast-generated G3P access the PD during systemic transport? How do G3P, DIR1 and AZI1 feedback regulate each other, and what is the nature of the DIR1/AZI1 interactome that aids systemic mobility of G3P? What is the identity of the SA transporter and do cutin components affect transport and/or activity of other SAR inducers besides SA? If SA transport is defective in the *acp4* mutant, how does it generate the SAR signal? Does this support the assumption that transport of an existing molecule is key for SAR? What is the importance of MeSA when SA itself is mobile? If MeSA functioned only by being converted to SA, why does it exhibit differential ability to rescue SAR in different cuticle defective mutants? And finally, does selective breeding for genetic resistance affect the plant's ability to manifest SAR under varied conditions?

Summary

- Several structurally diverse chemicals function as mobile regulators of SAR via a central bifurcate signaling pathway superimposed with additional nonlinear interactions among some of them.
- The biosynthesis of key SAR inducers originates through central carbohydrate and fatty acid metabolic pathways.
- The PD, apoplast, and the cuticle are essential components of the transport routes for key SAR inducers.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

ACBP, acyl CoA-binding protein; ACP4, acyl carrier protein 4; AzA, azelaic acid; AZI, AzA-induced 1; CAMTA, calmodulin-binding transcription factor; CBP, calmodulin binding protein; CHE, circadian clock associated 1 hiking expedition; DA, dehydroabietinal; DGDG, digalactosyldiacylglycerol; DHA, dihydroxyacetone; DHAP, dihydroxyacetone phosphate; DIR1, defective in induced resistance 1; EDS5, enhanced disease susceptibility 5; EPS1, enhanced pseudomonas

susceptibility 1; FA, fatty acids; G3P, glycerol-3-phosphate; G3Pdh, G3P dehydrogenase; GK, glycerol kinase; Gld-3-P, glyceraldehyde-3-phosphate; IC, isochorismate; ICS, isochorismate synthase; MeSA, methyl SA; MGDG, monogalactosyldiacylglycerol; NHP, N-hydroxy Pip; NOA1, NO associated 1; NO, nitric oxide; PAL, phenylalanine ammonia lyase; PBS3, avrPphB susceptible 3; PD, plasmodesmata; PDLP, PD-localizing protein; Phe, phenylalanine; Pip, pipecolic acid; PR, pathogenesis related; ROS, reactive oxygen species; SA, salicylic acid; SABP2, SA-binding protein 2; SAR, systemic acquired resistance; SARD1, SAR-deficient 1; sid2, SA induction-deficient 2; TAG, triacylglycerol; TF, transcription factor; TLC, thin-layer chromatography; UDP, uridine diphosphate.

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