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# The Quest for Long-Distance Signals in Plant Systemic Immunity

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**Plants induce long-lasting systemic immunity after local pathogen attack by emitting resistance-priming signals from infection sites. A number of plant molecules have been proposed as mobile factors for this response, but many do not fully satisfy criteria for timing and action in systemic immunity. Azelaic acid has been identified as a pathogen-induced metabolite in *Arabidopsis* vascular sap that has several properties of a long-distance resistance-priming signal.**

Higher plants have evolved a multilayered innate immune system that prevents most microbial pathogens from invading tissues and causing disease. This immune competence depends on a large repertoire of germ line-encoded receptors that trigger resistance in attacked cells by recognizing particular pathogen molecules (1). A local immune response against pathogens is rapid (a matter of minutes to hours) and is accompanied by extensive host cell reprogramming that can often lead to controlled plant cell death (2). Researchers have appreciated for many years that plants also possess a kind of immunological “memory” by which a local resistance response leads to protection of the whole plant against subsequent pathogen infection over an extended period (days to weeks) (3). We know that this systemic immunity depends on the generation of long-distance signals by infected tissues that “prime” defense responses in uninfected, distal cells (3, 4). Priming, a mechanism by which plants induce an accelerated resistance response if pathogens attack a second time, is probably a valuable survival strategy for plants in nature because it avoids constitutive activation of energy-consuming defenses (5). There is now a lively debate about the nature and modes of action of plant mobile resistance signals. A paper from the group of Jean Greenberg at the University of Chicago (6) identifies a small molecule called azelaic acid in the model plant *Arabidopsis* that accumulates in vascular sap in response to bacterial infection. This dicarboxylic acid has a number of characteristics consistent with it being a component

of defense priming in plant systemic immunity. Results of the study, together with data from other labs, provide some important leads to how an exquisitely poised innate immune system operates at the level of individual cells and the whole plant.

One essential component of systemic acquired resistance (SAR) (a form of systemic immunity effective against biotrophic pathogens that thrive on living host tissues) is the phenolic molecule salicylic acid (SA) (3). Pathogen-inducible SA is derived mostly from isochlorismate in leaf chloroplasts, and accumulation of SA in local and systemic tissues is needed for the induction of SAR (7, 8). Results of grafting experiments in tobacco argued against SA itself being the mobile resistance-inducing factor (9). The search was therefore on for other molecules that would fit the bill of a long-distance defense signal. SA and SA-related benzoic acids can be converted to various conjugated forms that have different biophysical properties and activities but are otherwise poorly defined (10–12). One volatile SA derivative, methyl-SA (MeSA), is produced locally in large amounts in response to pathogen attack and is found at much lower amounts in the sap of vascular tubes that connect leaves with the shoot (13–15). Most of the MeSA is released into the air, where it becomes part of a volatile blend determining plant-insect ecology (16, 17). Conversion of SA to MeSA is catalyzed by a methyl transferase (14, 18). Also, a tobacco SA-binding protein (an esterase called SABP2) has been identified that can convert MeSA back to SA and is product-inhibited by SA (19). Related SABP2 proteins have been found in *Arabidopsis* (20). Results from studies in tobacco that manipulated SA methyl transferase and SABP2 activities pointed to MeSA being a critical long-distance signal

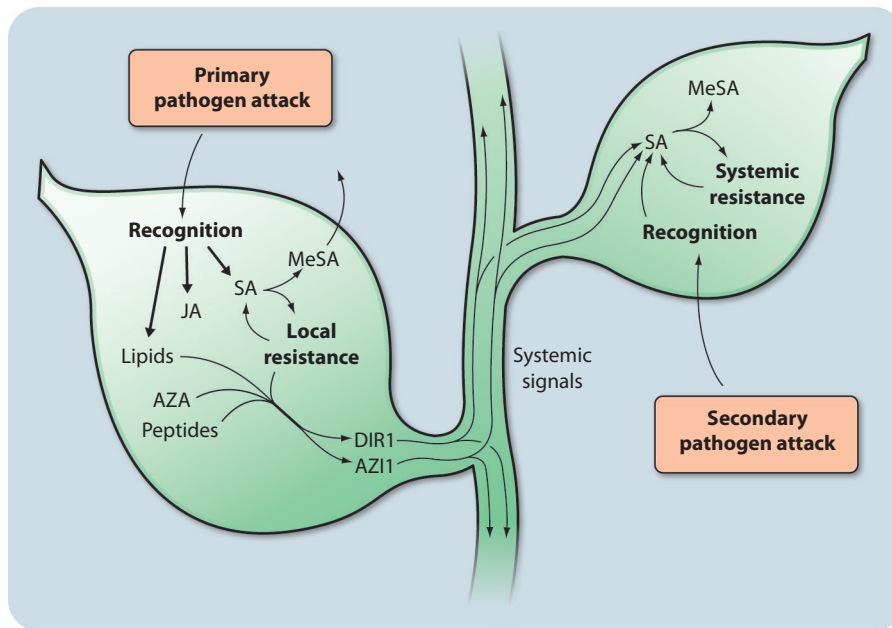
in SAR (14). However, other experiments using mutants of *Arabidopsis*—including one in the SA-converting methyl transferase gene that depletes pathogen-induced MeSA production to below the detection limit (18)—argue against MeSA being the active mobile component in this plant species (15). Rather, the data suggest that the induction of systemic immunity is associated with de novo SA biosynthesis and signaling in secondary leaves (15) (Fig. 1). The relevance of MeSA as a broadly conserved plant defense signal is therefore brought into question. A different study reported early, transient accumulation of the oxygenated fatty acid hormone jasmonic acid (JA) in *Arabidopsis* vascular sap after bacterial inoculation of leaves and found that JA signaling mutants have diminished SAR (21). JA and certain JA conjugates are pivotal signals during plant development and in defense against insect feeding or attack by necrotrophic pathogens (22). However, analyses of *Arabidopsis* JA biosynthetic and signaling mutants tend to uncouple JA production and signaling from systemic immune competence and thus do not support a role of JA or its derivatives in SAR (15, 23).

The work of Jung *et al.* (6) considers how a newly discovered metabolite, azelaic acid, might contribute to plant systemic immunity. The authors first established that vascular sap (otherwise known as petiole exudates) derived from bacteria-infected leaves was biologically active in that it promoted resistance to virulent bacteria when applied to healthy leaves several hours before pathogen inoculation. Furthermore, the exudates failed to induce resistance in a number of known *Arabidopsis* mutants defective in SAR, indicating that the enhanced immune response requires components of systemic resistance. The team then used gas chromatography linked to mass spectrometry to identify small molecules differentially accumulating in petiole samples from mock- and bacteria-inoculated plants and isolated azelaic acid. By itself this compound does not have potent antimicrobial activity, but when sprayed onto leaves, it behaves as a resistance-priming molecule by stimulating the plant’s capacity to activate defenses once a pathogen attacks. It could be argued that azelaic acid promotes resistance in a rather nonspecific manner by, for example, creating an imbalance in stress hormone signaling networks (24). However, Jung *et al.* show that azelaic acid application also

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induces resistance through known SAR components, and the molecule displays some structural specificity because related dicarboxylic acids could not promote resistance (6). Moreover, azelaic acid can be transported in the plant, as shown by local application of a deuterium-labeled derivative. These characteristics, combined with an ability to amplify production of SA and expression of SA-response genes in leaves only after infection, fit the criteria of a resistance-priming factor.

The mechanism and timing of azelaic acid action in plant systemic immunity are unclear. Also, its biosynthesis needs to be defined, and it would be interesting to know how widespread the molecule is in different plant species. We assume that azelaic acid comes from the plant, because Jung and colleagues were careful to remove contaminating bacteria from petiole exudates; however, we cannot exclude a microbial origin at this point. As to its position in a systemic resistance signaling network, Jung *et al.* offer some ideas based on characterization of several *Arabidopsis* defense mutants (6). Notably, insertion mutants of one gene, *AZII* (*AZELAIC ACID INDUCED 1*), which is rapidly and transiently responsive to active exudates or azelaic acid application, could not induce a systemic immune response, although local resistance to infection remained intact. In essence, *azi1* mutants could still recognize a defense-priming signal produced by wild-type plant exudates, but sap produced in mutants in response to bacteria failed to protect wild-type plants against infection. Thus, *AZII* appears to be important for the local production, modification, or translocation of a mobile SAR signal (Fig. 1). *AZII* belongs to a family of predicted secreted protease inhibitor or lipid transfer proteins (LTPs), and its overexpression is associated with enhanced resistance to a necrotrophic fungus (25). It is notable that a different *Arabidopsis* LTP-like gene, *DIR1*, was identified previously as a component of SAR (26). The *dir1* mutant is also insensitive to azelaic acid treatment (6), which suggests that *DIR1* activity is required, in addition to *AZII*, for azelaic acid-induced resistance (Fig. 1). Given that azelaic acid has some mobility in the vasculature, it is conceivable that it modifies or activates a lipid that can be mobilized by extracellular LTPs at various sites responding to pathogen attack. An expanding body of evidence suggests that plastid-derived glycerolipids contribute together



**Fig. 1.** A signaling scheme in plant systemic immunity. Pathogen recognition by immune receptors in an attacked primary leaf leads to accumulation of SA and other potential defense metabolites (such as JA and lipids). A de novo SA generation and response cycle is important for resistance in locally infected leaves and in secondary leaves upon subsequent pathogen recognition. SA can be converted to MeSA (which is unlikely to be the vascular signal because of its volatility) and to other SA derivatives, which may have roles in partitioning and mobilizing resistance intermediates. Current evidence points to a multifactorial systemic signaling process requiring locally produced azelaic acid (AZA) in combination with lipid-derived molecules or lipopeptides (or both). Emission of systemic resistance signals from primary infected leaves requires LTP-like proteins (such as *DIR1* and *AZI1*) and leads to priming of defenses in tissues against further pathogen infection. The molecular mechanisms underlying immunological memory in systemic immune responses are still unclear.

with *DIR1* to the establishment of SAR (23, 27). Thus, we can picture the generation of a modified lipid or possibly lipopeptide (28, 29) as a systemic resistance signal (Fig. 1). Such a multifactorial defense system would need proper temporal and spatial integration to confer lasting disease resistance.

Our understanding of how plants coordinate local and systemic immune responses is still fragmentary. The results of Jung *et al.* and other groups described here provide a framework for more detailed studies on cell-nonautonomous signaling and long-distance transport of mobile signals in inducible resistance pathways in plants. These may answer the question of how mobile molecules contribute to the induction of plant immunological “memory” needed to induce defenses against pathogens after a certain lapse of time. Emerging evidence points to changes in chromatin as a means of storing such information (30, 31). Reversible chromatin modifications might

allow particular transcription-activating or transcription-repressing complexes to act in a context-dependent manner after a second pathogen trigger (32, 33). Such mechanisms would enable the plant to maintain defense flexibility in a fluctuating environment with varying pathogen pressures. The ability to turn resistance pathways on and off according to need is likely to be a strong evolutionary driving force in plant fitness and survival.

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