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Oxylipin signaling: a distinct role for the jasmonic acid precursor *cis*-(+)-12-oxo-phytodienoic acid (*cis*-OPDA)

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Oxylipins are lipid-derived compounds, many of which act as signals in the plant response to biotic and abiotic stress. They include the phytohormone jasmonic acid (JA) and related jasmonate metabolites *cis*-(+)-12-oxo-phytodienoic acid (*cis*-OPDA), methyl jasmonate, and jasmonoyl-*L*-isoleucine (JA-Ile). Besides the defense response, jasmonates are involved in plant growth and development and regulate a range of processes including glandular trichome development, reproduction, root growth, and senescence. *cis*-OPDA is known to possess a signaling role distinct from JA-Ile. The non-enzymatically derived phytoprostanes are structurally similar to *cis*-OPDA and induce a common set of genes that are not responsive to JA in *Arabidopsis thaliana*. A novel role for *cis*-OPDA in seed germination regulation has recently been uncovered based on evidence from double mutants and feeding experiments showing that *cis*-OPDA interacts with abscisic acid (ABA), inhibits seed germination, and increases ABA INSENSITIVE5 (ABI5) protein abundance. Large amounts of *cis*-OPDA are esterified to galactolipids in *A. thaliana* and the resulting compounds, known as Arabidopsides, are thought to act as a rapidly available source of *cis*-OPDA.

Keywords: oxylipins, jasmonates, 12-oxo-phytodienoic acid, jasmonic acid, phytoprostanes, seed germination, seed dormancy, lipid signaling

SYNTHESIS OF OXYLIPINS

Oxylipins are a diverse group of lipid-derived signaling compounds that are generated following oxidation of polyunsaturated fatty acids (PUFAs) such as linoleic acid (18:2), octadecatrienoic acid (18:3n-3), and hexadecatrienoic acid (16:3n-3; Wasternack, 2007; Mosblech et al., 2009; Wasternack and Kombrink, 2010). These fatty acids are released from plastidial membrane lipids by lipases including DEFECTIVE IN ANTHER DEHISCENCE1 (DAD1) and DONGLE (DGL; Ishiguro et al., 2001; Hyun et al., 2008; Ellinger et al., 2010) and are subsequently oxidized by lipoxygenases (LOX) to form hydroperoxides (Vick and Zimmerman, 1983; Bell et al., 1995). As shown in **Figure 1**, the octadecanoid pathway in *Arabidopsis thaliana* that gives rise to jasmonic acid (JA), initiates in the plastid with the oxidation of octadecatrienoic acid (18:3n-3) by 13-lipoxygenase (13-LOX) to form 13-hydroperoxylinolenic acid. This is then acted on by allene oxide synthase (AOS) and allene oxide cyclase (AOC) to give *cis*-(+)-12-oxo-phytodienoic acid (*cis*-OPDA). *cis*-OPDA then travels via the cytosol to the peroxisome with uptake into this organelle being mediated, at least in part, by the ATP binding cassette (ABC) transporter protein, COMATOSE (CTS; Theodoulou et al., 2005). Once in the peroxisome *cis*-OPDA is reduced (Sanders et al., 2000; Schaller et al., 2000; Stintzi and Browse, 2000) and activated to the CoA ester (Schneider et al., 2005; Koo et al., 2006; Kienow et al., 2008) prior to undergoing three rounds of β-oxidation to form JA (Cruz Castillo et al., 2004; Pinfield-Wells et al., 2005; Schilmiller et al., 2007; **Figure 1**).

In addition to the action of AOS on plastidial fatty acid hydroperoxides, they are also cleaved by hydroperoxide lyases (HPLs) to produce C_6-aldehydes such as (2*E*)-hexenal, (3*Z*)-hexenal and their volatile derivatives termed collectively as green leaf volatiles (GLVs; Chehab et al., 2008). HPL and AOS compete for hydroperoxide substrates and it has been shown that JA and *cis*-OPDA accumulation are reduced upon *HPL* overexpression (Chehab et al., 2008). These authors also showed that JA is involved in the direct defense response while the GLV hexenyl acetate mediates the indirect defense response. Moreover, HPL activity is not indispensable for normal growth, development, or defense since it has been shown that functional HPL activity is absent in the *A. thaliana* ecotype Col-0 (Duan et al., 2005).

A third branch of the oxylipin biosynthetic pathway originating from plastidial hydroperoxides originates through the activity of divinyl ether synthases that produce divinyl ether oxylipins which have also been shown to play a role in plant defense in a number of systems (Weber et al., 1999; Itoh and Howe, 2001). However, Eschen-Lippold et al. (2010) have more recently reported that oxylipins resulting from the action of divinyl ether synthase are not required for the *R*-gene-mediated resistance in potato.

While much is known about the physiological role of JA and the mechanistic basis of how jasmonate signaling operates (Browse, 2009), much less is understood about the biological functions of the other oxylipins. This mini-review will summarize recent developments in our understanding of the role played by the JA precursor *cis*-OPDA and the structurally similar phytoprostanes, which are synthesized by a non-enzymatic route.

A DISTINCT ROLE FOR *cis*-OPDA IN PLANT SIGNALING

cis-OPDA, JA, JA-Ile, and methyl jasmonate (MeJA) are collectively referred to as jasmonates which in addition to the involvement in the response to stress also play a role in regulating processes such as

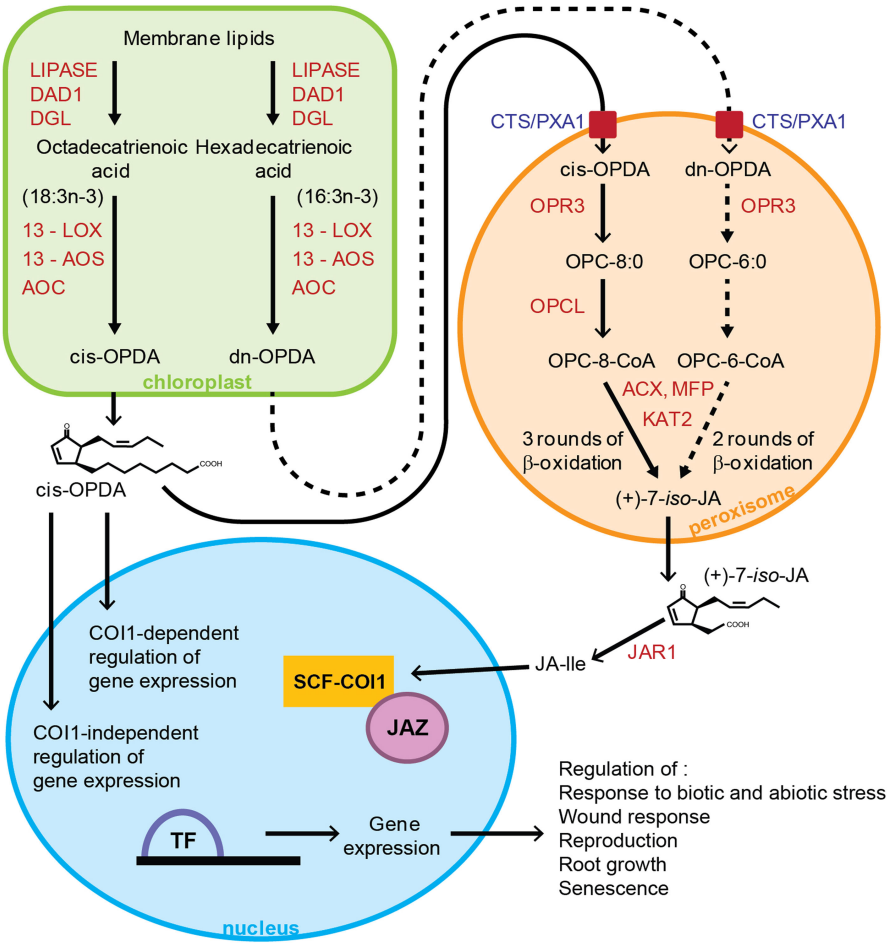

FIGURE 1 | Oxylipin biosynthesis pathway and signal transduction in *Arabidopsis thaliana*. JA biosynthesis initiates in the plastid with release of octadecatrienoic acid or hexadecatrienoic acid from membrane lipids by lipases such as DAD1 and DGL. *cis*-OPDA and dn-OPDA are formed following sequential steps catalyzed by 13-LOX, 13-AOS, and AOC. *cis*-OPDA is transported to the peroxisome via the CTS transporter, where after reduction by OPR3, OPC-8:0 is formed. This is activated to its CoA ester by OPCL1, which then undergoes three rounds of β-oxidation catalyzed by ACX, KAT, and MFP to give (+)-7-*iso*-JA. JAR1 catalyzes formation of the amino acid conjugate JA-Ile from JA in the cytosol, which is the active form of the hormone involved in JA signaling. JAZ proteins repress expression of JA-responsive genes. In response to JA-Ile, the JAZ proteins are targeted by SCF^{COI1} for degradation, thus leading to JA-dependent gene expression and ultimately the regulation of various physiological processes. The model proposes formation of the COI1-JAZ complex in the nucleus. *cis*-OPDA's regulation of gene expression can be COI1-dependent or COI1 independent, although *cis*-OPDA has not been shown to promote binding of COI1 and JAZ. Enzyme names are shown in red. Dashed arrows indicate route to JA biosynthesis via dn-OPDA, where these steps are yet to be proven experimentally. DAD1, DEFECTIVE IN ANTHER DEHISCENCE1; DGL, DONGLE; 13-LOX, 13-lipoxygenase; 13-AOS, 13-allene oxide synthase; AOC, allene oxide cyclase; OPR3, 12-oxophytodienoate reductase3; OPCL1, OPC-8:CoA ligase1; CTS, COMATOSE; ACX, acyl CoA oxidase; KAT, 3-l-ketoacyl-CoA-thiolase; MFP, multifunctional protein; JA, jasmonic acid; *cis*-OPDA, *cis*-(+)-12-oxo-phytodienoic acid; dn-OPDA, dinor-oxo-phytodienoic acid; JA-Ile, jasmonoyl-*L*-isoleucine; COI1, CORONATINE-INSENSITIVE1; JAZ, jasmonate ZIM domain.

root growth, tendril coiling, senescence, glandular trichome development, and reproduction (Staswick et al., 1992; Feys et al., 1994; Xie et al., 1998; Li et al., 2004; Balbi and Devoto, 2008; Wasternack and Kombrink, 2010). By far the best characterized jasmonate signaling mechanism is the transcriptional control of JA-responsive genes. JA is conjugated to amino acids in *A. thaliana* by an enzyme encoded by *JAR1* (Staswick and Tiryaki, 2004). One such conjugate, jasmonoyl-L-isoleucine (JA-Ile), rather than JA or *cis*-OPDA plays the crucial role in transcriptional control via the jasmonate ZIM domain (JAZ) repressor proteins (Chini et al., 2007; Thines et al., 2007; Yan et al., 2007). JA-Ile promotes binding of the F-box protein CORONATINE-INSENSITIVE1 (COI1) and JAZ proteins resulting in the degradation of JAZ proteins by the 26S-proteasome (Chini et al., 2007; Thines et al., 2007). A cytochrome P450 encoded by *CYP94B3* metabolizes JA-Ile to 12OH-JA-Ile (Kitaoka et al., 2011; Koo et al., 2011; Heitz et al., 2012) which is less effective than JA-Ile at promoting COI1-JAZ binding (Koo et al., 2011), thus suggesting a role for this enzyme in the inactivation of JA-Ile and attenuation of the jasmonate response (Koo et al., 2011). An additional enzyme, CYP94C1 is also involved in the oxidative catabolism of JA-Ile, by converting it to 12COOH-JA-Ile (Heitz et al., 2012).

That signals other than JA-Ile are involved in oxylipin signaling was suggested through the use of a mutant defective in *12-oxophytodienoate reductase3* (*opr3*), which is compromised in the conversion of *cis*-OPDA to JA (Stintzi et al., 2001), yet it still undergoes a defense response. Treating the *opr3* mutant with *cis*-OPDA revealed two separate downstream signaling pathways, one dependent on COI1 and the other independent (Stintzi et al., 2001). In the case of the *A. thaliana* defense response, JA, and *cis*-OPDA appear to act in concert to fine tune the expression of defense genes. However, in other cases the roles of JA and *cis*-OPDA are distinct as demonstrated for example by the fact that the male sterility phenotype of *opr3* is rescued by JA but not *cis*-OPDA (Stintzi and Browse, 2000). A recent publication reports that *opr3* is not a complete null mutant and concludes that the defense response displayed by *opr3* plants against a necrotrophic fungus is likely due to JA and not *cis*-OPDA (Chehab et al., 2011). Nevertheless, data from other publications do strongly suggest that *cis*-OPDA is capable of distinct signaling (Weiler et al., 1993; Blechert et al., 1999; Taki et al., 2005; Mueller et al., 2008; Ribot et al., 2008; Böttcher and Pollmann, 2009; Dave et al., 2011; Schäfer et al., 2011). In the tendril coiling response of *Bryonia dioica*, (Weiler et al., 1993; Blechert et al., 1999), the *cis*-OPDA-methyl ester acts faster and requires a much lower concentration than MeJA to elicit the response (Weiler et al., 1993). Taki et al. (2005) showed that in addition to a set of genes whose expression is induced by both JA and *cis*-OPDA, a subset of 157 of the 21,500 genes analyzed were found to be induced by *cis*-OPDA but not JA or MeJA. Half of these *cis*-OPDA-specific response genes (ORGs) were induced by wounding but their regulation was found to be COI1 independent (Taki et al., 2005). Similarly, the *PHO1;H10* gene in *A. thaliana* which is induced by various abiotic and biotic stresses, responds to *cis*-OPDA application, but not JA and in this case the effect of *cis*-OPDA is COI1-dependent (Ribot et al., 2008).

While a number of signaling roles have been demonstrated for *cis*-OPDA, the 16 carbon homolog dinor-oxo-phytodienoic acid (dn-OPDA) which is synthesized from hexadecatrienoic acid via a parallel hexadecanoid pathway (Weber et al., 1997; Acosta and Farmer, 2010; **Figure 1**) has not as yet had any signaling function ascribed.

cis-OPDA AS A NEW PLAYER IN SEED GERMINATION CONTROL

We recently uncovered an additional role for *cis*-OPDA when investigating the mechanism by which the ABC transporter COMATOSE (CTS) regulates germination potential in *A. thaliana* (Dave et al., 2011). The severely impaired germination phenotype of *cts* mutants is also observed in other mutants that are compromised in peroxisomal β-oxidation, including *kat2*, *acx1 acx2*, and *csy2 csy3* (Pinfield-Wells et al., 2005; Pracharoenwattana et al., 2005; Footitt et al., 2006). Since JA synthesis is dependent on the uptake of *cis*-OPDA into peroxisomes (Acosta and Farmer, 2010) and three rounds of peroxisomal β-oxidation (Cruz Castillo et al., 2004; Pinfield-Wells et al., 2005; Schilmiller et al., 2007) we analyzed oxylipin levels in mutant seed to establish if there is any correlation with germination potential. Surprisingly, we found elevated levels of not only *cis*-OPDA but also JA and JA-Ile in the *cts* and β-oxidation mutants compared to wild type. Previously, we had quantified JA in wounded and unwounded leaves of the *cts* mutant and found that although levels were reduced relative to wild type they were still quantifiable, suggesting that while the CTS transporter is involved in peroxisome import, another transport mechanism such as ion trapping may also operate (Theodoulou et al., 2005). Analysis of developing seeds revealed that the oxylipins accumulate during late seed maturation and double mutant analysis revealed that *cis*-OPDA rather than JA or JA-Ile contributes to the block in seed germination in *A. thaliana* (Dave et al., 2011). Seed treatments revealed that *cis*-OPDA is much more effective than JA at inhibiting wild type seed germination and this effect is independent of COI1 but synergistic with the seed germination antagonist, abscisic acid (ABA). The *ABA INSENSITIVE5* (*ABI5*) locus rescues the impaired germination phenotype of *ped3*, an allele of *cts* (Kanai et al., 2010). Consistent with these observations we found that *cis*-OPDA treatment increased ABI5 protein abundance in a manner that parallels the inhibitory effect of *cis*-OPDA and *cis*-OPDA + ABA on seed germination. Previous results from our laboratory showed that ABI5 is expressed specifically in the micropylar region of the single cell endosperm layer through which the radicle has to emerge for germination to proceed in *A. thaliana* (Penfield et al., 2006). The work of Kanai et al. (2010) highlights the correlation between ABI5 transcripts and those encoding polygalacturonase inhibiting proteins (PGIPs) which reduce cell wall pectin degradation. Thus we can propose a mechanism by which *cis*-OPDA together with ABA controls protein levels of the ABI5 transcription factor and this in turn regulates abundance of the PGIPs at the micropylar region of the endosperm, and in so doing determines whether or not the radicle can break through the endosperm barrier leading to seed germination. Our work is now focused on elucidating the mechanism by which *cis*-OPDA operates to control levels of proteins such as ABI5 and what regulates *cis*-OPDA levels in developing wild type seeds.

CHEMICALLY REACTIVE CYCLOPENTENONE OXYLIPINS

Various stress stimuli, such as wounding and pathogen infection, result in the activation of biosynthetic enzymes responsible for accumulation of *cis*-OPDA and JA (Wasternack, 2007; Mosblech et al., 2009). In addition to this enzymatic route, a non-enzymatic route for oxylipin formation triggered by reactive oxygen species (ROS) and free radicals also operates to produce an array of oxidized lipids including phytoprostanes and hydroxy fatty acids (Imbusch and Mueller, 2000; Mosblech et al., 2009). Phytoprostanes and *cis*-OPDA are structurally similar cyclopentenones that contain a chemically reactive α,β-unsaturated carbonyl structure that can bind to free thiol groups and modify cellular proteins. This has led to their classification as reactive electrophilic species (RES) and it has been proposed that this RES subgroup of oxylipins induce a common cluster of defense genes (Almeras et al., 2003; Weber et al., 2004; Farmer and Davoine, 2007) but other reports indicate that chemical reactivity and gene expression do not always correlate (Mueller et al., 2008). Microarray analysis in *A. thaliana* has shown that phytoprostanes and *cis*-OPDA induce the expression of genes associated with cellular detoxification, stress responses, and secondary metabolism with 60 and 30% of the genes induced by phytoprostanes and *cis*-OPDA respectively being dependent on the basic leucine zipper containing TGA class of

transcription factors in *A. thaliana* (Mueller et al., 2008; Mosblech et al., 2009). JA, which is a cyclopentanone and much less chemically reactive, does not induce this same group of genes. Furthermore, there was no significant overlap observed between the cyclopentenone oxylipin regulated genes described by Mueller et al. (2008) and genes altered in expression in *cts* developing seeds that have high levels of both JA and *cis*-OPDA (Dave et al., 2011). Much remains to be done to establish the details of how these various oxylipins are perceived and how the resulting signals elicit the variety of observed responses.

ARABIDOPSIDES

Galactolipids containing esterified *cis*-OPDA and dn-OPDA have been found in *A. thaliana* and some other related species of the genus *Arabidopsis*, and these complex lipids are referred to as Arabidopsides (Stelmach et al., 2001; Hisamatsu et al., 2003, 2005; Andersson et al., 2006; Buseman et al., 2006; Böttcher and Weiler, 2007; Kourtchenko et al., 2007). A number of Arabidopsides have been identified and named according to the position at which *cis*-OPDA is found esterified to the monogalactosyl diacylglycerol (MGDG) or digalactosyl diacylglycerol (DGDG) instead of the fatty acyl moiety. For example Arabidopside A and Arabidopside C are MGDG and DGDG derivatives respectively containing *cis*-OPDA esterified at positions *sn*-1 and dn-OPDA at *sn*-2 positions (Hisamatsu et al., 2003, 2005). Arabidopsides are reported to accumulate following wounding of leaves (Buseman et al., 2006; Böttcher and Weiler, 2007; Kourtchenko et al., 2007). Kourtchenko et al. (2007) also demonstrated that Arabidopsides accumulate during the hypersensitive response to bacterial pathogens. Moreover, they show that in both the wounding and hypersensitive responses, Arabidopside formation is dependent on intact JA signaling as levels of Arabidopsides are severely reduced in the *coi1* and *jar1* mutants compared to wild type following the two stimuli. Recently Vu et al. (2012) have reported that the basal composition of these complex oxidized lipids is different from those that are formed following various stress treatments. Based on the rapid and large increase in Arabidopsides following wounding, Buseman et al. (2006) hypothesize that galactolipids are the substrates of *cis*-OPDA/dn-OPDA synthesizing enzymes rather than free fatty acids being converted to *cis*-OPDA/dn-OPDA and then esterified to the galactolipids. This suggests that enzymes involved in *cis*-OPDA/dn-OPDA biosynthesis can act not only on free fatty acids, but also on lipid-bound fatty acids.

A number of functions have been described for Arabidopsides. It has been hypothesized that they may function as a storage pool that could release *cis*-OPDA for direct signaling or as a substrate for production of JA (Kourtchenko et al., 2007; Ibrahim et al., 2011). Stelmach et al. (2001) have shown that *cis*-OPDA at the *sn*-1 position in Arabidopsides can be released by *sn*-1-specific lipases from *Rhizopus arrhizus*. Schäfer et al. (2011) report that lipase activity of grasshopper oral secretions are instrumental in release of *cis*-OPDA from Arabidopsides and hence play a role in defense response to herbivory. Some of the Arabidopsides display growth-inhibiting effects on bacterial and fungal pathogens (Andersson et al., 2006; Kourtchenko et al., 2007). A senescence promoting effect for Arabidopside A has also been described (Hisamatsu et al., 2006).

As Arabidopsides have so far only been detected from a very limited range of species from the genus *Arabidopsis* it would appear that either these compounds are present in miniscule amounts in other plants or are completely absent (Mosblech et al., 2009). Based on current evidence it appears that this intriguing class of complex lipids do not have a generic role across species but have arisen by adaptation in just a few (Böttcher and Weiler, 2007).

CONCLUSION

A wide array of oxylipins are generated in response to various environmental stimuli and developmental cues. In some cases, such as plant defense, multiple oxylipins are involved while in others, such as reproductive development and seed germination, JA, and *cis*-OPDA respectively play the main role. Fine-tuning of jasmonate levels by factors such as environmental stress and developmental stage of the tissue is obviously important in eliciting a physiological response. Equally important is the responsiveness of different cell and tissue types to specific oxylipins or combinations of different oxylipins. Our recent demonstration of a specific role for *cis*-OPDA in regulating germination potential in developing seeds provides an opportunity to further dissect the underlying mechanism. Establishing the role played by oxylipin signaling in the environmental and genetic control of seed dormancy and germination is an important challenge for the future.

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