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Fatty acids and early detection of pathogens

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Early in interactions between plants and pathogens, plants recognize molecular signatures in microbial cells, triggering a form of immunity that may help resist infection and colonization by pathogens. Diverse molecules provide these molecular signatures, called pathogen-associated molecular patterns (PAMPs), including proteins, polysaccharides, and lipids. Before and concurrent with the onset of PAMP-triggered immunity, there are alterations in plant membrane lipid composition, modification of membrane fluidity through desaturase-mediated changes in unsaturated fatty acid levels, and enzymatic and non-enzymatic genesis of bioactive lipid mediators such as oxylipins. These complex lipid changes produce a myriad of potential molecular signatures that are beginning to be found to have key roles in the regulation of transcriptional networks. Further, research on fatty acid action in various biological contexts, including plant–pathogen interactions and stress network signaling, is needed to fully understand fatty acids as regulatory signals that transcend their established role in membrane structure and function.

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Introduction

Fatty acids (FAs) and fatty acid-metabolites are not only major structural and metabolic constituents of the cell but they also function as modulators of a multitude of signal transduction pathways evoked by environmental and developmental stimuli. Emerging evidence identifies fatty acids as second messengers and regulators of signal transducing molecules or transcription factors. Many functions of FAs in living organisms are linked to changes in membrane lipid composition and adjustment of membrane fluidity, largely mediated by desaturases, as critical for the function of integral membrane proteins that ultimately affect cell signaling mechanisms [1,2]. In addition to structural signaling, FAs also have regulatory activities upon their release by lipases, followed by enzymatic and non-enzymatic generation of bioactive lipid mediators such as oxidatively modified lipids which specifically trigger diverse cellular processes and play an important role in numerous innate immune functions [3,4]. In a broader context, FAs can also modulate signal transduction pathways by functioning as hydrophobic hormones where they bind to and regulate the activity of receptor proteins controlling major regulatory networks that impact cell metabolism and signaling systems [1,5,6]. In addition, ample studies have established that specific FAs also interact with diverse transcription factors to provide direct or indirect regulation of primary organismal physiology [7–9]. The effects of FAs on gene expression are also being found to extend to post-transcriptional regulatory mechanisms such as directly mediating the rate of mRNA turnover for specific transcripts [1,6,10,11]. Thus, FAs because of their chemical diversity have the potential to provide an intricate regulatory capacity in many cellular processes.

In contrast to the vast body of knowledge of fatty acid signaling in animals, this information is rather limited in plants. Intriguingly however, despite shared aspects of FA signaling in plants and animals, mechanistic features unique to plants are now being recognized. Detailed understanding of FA signaling in plants will therefore provide information critical for revealing these mechanistic differences across kingdoms.

Structural properties of fatty acids in relation to disease and defense

A FA function is specifically determined by the length, position and desaturation level of its lipophilic acyl chain; therefore it is critical to quantitatively determine how different fatty acids alter functional properties of a

multitude of signaling components and ultimately cellular responses.

Levels of free fatty acids increase in response to various stresses and play a pivotal role in plant–microbe interactions. For example, fatty acid synthesis in the obligate biotrophism of arbuscular-mycorrhizal fungi is dependent on plant-derived C16 FAs [12]. Furthermore, eggplants with enhanced levels of palmitoleic acid (16:1) exhibited increased resistance to *Verticillium dahlia*, suggesting increasing the production of plant 16:1 as a viable approach to enhance crop resistance to fungal diseases [13]. Seed fatty acid composition is also suggested to be a component of pathogen susceptibility and seed colonization. For instance colonization of soybean seeds by *Cercospora kikuchii* is found to be correlated with the oleic acid (18:1)/linoleic (18:2) ratio, and that mid-18:1 soy genotypes in the field are more extensively colonized by this fungal pathogen [14]. Interestingly, mounting evidence suggests that reduced levels of 18:1 in the chloroplast caused by a mutation in *SUPPRESSOR OF SA INSENSITIVITY OF npr1-5* (*SSI2*), encoding one of the stearoyl-ACP desaturase isoforms, results in the constitutive activation of defense responses [15–17]. Reducing the level of 18:1 leads to a stabilization of NITRIC OXIDE ASSOCIATED1 (NOA1), an enzyme that regulates nitric oxide (NO) levels and thus increases endogenous NO levels. This triggers transcriptional upregulation of NO responsive nuclear genes, thereby activating disease resistance. In fact application of NO or reduction in 18:1 levels induces the expression of similar sets of nuclear genes [18••]. Thus, NOA1/18:1 may provide a direct mechanistic link between membrane integrity and transcriptional regulation of plant defense responses. 18:1 is also found to be a stimulator of the signaling enzyme phospholipase D (PLDδ), which has an anti-cell-death function [19]

Polyunsaturated FAs (PUFAs), major constituents of membrane lipids, are released from membranes by lipases in response to attacks by biotic agents. These FAs play a pivotal role in plant–microbe interactions either directly as free FAs or through the function of oxylipins, the vast and diverse family of oxygenated derivatives of PUFAs (Figure 1). As free FAs, 18:2 levels partly regulate development, seed colonization, and mycotoxin production by *Aspergillus spp.* [20]. Moreover, elevation of 18:2 levels elicit enhanced resistance to attack by the fungal pathogen, *Colletotrichum gloeosporioides* [21].

Trienoic FAs (TAs), the major polyunsaturated fatty acid species in the membrane lipids in plant cells, are involved in defense responses against pathogens, and mutant plants compromised in TA production are more susceptible to *Pseudomonas syringae* pv. *tomato* (*Pst*). In particular the most abundant TA, linolenic acid (18:3) is reported to directly activate NADPH-oxidase and, by extension, to generate reactive oxygen intermediates after inoculation with *Pst* [22].

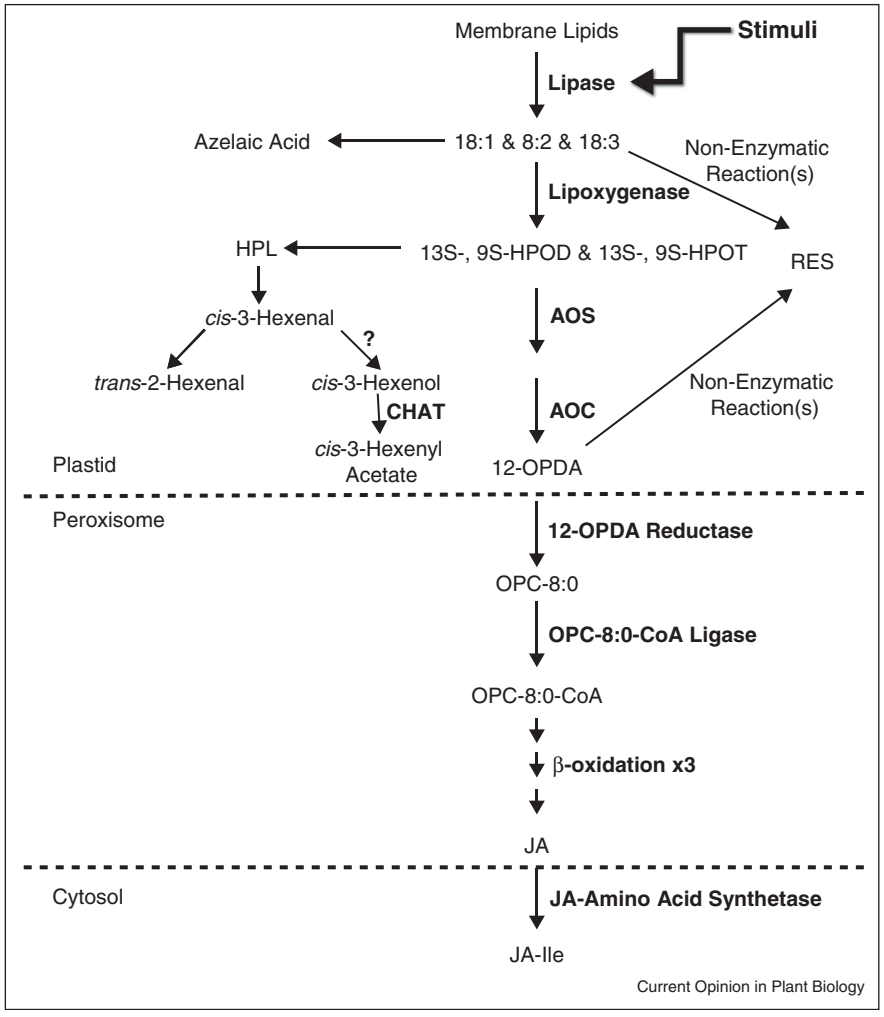
The eicosapolyenoic acids (EP), arachidonic acid (20:4) and eicosapentaenoic acid (20:5), common FAs in plant pathogenic oomycetes, and signals for immune responses and central nervous system development in mammals, function as conserved signaling molecules across eukaryotic kingdoms. EP released during infection of plants may serve as novel PAMPs that engage plant signaling networks to induce resistance to pathogens [23••,24]. EP, which do not occur in higher plants, elicit a cascade of responses in plants, including an oxidative burst and the transcriptional activation of genes involved in phytoalexin synthesis, lignification, programmed cell death, and other responses typically associated with the hypersensitive response (HR) to pathogens [24]. Structure–activity studies with PUFAs implicate the action of a 9-lipoxyenase (9-LOX) in the initial signal generation from EP that leads to a postulated reactive intermediate(s) to trigger the specific responses observed [24]. The presence of foreign EP may perturb plant oxylipin metabolism to produce novel or uncommon oxylipins that alter the course of 18:2 and 18:3 peroxidative metabolism to provoke the intense plant response. In Arabidopsis, EP-induced activation of defense responses occurs in a JA-dependent manner indicating additional downstream regulation within the allene oxide synthase (AOS) pathway [23••]. Thus, EP and other similar phylogenetically limited FAs enable plants to distinguish self from non-self-using FA-derived signals. Whether EP are recognized by pattern recognition receptors similar to bacterial PAMPs, such as flg22 and EF-Tu, is currently unknown [24].

Oxylipins as cross kingdom communication signals

One of the key processes in early plant defense signaling is enhanced lipid peroxidation and production of a vast array of oxylipins through parallel and competing branches of the AOS and hydroperoxide lyase (HPL) pathways (Figure 1) [25]. The AOS pathway is responsible for stress-inducible production of jasmonates [jasmonic acid (JA), methyl jasmonate (MeJA) and their biosynthetic precursor, 12-oxophytodienoic acid (12-OPDA)]. The HPL pathway produces C_6-aldehydes and corresponding derivatives [26,27]. The AOS and HPL pathways are both important for their production of signaling molecules in the elicitation of plant defense responses against biotic agents and in a broad array of other biological activities including intraplant and interplant communication [25,28,29••].

The jasmonates, however, are the most intensively studied plant oxylipins, in part because of their role as phytohormones in various plant processes as well as their novel cyclopentanone ring structure that provokes

Figure 1



Overview of enzymatic and non-enzymatic pathways involved in generation of FA-derived signals. 18:1, oleic acid; 18:2, linoleic acid; 18:3, linolenic acid; 9*S*-HPODE and 13*S*-HPODE, 9*S*-hydroperoxylinoleic and 13*S*-hydroperoxylinoleic acid; 9*S*-HPOTE or 13*S*-HPOTE, 9*S*-hydroperoxylinolenic or 13*S*-hydroperoxylinolenic acid; HPL, hydroperoxide lyase; CHAT, acetyl CoA:*cis*-3-hexenol acetyltransferase; AOS, allene oxide synthase; AOC, allene oxide cyclase; RES, reactive electrophilic species; 12-OPDA, 12-oxophytodienoic acid; OPC-8:0, 3-oxo-2-(*cis*-2′-pentenyl)-cyclopentane-1-octanoic acid; OPC-8:0-CoA, 3-oxo-2-(*cis*-2′-pentenyl)-cyclopentane-1-octanoyl CoA.

analogies to mammalian prostaglandins [30]. The JA isoleucine conjugate, jasmonoyl-L-isoleucine (JA-Ile), is the endogenous active receptor ligand which binds to the F-box component COI1 to promote its interaction with the JAZ transcriptional repressors. This targets the JAZ proteins for degradation by the proteasome system to relieve their repression of gene expression [31]. Recently, a jasmonate pathway effector in the form of a jasmonate binding protein, cyclophilin 20-3 was identified as a key effector protein that links OPDA signaling to amino acid biosynthesis and cellular redox homeostasis in stress responses [32••]. Specifically the authors show that binding of CYP20-3, to 12-OPDA promotes formation of a complex responsible for increased levels of thiol metabolites and the buildup of cellular reduction potential. The enhanced redox capacity in turn coordinates the expression of a subset of OPDA-responsive genes [32••].

Interestingly, fungal oxylipins also play similar regulatory roles, and recent work has shown that plants and pathogens may manipulate these common regulatory structures to interfere with each other [33,34]. Forty-three natural plant oxylipins had direct antimicrobial activities against a set of 13 plant pathogenic microorganisms including bacteria, oomycetes and fungi indicating that in general this family of fatty acid derivatives impairs growth of some plant microbial pathogens, including mycelial growth and spore germination [35]. More specifically, because *Aspergillus nidulans* psiBα oxylipins are also derived from 18:3, plant seed FAs are postulated to

regulate fungal development by mimicking and/or interfering with signals that regulate fungal sporogenesis [33,36]. Further, following recognition of the *Pst* effector protein AvrRpm1, synthesis of oxylipins such as jasmonic acid, 12-oxo phytodienoic and dinor-oxo phytodienoic acid is induced in Arabidopsis [37]. Importantly, the phytotoxin coronatine is a JA-Ile mimic and virulence determinant produced by various pathovars of *P. syringae* capable of eliciting many JA responses when applied to plants [38].

Bean leaves inoculated with the nonpathogenic *Pseudomonas putida* BTP1 produced significantly higher concentrations of the HPL-derived fungitoxic compound, Z-3-hexenal, evidence that induction of oxylipins could be associated with the bio-control and resistance inducing properties of this bacterium [39]. Volatile aldehydes from *Aspergillus*-resistant varieties of corn restricted the growth of and aflatoxin biosynthesis in *Aspergillus parasiticus* [40]. HPL-derived metabolites are also critical for intraplant and interplant, and plant–insect signaling to enable interacting attackers of plants to recognize or compete with each other [25,26,29••].

Fatty acid fragmentation and stress responses

Numerous biological stresses lead to a rapid generation of reactive oxygen species (ROS) at the various plant membranes. The presence of ROS has the capacity to fragment the fatty acids within the membranes into structurally diverse products that are known in humans to be specifically sensed by the organism and used to direct downstream responses. Recently, a FA fragmentation product azelaic acid (Figure 1) was shown to induce systemic acquired resistance (SAR) in Arabidopsis [41,42]. Similarly, lipid fragmentation products were suggested to play a role in SAR in other plant species [43]. *In vitro* data suggests that azelaic acid is produced as a direct result of ROS-mediated fragmentation of galactolipids within Arabidopsis in a process that also generated several other lipid fragmentation products [3]. Importantly, the biogenesis of these SAR-inducing signals appears to involve plastidic glycerolipid biosynthesis [43]. There is increasing evidence that non-enzymatic processes also significantly contribute to lipid peroxidation during the response to pathogens [3]. Particularly, non-enzymatic lipid peroxidation metabolites such as phytoprostanes, malondialdehyde and aldehydes are recognized as plant defense signals [44–46]. Given the diversity of chemicals produced by fragmentation of galactolipids, these could provide a highly refined chemical pattern by which the plant could detect a stress and rapidly and specifically respond to that stress.

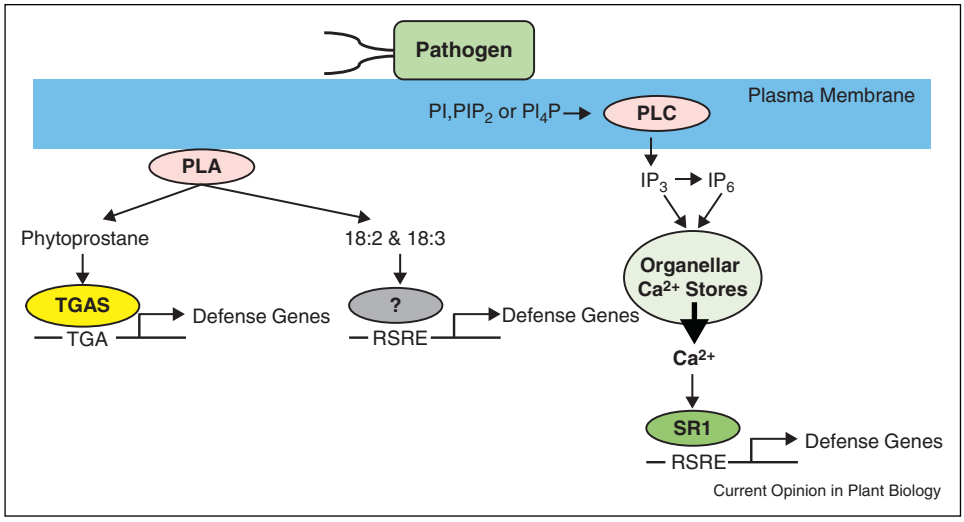
Fatty acid mediated transcriptional regulation

In contrast to the potential importance of diverse FAs providing specific regulatory compounds, relatively little is known about the underlying molecular mechanisms in plants. Given their ability to be produced either enzymatically or non-enzymatically, FAs likely operate as rapid response components on minute or less timescales, which complicates analyses. Understanding how FA-mediated signaling rapidly remodels transcriptional regulatory networks in response to stress is instrumental to gaining insight into their role in plant defense. Recent work has uncovered specific *cis*-regulatory elements underpinning initial transcriptional responses triggered by lipid mediated defense signaling. One such element is the Rapid Stress Response Element (RSRE; CGCGTT), which responds to a wide range of abiotic and biotic stresses rapidly (within 5 min) and transiently [47•]. Particularly, the RSRE is promptly activated by exogenous application of a number of FAs including 18:2 and 18:3 [23••]. These results are not surprising since unsaturated FAs, including 18:2 and 18:3, increase rapidly in response to pathogen attack [22,42,48,49] and are released from membranes by phospholipase A enzymes [2,4].

While the transcription factor(s) that bind the RSRE remain unknown a likely candidate is the Ca^{2+}/calmodulin-binding transcription factor SIGNAL RESPONSE 1 (SR1; also known as CAMTA3) [50]. Specifically, SR1 binds the CGCG box, (A/C/G)CGCG(G/T/C), which is similar to the RSRE. Consistent with the RSRE responding to a range of stresses, SR1 acts as a negative regulator of salicylic acid mediated immunity and a positive regulator of the freezing tolerance and insect resistance [51–53]. SR1, which requires Ca^{2+}/CaM binding for activity [52], may be regulated by phospholipase C (PLC). PLC is an enzyme responsible for cleavage of phospholipids that is activated by pathogens. Further, PLC activity results in increased inositol 1,4,5-trisphosphate (IP_3) and *myo*-inositol hexakisphosphate (IP_6), which are known to trigger the release of Ca^{2+} from internal organellar compartments [4,54]. This PLC/FA dependent release of Ca^{2+} may in turn signal for activation of SR1. Taken together these reports suggest that pathogen induced transcriptional changes mediated via the RSRE are due, at least in part, to FA signaling (Figure 2).

A second *cis*-regulatory element implicated in lipid mediated defense signaling networks is the TGA motif (TGACG), which is bound by redox-regulated TGA transcription factors [55]. The TGA motif was found to be overrepresented in promoters of genes induced by phytoprostane, a reactive electrophilic species (RES) oxylipin [56•]. Further, the majority of genes induced by phytoprostane treatment of wild-type plants are not induced in the *tga2-5-6* triple mutant. Thus, redox-modification of TGAs represents a potential mechanism for phytoprostane to rapidly alter transcriptional networks in response to pathogen attack (Figure 2).

Figure 2



A model of FA mediated transcriptional responses during plant defense. Pathogen recognition induces phospholipase activity. Phospholipase A (PLA) cleaves 18:2 and 18:3 from the plasma membrane resulting in activation of the RSRE. Additionally, phytoprostanes formed non-enzymatically from 18:2 and 18:3 signal for defense gene induction, which is mediated in part by TGA transcription factors (TGA2, TGA5 and TGA6). While PLC produces inositol trisphosphate (IP_3) that triggers release of Ca^{2+} from internal compartments, potentially inducing RSRE dependent transcription through the activation of the Ca^{2+}/calmodulin-binding transcription factor SR1.

Conclusion

The enzymatic and non-enzymatic cleavage of FAs within a plant provides a huge pool of chemicals that can provide specific information about the source of stress that the plant is encountering. Recent work has shown that a number of key short and long-term regulatory processes are stimulated by structurally specific FAs leading to increased plant defense against pathogens and insects. However, very little is known about how the plant senses changes in response to specific FA products much less how the changes in the FA mixtures may be integrated together into a cohesive response. Future work investigating rapid temporal changes and structural specific FA signaling will be essential to understand how the plant senses FAs to provide regulatory control over plant stress responses.

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