OPDA, more than just a jasmonate precursor.

Guillermo H Jimenez Aleman[1#,] Venkatesh P. Thirumalaikumar[1#], Georg Jander[1], Alisdair R. Fernie[3*], Aleksandra Skirycz[1*]

1. Boyce Thompson Institute, Ithaca, NY 14853, USA
2. Max Planck Institute of Molecular Plant Physiology, 14476 Potsdam, Germany

*Correspondence: Aleksandra Skirycz as4258@cornell.edu, Alisdair R. Fernie fernie@mpimp-golm.mpg.de

[#]equal contribution

Abstract

The oxylipin 12-oxo-phytodienoic acid (OPDA) is known as a biosynthetic precursor of the important plant hormone jasmonic acid. However, OPDA is also a signaling molecule with functions independent of jasmonates. OPDA involvement in diverse biological processes, from plant defense and stress responses to growth regulation and development, has been documented across plant species. OPDA is synthesized in the plastids from alpha-linolenic acid, and OPDA binding to plastidial cyclophilins activates TGA transcription factors upstream of genes associated with stress responses. Here, we summarize what is known about OPDA metabolism and signaling while briefly discussing its jasmonate dependent and independent roles. We also describe open questions, such as the speculated covalent binding of OPDA to proteins and the biological roles of OPDA conjugates.

Highlights

► OPDA is not only a metabolic precursor of jasmonic acid but also a signaling molecule ► OPDA regulates diverse biological processes in a jasmonate-independent manner ► OPDA binds to cyclophilin proteins upstream of redox metabolism and gene expression ► OPDA bioactivity can be attributed to its electrophilic properties ► OPDA covalently binds to proteins *in vitro* to modulate their activity

OPDA metabolism

12-oxo-Phytodienoic acid (OPDA) belongs to a large group of natural compounds, collectively called oxylipins, that are produced through oxygenation of polyunsaturated fatty acids (Gerwick et al., 1991). OPDA is found throughout the plant kingdom, including in the non-vascular model plants *Marchantia polymorpha* (Marchantia) and *Physcomitrium patens* (Mukhtarova et al., 2020). OPDA is synthesized in plastids from alpha-linolenic acid (α-LA , 18:3n3) (Vick and Zimmerman, 1983; Wasternack and Feussner, 2018), and reported intracellular concentrations vary among plant species, from less than 4 ng g^{-1} in *Nicotiana tabacum* to over 1000 ng g^{-1} in Arabidopsis (*Arabidopsis thaliana*) *(Stelmach et al., 1998)*. It is widely accepted that OPDA biosynthesis is initiated after α-LA release from membrane-embedded glycerolipids by the activity of phospholipases, for instance defective in anther dehiscence 1 (DAD1) in stamen filaments (Ishiguro et al., 2001) and plastid lipases 2/3 (PLIP 2/3) in response to abscisic acid elicitation (Wang et al., 2018) (**Figure 1**). Lipase-mediated liberation of α-LA is also a major regulatory step in OPDA synthesis, and activity of the lipases is subject the transcriptional control (Ito et al., 2007). Nevertheless, the existence of arabidopsides, which contain OPDA esterified to glycerolipids (Andersson et al., 2006; Hisamatsu et al., 2003), raises the question whether the release of α-LA may be bypassed for OPDA production. α-LA is converted into OPDA by sequential oxidation, dehydration, and cyclization catalyzed by a 13-lipoxygenase (13-LOX) (Bannenberg et al., 2009), allene oxide synthase (AOS) (Lee et al., 2008), and allene oxide cyclase (AOC) (Hofmann et al., 2006), respectively. In Arabidopsis, there are four 13-LOX, one AOS, and four AOC isoenzymes. All four 13-LOXs contribute to OPDA synthesis (Chauvin et al., 2013), but they differ in their expression profiles, activity, and allosteric regulation. For instance, LOX3 and LOX4 are required for jasmonate production during stamen and filament formation (Caldelari et al., 2011), whereas LOX2 and LOX6 are the major forms responsible for OPDA accumulation in mature and young leaves, respectively, in response to wounding (Chauvin et al., 2013; Glauser et al., 2009). The four LOXs are also differentially activated by divalent cations and inhibited by OPDA supplementation (Maynard et al., 2021a), which suggests OPDA-regulated OPDA biosynthesis. Analogously to the LOXs, the four *AOC* genes differ in their expression patterns and encoded enzyme activities (Otto et al., 2016; Stenzel et al., 2012), in addition to being regulated by heteromultimerization (Otto et al., 2016). Additionally, 11-LOX, AOS, and AOC enzymes are involved in synthesizing a different bioactive oxylipin, namely 12-dinor-OPDA (dn-OPDA), starting from membrane-liberated hexadecatrienoic acid (Weber et al., 1997). Finally, LOX, AOS, and AOC function is ancient and evolutionarily conserved across vascular and non-vascular plants (Kanamoto et al., 2012; Koeduka et al., 2015; Yamamoto et al., 2015).

OPDA can be further metabolized to s jasmonic acid (JA) and the plant hormone (+)-7-*iso*-jasmonoyl-L-isoleucine (JA-Ile). After synthesis in the plastids, OPDA is transported to the peroxisomes and converted to JA by OPDA reductase 3 (OPR3) (Schaller and Weiler, n.d.) and three cycles of β-oxidation yielding cyclopentanone compounds, OPC-8:0, OPC-6:0, OPC-4:0, and finally OPC-2:0, i.e. JA. The recent identification of the OPDA transporter JASSY at the outer membrane of the plastids (Guan et al., 2019), completed the elucidation of the JA pathway in vascular plants. Notably, JA-Ile was shown to induce the expression of *LOX*, *AOS*, and *AOC* genes, suggesting a positive-feedback loop in OPDA biosynthesis (Pauwels et al., 2008; Wasternack and Hause, 2013). *LOX* expression is also regulated by transcription factors of the TCP family, which is involved in plant growth control (Danisman et al., 2012), and Myb60, a guard-cell specific transcription factor (Simeoni et al., 2022). In vascular plants, OPDA is the primary precursor for JA synthesis via the above-mentioned OPR3 pathway. However, the existence of an alternative pathway was recently reported by Chini et al. (2018). This alternative route involves direct peroxisomal β-oxidation of OPDA to 4,5-didehydro-JA, which is reduced to JA by the cytoplasmic enzyme OPR2. The functional implications of this work are outlined later in this review. In addition to the β-oxidation leading to JA, OPDA can potentially undergo other chemical reactions. Specifically, due to the electrophilic character of the alpha-beta unsaturated carbonyl system, it behaves as a Michael acceptor. For instance, OPDA can be found conjugated to glutathione *in planta* (Ohkama-Ohtsu et al., 2010). Since the α,β-unsaturated system of OPDA is highly reactive and toxic for insect larvae, conjugation to glutathione in the gut of some insect species (Dabrowska et al., 2009) has been proposed as a detoxification mechanism (Shabab et al., 2014).

Although OPDA metabolism and its regulation have been extensively studied, there are still many open questions. For instance, substrate channeling in OPDA biosynthesis is suggested by the identification of LOX2, AOS, and AOC as constituents of a protein complex (Pollmann et al., 2019). Also unknown are the identity of the lipases that would release OPDA from arabidopsides, the exact role of the reported post-translational regulation of OPDA biosynthetic enzymes (Maynard et al., 2018) and the regulatory importance of the cross-talk with other oxylipin biosynthetic pathways.

OPDA functions and mode of action: COI1-dependent bioactivity

Although the so-called COI1-dependent OPDA functions (*i.e.*, OPDA functioning primarily as a JA precursor) are beyond the scope of this review, for the sake of clarity, we will briefly outline current knowledge concerning JA-dependent OPDA signaling. For a broader coverage of COI1-dependent OPDA activities we recommend excellent recent reviews on JA signaling (Fàbregas and Fernie, 2021; Goossens and Farmer, 2019; Wasternack and Feussner, 2018; Wasternack and Strnad, 2018).

Following mechanical wounding or herbivory, OPDA biosynthesis is rapidly activated, leading to a significant accumulation of JA, which is conjugated to isoleucine to produce JA-Ile, the bioactive jasmonate in vascular plants (**Figure 1**). Specifically, JA-Ile binds to a coreceptor complex composed of the F-box protein coronatine insensitive 1 (COI1) and a jasmonate zim-domain (JAZ) proteins, which, in the resting state, represses MYC family transcription factors (Chico et al., 2020; Liu et al., 2019; Lorenzo et al., 2004; Peñuelas et al., 2019). The JAZs can interact with the co-repressor TOPLESS and the adaptor protein NINJA (Pauwels et al., 2010), thereby linking JA-Ile perception to alterations in gene expression. Thereby, the JAZ proteins can be seen as an on-off switch regulating the broad repertoire of JA-Ile (*i.e.*, COI1) dependent plant responses. JA-Ile signaling is a hyper-regulated pathway, reminiscent of auxin signaling in that the first step comprises an E3 ubiquitin ligase complex, which ubiquitinates protein substrates, marking them for degradation by the proteasome (Devoto et al., 2002). JA-Ile regulates many different processes in the plant, including root growth (Fernández-Calvo et al., 2011; Wasternack, 2017), flower development (Wasternack, 2007), seed germination (Creelman and Mullet, 1997), formation of tubers in potato (Fernie and Willmitzer, 2001; Pelacho and Mingo-Castel, 1991), microbial symbioses (Hause and Schaarschmidt, 2009), cell death (Reinbothe et al., 2009), and leaf senescence (Griffiths, 2020). That said, the best understood and most extensively studied role of JA-Ile and therefore, indirectly, the COI1-dependent OPDA role, pertains to wound responses and plant defense.

OPDA functions and mode of action: COI1-independent roles

OPDA is not only the main precursor of JA-Ile but also a signaling molecule in its own right (Dave and Graham, 2012; Liu and Park, 2021; Maynard et al., 2018). Here, we outline the experimental evidence supporting OPDA regulatory roles independent of JA-Ile, *i.e.*, independent of the COI1 receptor. It has been known for a long time that the conversion of OPDA to JA/JA-Ile can be uncoupled, pointing to OPDA being more than a JA-Ile precursor. For instance, accumulation of OPDA, but not of jasmonates, has been observed in response to drought (Savchenko et al., 2014) and in differentiating leaf primordia (Omidbakhshfard et al., 2021).

OPDA supplementation triggers multiple responses in plants. Not surprisingly, as OPDA is a JA precursor, many but not all of these responses can be traced to JA-Ile. However, a comparative gene expression analysis of the wild-type Arabidopsis plants treated with OPDA, JA, and methyl JA (MeJA) identified approximately 150 transcripts, including multiple heat shock proteins and glutathione-*S*-transferases (Taki et al., 2005), that exhibit stronger responses to OPDA. Along similar lines, exogenous OPDA and JA application induced different volatile production patterns in lima beans (Koch et al., 1999), OPDA but not JA-Ile treatment rescued the compromised phytoalexin production in *hebiba*, an oxylipin-deficient rice mutant (Shinya et al., 2022), and OPDA was more effective in closing Arabidopsis stomata than MeJA (Savchenko et al., 2014). In rice, over-expression of *AOS* but not *OPR3* improved resistance to the brown planthopper (*Nilaparvata lugens*) (Guo et al., 2014). Consistent with this observation, treatment with OPDA but not JA or JA-Ile increased rice resistance to planthoppers (Guo et al., 2014). Moreover, comparative transcriptional analysis of *AOS* and *OPR3* over-expressing rice lines identified dozens of OPDA-responsive genes (Guo et al., 2014). In the maize inbred line Mp708, which accumulates OPDA in response to caterpillar feeding (Shivaji et al., 2010), corn leaf aphid

(*Rhopalosiphum maidis*) resistance was attributed to increased callose deposition (Varsani et al., 2019).

As illustrated by the above examples, boosting OPDA levels by either exogenous application or overexpression of the biosynthetic enzymes was instrumental in identifying the OPDA-specific responses. However, such approaches are inherently compromised by OPDA conversion to jasmonates, *i.e.*, it is difficult to distinguish COI1-dependent from independent OPDA-regulated responses. To better distinguish between the OPDA and JA-Ile dependent events, the two pathways can be uncoupled using mutants defective in the OPDA conversion to JA-Ile, such as the *opr7 opr8* double mutant in maize, which accumulates near-normal levels of OPDA and has an 80% reduction in foliar JA levels (Yan et al., 2012). Supporting the role of OPDA in defense against aphids, *opr7 opr8* mutants but not wild type plants were more resistant to corn leaf aphid infestation after OPDA addition (Varsani et al., 2019). However, accumulation of OPDA, JA, and other oxylipins in wildtype and *opr7 opr8* mutant maize after exogenous OPDA addition was not measured in this experiment.

Many published studies of Arabidopsis oxylipin signaling rely on the *opr3-1* mutant (Stintzi et al., 2001; Stintzi and Browse, 2000). However, *opr3-1* is not a complete loss of function mutant, and Arabidopsis has an alternate JA biosynthetic pathway dependent on the OPDA reductase OPR2 (Chini et al., 2018) (**Figure 1**). As a result, and especially under conditions that activate OPR2, *opr3-1* mutants accumulate a significant amount of bioactive jasmonates (Chini et al., 2018), putting in question previous reports of OPDA-specific responses that were based only on the analysis of *opr3* mutants (Dave et al., 2011; Mueller et al., 2008; Ribot et al., 2008; Stintzi et al., 2001; Taki et al., 2005). In contrast to *opr3* single mutants, the newly isolated *opr2 opr3* double mutant is characterized by the absence of jasmonates and constitutes a novel and vital genetic resource to decouple OPDA and JA-Ile dependent events (Chini et al., 2018). For instance, in contrast to *opr3*, the *opr2 opr3* mutant is severely compromised in its resistance to *Botrytis cinerea* and *Alternaria brassicicola* (Chini et al., 2018) arguing against the previously reported OPDA role in defense against the fungal pathogens. A different line that can be used to delineate OPDA-specific responses is the JA-Ile insensitive *opr3 coi1* double mutant. Transcriptional analysis of OPDA-treated *opr3 coi1* plants identified more than 500 differentially regulated genes (Monte et al., 2020). These were enriched in transcripts related to heat, redox, chemical stress, and other abiotic stresses, such as high light.

In addition to the stomatal opening, thermotolerance, and response to insects and pathogens described above, OPDA was also associated with the regulation of seed germination (Dave et al., 2016, 2011), embryo development (Goetz et al., 2012), and plant growth (see below). Moreover, OPDA can constitute a mobile signal. In Arabidopsis, OPDA produced in wounded leaves was transported *via* the phloem to the roots where it was converted to JA (Schulze et al., 2019).

How does OPDA exert its regulatory functions? In response to stress, and in the chloroplast where it is produced, OPDA reversibly binds the cyclophilin 20-3 (CYP20-3) (Maynard et al., 2021b; Park et al., 2013) (**Figure 2**). Cyclophilins are evolutionarily conserved proteins characterized by peptidyl-prolyl isomerase activity, which catalyzes the isomerization of peptide bonds from '*trans*' to '*cis*' at proline residues to facilitate protein folding. CYP20-3 can also transfer electrons from thioredoxins to peroxide substrates. OPDA binding to CYP20-3 leads to the stabilization of enzymes involved in cysteine synthesis. The resulting boost in the cysteine production increases glutathione levels, leading to redox changes in both the plastid and the cytosol, as well as activation of the TGA transcription factors upstream of OPDA-responsive genes (Mueller et al., 2008). CYP20-3 was also shown to activate plastidial 2-cysteine peroxiredoxin A (2-CysPrx), which is involved in protecting and optimizing photosynthesis (Mueller et al., 2008).

The OPDA molecule carries a highly reactive α,β-unsaturated carbonyl group that defines the reactive electrophile species that can further contribute to OPDA bioactivities. At least *in vitro*, OPDA can covalently bind to proteins by forming a sulfide bridge with cysteine thiols and, as a result, affect their activity (Dueckershoff et al., 2008; Findling et al., 2018). In a recent example, OPDA binding to two cysteinyl residues of plastidial thioredoxin, TRX-f1, impaired its ability to activate the Calvin-Benson-cycle enzyme fructose-1,6-bisphosphatase (Maynard et al., 2021b). However, although the *in vitro* evidence is highly encouraging, data supporting the occurrence and function of OPDA binding *in vivo* is still lacking. It is also unclear whether CYP20-3 is the sole OPDA receptor and whether the binding is limited to the plastidial proteins, where OPDA is biosynthesized. Given both the chemical resemblance and an accumulation pattern similar to OPDA, it is enticing to hypothesize that dn-OPDA, which is produced from the hexadecanoid pathway, may also interact with CYP20-3 (Soriano et al., 2022). Comprehensive identification of the OPDA protein interactome (covalent and non-covalent interactions) constitutes one of the grand challenges to understanding OPDA-mediated regulation in plants.

Several conjugates of OPDA have been identified (Floková et al., 2014; Shinya et al., 2022). Thylakoid membrane-associated mono- and digalactosyl diacylglycerol (MGDG and DGDG, respectively) OPDA conjugates, known as arabidopsides, have been described as an OPDA storage pool, and their metabolism contributes to cellular regulation of OPDA levels (Kourtchenko et al., 2007). In Arabidopsis, the amino acid conjugate OPDA-Ile was proposed to act as a regulatory molecule in a JA-dependent manner, although results of this study should be taken cautiously due the employment of the above-mentioned leaky *opr3* mutant (Arnold et al., 2016). Likewise, in rice, several OPDA amino acid conjugates have been proposed as non-canonical signaling molecules (Shinya et al. 2022). However, the study was largely conducted in cell cultures and only small amounts of OPDA-Asp were detected in chitooligosaccharide-treated plants. Moreover, the *AOC* gene was targeted to generate the JA-impaired cell line, and it is long-known that OPDA can be produced without AOC participation (Hebert et al., 2016; Wasternack and Feussner, 2018). Therefore, it is difficult to rule out JA-Ile-dependent activity in this experiment. Indeed, the typical JA-Ile concentration is approximately ten-fold lower than that of JA, and 100-fold, or more, lower than OPDA. This leads to one of the oldest questions in JA signaling, namely how much jasmonates are actually needed to activate the characteristic jasmonate responses of plants.

OPDA, a novel regulator of plant growth?

The trade-off between growth and defense responses is a well-documented phenomenon. In response to stress, both abiotic and biotic, plants actively reduce growth rates to preserve resources that are required for initiating stress responses (Skirycz and Inzé, 2010). However, some studies suggest that this trade-off is governed by fine-tuned signaling mechanisms, independent of resource availability, with oxylipins playing a central role (Huang et al., 2017; Major et al., 2017). The involvement of OPDA, both JA-Ile-dependent and independent, in boosting plant resistance and growth arrest is also known, and has been recently reviewed by (Liu and Park, 2021). OPDA treatment was shown to inhibit plant growth and promote mitotic arrest. Specifically, exogenous application of OPDA reduced leaf area (Zhang and Turner, 2008) and root length (Mueller et al., 2008) of wild-type Arabidopsis plants. Markedly, an absent (Zhang and Turner, 2008) or less pronounced inhibitory effect (Mueller et al., 2008) was observed in the *opr3-1* mutant, which is deficient but not devoid of JA-Ile (see previous section). Conversely, a loss-of-function mutant of *AOS*, which lacks both OPDA and JA-Ile, was reported to have bigger leaves, due to an increase in cell number, implicating OPDA and/or JAs in the regulation of leaf growth (Noir et al., 2013). Along similar lines, OPDA, but notably not JA-Ile, accumulation was shown to coincide with the disappearance of the Arabidopsis leaf meristem (Omidbakhshfard et al., 2021), further suggesting a role of OPDA in the regulation of leaf growth. Existence of a plastid-derived signal upstream of the exit from proliferation has been hypothesized (Andriankaja et al., 2012), and we speculate that OPDA may constitute a small-molecule signal coordinating the onset of photomorphogenesis with the leaf meristem arrest. It will be particularly informative to examine the timing of leaf meristem arrest in mutants that are defective in OPDA and JA-Ile synthesis, and most importantly the *opr2-1 opr3-3* double mutant Considering the importance of plant growth for yield, further dissection of the OPDA role in the regulating meristematic activity will be quite interesting.

The potential anti-cancer activity of oxylipins has also been explored; briefly reviewed in (Wasternack, 2014). Intriguingly, OPDA, a homolog of animal prostaglandins but not JA was shown to arrest proliferation in breast cancer cells by promoting degradation of G1 cyclin D1 (Altiok et al., 2008). Moreover, among several tested jasmonates including, JA, 12-OH-JA, MeJA, and JA-Ile, only OPDA suppressed H_2O_2-induced cytotoxicity. OPDA pretreatment inhibited the H_2O_2-induced reactive oxygen species (ROS) increase and mitochondrial membrane potential decrease. In addition, OPDA induced the nuclear translocation of the nuclear factor erythroid 2-related factor 2 (Nrf2), increased intracellular GSH level, and elevated expression of the Nrf2-regulated phase II antioxidant enzymes heme oxygenase-1, NADPH quinone oxidoreductase 1, and glutathione reductase (Taki-Nakano et al., 2014). Together, these results suggest that the anti-ROS activity of OPDA may have homologous effects on enzymes in plants and animals.

OPDA metabolism and functions are conserved in non-vascular plants

In contrast to vascular plants, non-vascular plants such as Marchantia, and *P. patens* produce OPDA and dn-OPDA but not jasmonates, making them excellent models for studying both OPDA-specific responses and the evolution of OPDA and JA-Ile signaling (Bowman et al., 2017; Monte et al., 2020, 2018; Soriano et al., 2022). These bryophyte studies constitute, arguably, the strongest evidence of OPDA-dependent responses that are independent of JA and JA-Ile. Analogous to higher plants, OPDA synthesis in Marchantia was induced by wounding. Growth was suppressed by elevating OPDA levels, either through exogenous application or overexpression of the OPDA biosynthetic gene Mp*AOC* (Yamamoto et al., 2015). Conversely, the loss of OPDA production by Mp*AOS1/2* disruption reduced defense against spider mites (*Tetranychus urticae*) (Koeduka et al., 2022), consistent with the reported OPDA role regulating insect resistance in vascular plants. Interestingly, dn-OPDA but not OPDA is perceived by the evolutionarily conserved COI1 receptor in Marchantia. A single-residue substitution is sufficient to switch the ligand specificity from JA-Ile to dn-OPDA (Monte et al., 2018). Other key signaling components, including the JAZ repressor and MYC transcription factors, are also conserved (Monte et al., 2019) (Peñuelas et al., 2019). Moreover, transcriptional analysis of wild-type and Mp*coi1* plants treated with OPDA identified the existence of CO1-independent regulatory networks upstream of the thermotolerance-related genes, and treatment with OPDA protects Marchantia against heat stress (Monte et al., 2020). This was also true for dn-*cis*-OPDA but not for dn-*iso*-OPDA, which possesses a much less reactive (more stable) tetra-substituted double bond (compared to that of OPDA or dn-*cis*-OPDA) in the alpha position relative to the carbonyl group (Monte et al., 2020).

Outlook

Although OPDA metabolism and functions in plant physiology and stress responses have been studied extensively, many open questions remain, including the regulation of OPDA biosynthesis, the roles of OPDA conjugates, and the occurrence and function of OPDA binding to proteins. We suggest several future avenues of OPDA research: 1) All published data employing *opr3* single mutants should be examined carefully, and generation of new data based on described leaky alleles must be avoided. 2) The potential of the Arabidopsis the *opr2 opr3* double mutant (Chini et al., 2018) alone, and in combination with other biosynthetic (*e.g.*, *jar1*) or perception (*coi1*) mutants should be fully explored, in order to comprehensively dissect the physiological relevance of OPDA. 3) Similar experiments should be conducted other plant species, in particular monocots, to determine whether effects observed in Arabidopsis are conserved. 4) Researchers should make use of the evolutionary conservation of OPDA metabolism and functions to focus physiological studies on the bryophytes that accumulate OPDA and dn-OPDA but not JA and JA-Ile. 5) Newly developed biochemical methods, including thermal proteome profiling (Savitski et al., 2014), limited proteolysis (Piazza et al., 2018), and PROMIS (Veyel et al., 2018) for comprehensive identification of OPDA protein partners (Luzarowski and Skirycz, 2019; Venegas-Molina et al., 2021; Wagner et al., 2021), should be employed for oxylipin target identification.

Acknowledgments

This work was supported by XXX to AS, US National Science Foundation award 2019516 and United States Department of Agriculture award 2021-67014-342357 to GJ, and a grant from the Triad Foundation. Figures were created with BioRender.com.

References

Altiok, N., Mezzadra, H., Patel, P., Koyuturk, M., Altiok, S., 2008. A plant oxylipin, 12-oxo-phytodienoic acid, inhibits proliferation of human breast cancer cells by targeting cyclin D1. Breast Cancer Res. Treat. 109, 315–323.

Andersson, M.X., Hamberg, M., Kourtchenko, O., Brunnström, A., McPhail, K.L., Gerwick, W.H., Göbel, C., Feussner, I., Ellerström, M., 2006. Oxylipin profiling of the hypersensitive response in Arabidopsis thaliana. Formation of a novel oxo-phytodienoic acid-containing galactolipid, arabidopside E. J. Biol. Chem. 281, 31528–31537.

Andriankaja, M., Dhondt, S., De Bodt, S., Vanhaeren, H., Coppens, F., De Milde, L., Mühlenbock, P., Skirycz, A., Gonzalez, N., Beemster, G.T.S., Inzé, D., 2012. Exit from proliferation during leaf development in Arabidopsis thaliana: a not-so-gradual process. Dev. Cell 22, 64–78.

Arnold, M.D., Gruber, C., Floková, K., Miersch, O., Strnad, M., Novák, O., Wasternack, C., Hause, B., 2016. The Recently Identified Isoleucine Conjugate of cis-12-Oxo-Phytodienoic Acid Is Partially Active in cis-12-Oxo-Phytodienoic Acid-Specific Gene Expression of Arabidopsis thaliana. PLOS ONE. https://doi.org/10.1371/journal.pone.0162829

Bannenberg, G., Martínez, M., Hamberg, M., Castresana, C., 2009. Diversity of the enzymatic activity in the lipoxygenase gene family of Arabidopsis thaliana. Lipids 44, 85–95.

Bowman, J.L., Kohchi, T., Yamato, K.T., Jenkins, J., Shu, S., Ishizaki, K., Yamaoka, S., Nishihama, R., Nakamura, Y., Berger, F., Adam, C., Aki, S.S., Althoff, F., Araki, T., Arteaga-Vazquez, M.A., Balasubrmanian, S., Barry, K., Bauer, D., Boehm, C.R., Briginshaw, L., Caballero-Perez, J., Catarino, B., Chen, F., Chiyoda, S., Chovatia, M., Davies, K.M., Delmans, M., Demura, T., Dierschke, T., Dolan, L., Dorantes-Acosta, A.E., Eklund, D.M., Florent, S.N., Flores-Sandoval, E., Fujiyama, A., Fukuzawa, H., Galik, B., Grimanelli, D., Grimwood, J., Grossniklaus, U., Hamada, T., Haseloff, J., Hetherington, A.J., Higo, A., Hirakawa, Y., Hundley, H.N., Ikeda, Y., Inoue, K., Inoue, S.-I., Ishida, S., Jia, Q., Kakita, M., Kanazawa, T., Kawai, Y., Kawashima, T., Kennedy, M., Kinose, K., Kinoshita, T., Kohara, Y., Koide, E., Komatsu, K., Kopischke, S., Kubo, M., Kyozuka, J., Lagercrantz, U., Lin, S.-S., Lindquist, E., Lipzen, A.M., Lu, C.-W., De Luna, E., Martienssen, R.A., Minamino, N., Mizutani, M., Mizutani, M., Mochizuki, N., Monte, I., Mosher, R., Nagasaki, H., Nakagami, H., Naramoto, S., Nishitani, K., Ohtani, M., Okamoto, T., Okumura, M., Phillips, J., Pollak, B., Reinders, A., Rövekamp, M., Sano, R., Sawa, S., Schmid, M.W., Shirakawa, M., Solano, R., Spunde, A., Suetsugu, N., Sugano, S., Sugiyama, A., Sun, R., Suzuki, Y., Takenaka, M., Takezawa, D., Tomogane, H., Tsuzuki, M., Ueda, T., Umeda, M., Ward, J.M., Watanabe, Y., Yazaki, K., Yokoyama, R., Yoshitake, Y., Yotsui, I., Zachgo, S., Schmutz, J., 2017. Insights into Land Plant Evolution Garnered from the Marchantia polymorpha Genome. Cell 171, 287–304.e15.

Caldelari, D., Wang, G., Farmer, E.E., Dong, X., 2011. Arabidopsis lox3 lox4 double mutants are male sterile and defective in global proliferative arrest. Plant Mol. Biol. 75, 25–33.

Chauvin, A., Caldelari, D., Wolfender, J.-L., Farmer, E.E., 2013. Four 13-lipoxygenases contribute to rapid jasmonate synthesis in wounded Arabidopsis thaliana leaves: a role for lipoxygenase 6 in responses to long-distance wound signals. New Phytol. 197, 566–575.

Chico, J.M., Lechner, E., Fernandez-Barbero, G., Canibano, E., García-Casado, G., Franco-Zorrilla, J.M., Hammann, P., Zamarreño, A.M., García-Mina, J.M., Rubio, V., Genschik, P., Solano, R., 2020. CUL3 E3 ubiquitin ligases regulate MYC2, MYC3, and MYC4 stability and JA responses. Proc. Natl. Acad. Sci. U. S. A. 117, 6205–6215.

Chini, A., Monte, I., Zamarreño, A.M., Hamberg, M., Lassueur, S., Reymond, P., Weiss, S., Stintzi, A., Schaller, A., Porzel, A., García-Mina, J.M., Solano, R., 2018. An OPR3-independent pathway uses 4,5-didehydrojasmonate for jasmonate synthesis. Nat. Chem. Biol. 14, 171–178.

Creelman, R.A., Mullet, J.E., 1997. BIOSYNTHESIS AND ACTION OF JASMONATES IN PLANTS. Annu. Rev. Plant Physiol. Plant Mol. Biol. 48, 355–381.

Dabrowska, P., Freitak, D., Vogel, H., Heckel, D.G., Boland, W., 2009. The phytohormone precursor OPDA is isomerized in the insect gut by a single, specific glutathione transferase. Proc. Natl. Acad. Sci. U. S. A. 106, 16304–16309.

Danisman, S., van der Wal, F., Dhondt, S., Waites, R., de Folter, S., Bimbo, A., van Dijk, A.D.J., Muino, J.M., Cutri, L., Dornelas, M.C., Angenent, G.C., Immink, R.G.H., 2012. Arabidopsis class I and class II TCP transcription factors regulate jasmonic acid metabolism and leaf development antagonistically. Plant Physiol. 159, 1511–1523.

Dave, A., Graham, I.A., 2012. Oxylipin Signaling: A Distinct Role for the Jasmonic Acid Precursor cis-(+)-12-Oxo-Phytodienoic Acid (cis-OPDA). Front. Plant Sci. 3, 42.

Dave, A., Hernández, M.L., He, Z., Andriotis, V.M.E., Vaistij, F.E., Larson, T.R., Graham, I.A., 2011. 12-oxo-phytodienoic acid accumulation during seed development represses seed germination in Arabidopsis. Plant Cell 23, 583–599.

Dave, A., Vaistij, F.E., Gilday, A.D., Penfield, S.D., Graham, I.A., 2016. Regulation of Arabidopsis thaliana seed dormancy and germination by 12-oxo-phytodienoic acid. J. Exp. Bot. 67, 2277–2284.

Devoto, A., Nieto-Rostro, M., Xie, D., Ellis, C., Harmston, R., Patrick, E., Davis, J., Sherratt, L., Coleman, M., Turner, J.G., 2002. COI1 links jasmonate signalling and fertility to the SCF ubiquitin-ligase complex in Arabidopsis. Plant J. 32, 457–466.

Dueckershoff, K., Mueller, S., Mueller, M.J., Reinders, J., 2008. Impact of cyclopentenone-oxylipins on the proteome of Arabidopsis thaliana. Biochim. Biophys. Acta 1784, 1975–1985.

Fàbregas, N., Fernie, A.R., 2021. The interface of central metabolism with hormone signaling in plants. Curr. Biol. 31, R1535–R1548.

Fernández-Calvo, P., Chini, A., Fernández-Barbero, G., Chico, J.-M., Gimenez-Ibanez, S., Geerinck, J., Eeckhout, D., Fabian Schweizer, Godoy, M., Franco-Zorrilla, J.M., Pauwels, L., Witters, E., Puga, M.I., Paz-Ares, J., Goossens, A., Reymond, P., De Jaeger, G., Solano, R., 2011. TheArabidopsisbHLH Transcription Factors MYC3 and MYC4 Are Targets of JAZ Repressors and Act Additively with MYC2 in the Activation of Jasmonate Responses. The Plant Cell. https://doi.org/10.1105/tpc.110.080788

Fernie, A.R., Willmitzer, L., 2001. Molecular and biochemical triggers of potato tuber development. Plant Physiol. 127, 1459–1465.

Findling, S., Stotz, H.U., Zoeller, M., Krischke, M., Zander, M., Gatz, C., Berger, S., Mueller, M.J., 2018. TGA2 signaling in response to reactive electrophile species is not dependent on cysteine modification of TGA2. PLoS One 13, e0195398.

Floková, K., Tarkowská, D., Miersch, O., Strnad, M., Wasternack, C., Novák, O., 2014. UHPLC–MS/MS based target profiling of stress-induced phytohormones. Phytochemistry 105, 147–157.

Gerwick, W.H., Moghaddam, M., Hamberg, M., 1991. Oxylipin metabolism in the red alga Gracilariopsis lemaneiformis: mechanism of formation of vicinal dihydroxy fatty acids. Arch. Biochem. Biophys. 290, 436–444.

Glauser, G., Dubugnon, L., Mousavi, S.A.R., Rudaz, S., Wolfender, J.-L., Farmer, E.E., 2009. Velocity estimates for signal propagation leading to systemic jasmonic acid accumulation in wounded Arabidopsis. J. Biol. Chem. 284, 34506–34513.

Goetz, S., Hellwege, A., Stenzel, I., Kutter, C., Hauptmann, V., Forner, S., McCaig, B., Hause, G., Miersch, O., Wasternack, C., Hause, B., 2012. Role of cis-12-oxo-phytodienoic acid in tomato embryo development. Plant Physiol. 158, 1715–1727.

Goossens, A., Farmer, E.E., 2019. Regulatory Oxylipins Anno 2019: Jasmonates Galore in the Plant Oxylipin Research Community. Plant Cell Physiol. 60, 2609–2612.

Griffiths, G., 2020. Jasmonates: biosynthesis, perception and signal transduction. Essays Biochem. 64, 501–512.

Guan, L., Denkert, N., Eisa, A., Lehmann, M., Sjuts, I., Weiberg, A., Soll, J., Meinecke, M., Schwenkert, S., 2019. JASSY, a chloroplast outer membrane protein required for jasmonate biosynthesis. Proc. Natl. Acad. Sci. U. S. A. 116, 10568–10575.

Guo, H.-M., Li, H.-C., Zhou, S.-R., Xue, H.-W., Miao, X.-X., 2014. Cis-12-oxo-phytodienoic acid stimulates rice defense response to a piercing-sucking insect. Mol. Plant 7, 1683–1692.

Hause, B., Schaarschmidt, S., 2009. The role of jasmonates in mutualistic symbioses between plants and soil-born microorganisms. Phytochemistry 70, 1589–1599.

Hebert, S.P., Cha, J.K., Brash, A.R., Schlegel, H.B., 2016. Investigation into 9(S)-HPODE-derived allene oxide to cyclopentenone cyclization mechanism via diradical oxyallyl intermediates. Org. Biomol. Chem. 14, 3544–3557.

Hisamatsu, Y., Goto, N., Hasegawa, K., Shigemori, H., 2003. Arabidopsides A and B, two new oxylipins from Arabidopsis thaliana. Tetrahedron Lett. 44, 5553–5556.

Hofmann, E., Zerbe, P., Schaller, F., 2006. The crystal structure of Arabidopsis thaliana allene oxide cyclase: insights into the oxylipin cyclization reaction. Plant Cell 18, 3201–3217.

Huang, H., Liu, B., Liu, L., Song, S., 2017. Jasmonate action in plant growth and development. J. Exp. Bot. 68, 1349–1359.

Ishiguro, S., Kawai-Oda, A., Ueda, J., Nishida, I., Okada, K., 2001. The DEFECTIVE IN ANTHER DEHISCIENCE gene encodes a novel phospholipase A1 catalyzing the initial step of jasmonic acid biosynthesis, which synchronizes pollen maturation, anther dehiscence, and flower opening in Arabidopsis. Plant Cell 13, 2191–2209.

Ito, T., Ng, K.-H., Lim, T.-S., Yu, H., Meyerowitz, E.M., 2007. The homeotic protein AGAMOUS controls late stamen development by regulating a jasmonate biosynthetic gene in Arabidopsis. Plant Cell 19, 3516–3529.

Kanamoto, H., Takemura, M., Ohyama, K., 2012. Cloning and expression of three lipoxygenase genes from liverwort, Marchantia polymorpha L., in Escherichia coli. Phytochemistry 77, 70–78.

Koch, T., Krumm, T., Jung, V., Engelberth, J., Boland, W., 1999. Differential induction of plant volatile biosynthesis in the lima bean by early and late intermediates of the octadecanoid-signaling pathway. Plant Physiol. 121, 153–162.

Koeduka, T., Ishizaki, K., Mwenda, C.M., Hori, K., Sasaki-Sekimoto, Y., Ohta, H., Kohchi, T., Matsui, K., 2015. Biochemical characterization of allene oxide synthases from the liverwort Marchantia polymorpha and green microalgae Klebsormidium flaccidum provides insight into the evolutionary divergence of the plant CYP74 family. Planta 242, 1175–1186.

Koeduka, T., Takaishi, M., Suzuki, M., Nishihama, R., Kohchi, T., Uefune, M., Matsui, K., 2022. CRISPR/Cas9-mediated disruption of ALLENE OXIDE SYNTHASE results in defective 12-oxo-phytodienoic acid accumulation and reduced defense against spider mite (Tetranychus urticae) in liverwort (Marchantia polymorpha). Plant Biotechnol. 39, 191–194.

Kourtchenko, O., Andersson, M.X., Hamberg, M., Brunnström, A., Göbel, C., McPhail, K.L., Gerwick, W.H., Feussner, I., Ellerström, M., 2007. Oxo-phytodienoic acid-containing galactolipids in Arabidopsis: jasmonate signaling dependence. Plant Physiol. 145, 1658–1669.

Lee, D.-S., Nioche, P., Hamberg, M., Raman, C.S., 2008. Structural insights into the evolutionary paths of oxylipin biosynthetic enzymes. Nature 455, 363–368.

Liu, W., Park, S.-W., 2021. 12-oxo-Phytodienoic Acid: A Fuse and/or Switch of Plant Growth and Defense Responses? Front. Plant Sci. 12, 724079.

Liu, Y., Du, M., Deng, L., Shen, J., Fang, M., Chen, Q., Lu, Y., Wang, Q., Li, C., Zhai, Q., 2019. MYC2 Regulates the Termination of Jasmonate Signaling via an Autoregulatory Negative Feedback Loop. Plant Cell 31, 106–127.

Lorenzo, O., Chico, J.M., Sánchez-Serrano, J.J., Solano, R., 2004. JASMONATE-INSENSITIVE1 encodes a MYC transcription factor essential to discriminate between different jasmonate-regulated defense responses in Arabidopsis. Plant Cell 16, 1938–1950.

Luzarowski, M., Skirycz, A., 2019. Emerging strategies for the identification of protein–metabolite interactions. Journal of Experimental Botany. https://doi.org/10.1093/jxb/erz228

Major, I.T., Yoshida, Y., Campos, M.L., Kapali, G., Xin, X.-F., Sugimoto, K., de Oliveira Ferreira, D., He, S.Y., Howe, G.A., 2017. Regulation of growth-defense balance by the JASMONATE ZIM-DOMAIN (JAZ)-MYC transcriptional module. New Phytol. 215, 1533–1547.

Maynard, D., Chibani, K., Schmidtpott, S., Seidel, T., Spross, J., Viehhauser, A., Dietz, K.-J., 2021a. Biochemical Characterization of 13-Lipoxygenases of Arabidopsis thaliana. Int. J. Mol. Sci. 22. https://doi.org/10.3390/ijms221910237

Maynard, D., Gröger, H., Dierks, T., Dietz, K.-J., 2018. The function of the oxylipin 12-oxophytodienoic acid in cell signaling, stress acclimation, and development. J. Exp. Bot. 69, 5341–5354.

Maynard, D., Viehhauser, A., Knieper, M., Dreyer, A., Manea, G., Telman, W., Butter, F., Chibani, K., Scheibe, R., Dietz, K.-J., 2021b. The In Vitro Interaction of 12-Oxophytodienoic Acid and Related Conjugated Carbonyl Compounds with Thiol Antioxidants. Biomolecules. https://doi.org/10.3390/biom11030457

Monte, I., Franco-Zorrilla, J.M., García-Casado, G., Zamarreño, A.M., García-Mina, J.M., Nishihama, R., Kohchi, T., Solano, R., 2019. A Single JAZ Repressor Controls the Jasmonate Pathway in Marchantia polymorpha. Mol. Plant 12, 185–198.

Monte, I., Ishida, S., Zamarreño, A.M., Hamberg, M., Franco-Zorrilla, J.M., García-Casado, G., Gouhier-Darimont, C., Reymond, P., Takahashi, K., García-Mina, J.M., Nishihama, R., Kohchi, T., Solano, R., 2018. Ligand-receptor co-evolution shaped the jasmonate pathway in land plants. Nat. Chem. Biol. 14, 480–488.

Monte, I., Kneeshaw, S., Franco-Zorrilla, J.M., Chini, A., Zamarreño, A.M., García-Mina, J.M., Solano, R., 2020. An Ancient COI1-Independent Function for Reactive Electrophilic Oxylipins in Thermotolerance. Curr. Biol. 30, 962–971.e3.

Mueller, S., Hilbert, B., Dueckershoff, K., Roitsch, T., Krischke, M., Mueller, M.J., Berger, S., 2008. General detoxification and stress responses are mediated by oxidized lipids through TGA transcription factors in Arabidopsis. Plant Cell 20, 768–785.

Mukhtarova, L.S., Lantsova, N.V., Khairutdinov, B.I., Grechkin, A.N., 2020. Lipoxygenase pathway in model bryophytes: 12-oxo-9(13),15-phytodienoic acid is a predominant oxylipin in Physcomitrella patens. Phytochemistry 180, 112533.

Noir, S., Bömer, M., Takahashi, N., Ishida, T., Tsui, T.-L., Balbi, V., Shanahan, H., Sugimoto, K., Devoto, A., 2013. Jasmonate controls leaf growth by repressing cell proliferation and the onset of endoreduplication while maintaining a potential stand-by mode. Plant Physiol. 161, 1930–1951.

Ohkama-Ohtsu, N., Sasaki-Sekimoto, Y., Oikawa, A., Jikumaru, Y., Shinoda, S., Inoue, E., Kamide, Y., Yokoyama, T., Hirai, M.Y., Shirasu, K., Kamiya, Y., Oliver, D.J., Saito, K., 2010. 12-Oxo-Phytodienoic Acid–Glutathione Conjugate is Transported into the Vacuole in Arabidopsis. Plant Cell Physiol. 52, 205–209.

Omidbakhshfard, M.A., Sokolowska, E.M., Di Vittori, V., de Souza, L.P., Kuhalskaya, A., Brotman, Y., Alseekh, S., Fernie, A.R., Skirycz, A., 2021. Multi-omics analysis of early leaf development in Arabidopsis thaliana. PATTER 2. https://doi.org/10.1016/j.patter.2021.100235

Otto, M., Naumann, C., Brandt, W., Wasternack, C., Hause, B., 2016. Activity Regulation by Heteromerization of Arabidopsis Allene Oxide Cyclase Family Members. Plants 5. https://doi.org/10.3390/plants5010003

Park, S.-W., Li, W., Viehhauser, A., He, B., Kim, S., Nilsson, A.K., Andersson, M.X., Kittle, J.D., Ambavaram, M.M.R., Luan, S., Esker, A.R., Tholl, D., Cimini, D., Ellerström, M., Coaker, G., Mitchell, T.K., Pereira, A., Dietz, K.-J., Lawrence, C.B., 2013. Cyclophilin 20-3 relays a 12-oxo-phytodienoic acid signal during stress responsive regulation of cellular redox homeostasis. Proc. Natl. Acad. Sci. U. S. A. 110, 9559–9564.

Pauwels, L., Barbero, G.F., Geerinck, J., Tilleman, S., Grunewald, W., Pérez, A.C., Chico, J.M., Bossche, R.V., Sewell, J., Gil, E., García-Casado, G., Witters, E., Inzé, D., Long, J.A., De Jaeger, G., Solano, R., Goossens, A., 2010. NINJA connects the co-repressor TOPLESS to jasmonate signalling. Nature 464, 788–791.

Pauwels, L., Morreel, K., De Witte, E., Lammertyn, F., Van Montagu, M., Boerjan, W., Inzé, D., Goossens, A., 2008. Mapping methyl jasmonate-mediated transcriptional reprogramming of metabolism and cell cycle progression in cultured Arabidopsis cells. Proc. Natl. Acad. Sci. U. S. A. 105, 1380–1385.

Pelacho, A.M., Mingo-Castel, A.M., 1991. Jasmonic Acid induces tuberization of potato stolons cultured in vitro. Plant Physiol. 97, 1253–1255.

Peñuelas, M., Monte, I., Schweizer, F., Vallat, A., Reymond, P., García-Casado, G., Franco-Zorrilla, J.M., Solano, R., 2019. Jasmonate-Related MYC Transcription Factors Are Functionally Conserved in. Plant Cell 31, 2491–2509.

Piazza, I., Kochanowski, K., Cappelletti, V., Fuhrer, T., Noor, E., Sauer, U., Picotti, P., 2018. A Map of Protein-Metabolite Interactions Reveals Principles of Chemical Communication. Cell 172, 358–372.e23.

Pollmann, S., Springer, A., Rustgi, S., von Wettstein, D., Kang, C., Reinbothe, C., Reinbothe, S., 2019. Substrate channeling in oxylipin biosynthesis through a protein complex in the plastid envelope of Arabidopsis thaliana. J. Exp. Bot. 70, 1483–1495.

Reinbothe, C., Springer, A., Samol, I., Reinbothe, S., 2009. Plant oxylipins: role of jasmonic acid during programmed cell death, defence and leaf senescence. FEBS J. 276, 4666–4681.

Ribot, C., Zimmerli, C., Farmer, E.E., Reymond, P., Poirier, Y., 2008. Induction of the Arabidopsis PHO1;H10 gene by 12-oxo-phytodienoic acid but not jasmonic acid via a CORONATINE INSENSITIVE1-dependent pathway. Plant Physiol. 147, 696–706.

Savchenko, T., Kolla, V.A., Wang, C.-Q., Nasafi, Z., Hicks, D.R., Phadungchob, B., Chehab, W.E., Brandizzi, F., Froehlich, J., Dehesh, K., 2014. Functional convergence of oxylipin and abscisic acid pathways controls stomatal closure in response to drought. Plant Physiol. 164, 1151–1160.

Savitski, M.M., Reinhard, F.B.M., Franken, H., Werner, T., Savitski, M.F., Eberhard, D., Martinez Molina, D., Jafari, R., Dovega, R.B., Klaeger, S., Kuster, B., Nordlund, P., Bantscheff, M., Drewes, G., 2014. Tracking cancer drugs in living cells by thermal profiling of the proteome. Science 346, 1255784.

Schaller, Weiler, n.d. Molecular Cloning and Characterization of 12-Oxophytodienoate Reductase, an Enzyme of the Octadecanoid Signaling Pathway fromArabidopsis thaliana …. J. Biol. Chem.

Schulze, A., Zimmer, M., Mielke, S., Stellmach, H., Melnyk, C.W., Hause, B., Gasperini, D., 2019. Wound-Induced Shoot-to-Root Relocation of JA-Ile Precursors Coordinates Arabidopsis Growth. Mol. Plant 12, 1383–1394.

Shabab, M., Khan, S.A., Vogel, H., Heckel, D.G., Boland, W., 2014. OPDA isomerase GST16 is involved in phytohormone detoxification and insect development. FEBS J. 281, 2769–2783.

Shinya, T., Miyamoto, K., Uchida, K., Hojo, Y., Yumoto, E., Okada, K., Yamane, H., Galis, I., 2022. Chitooligosaccharide elicitor and oxylipins synergistically elevate phytoalexin production in rice. Plant Mol. Biol. 109, 595–609.

Shivaji, R., Camas, A., Ankala, A., Engelberth, J., Tumlinson, J.H., Williams, W.P., Wilkinson, J.R., Luthe, D.S., 2010. Plants on constant alert: elevated levels of jasmonic acid and jasmonate-induced transcripts in caterpillar-resistant maize. J. Chem. Ecol. 36, 179–191.

Simeoni, F., Skirycz, A., Simoni, L., Castorina, G., de Souza, L.P., Fernie, A.R., Alseekh, S., Giavalisco, P., Conti, L., Tonelli, C., Galbiati, M., 2022. The AtMYB60 transcription factor regulates stomatal opening by modulating oxylipin synthesis in guard cells. Sci. Rep. 12, 533.

Skirycz, A., Inzé, D., 2010. More from less: plant growth under limited water. Curr. Opin. Biotechnol. 21, 197–203.

Soriano, G., Kneeshaw, S., Jimenez-Aleman, G., Zamarreño, Á.M., Franco-Zorrilla, J.M., Rey-Stolle, M.F., Barbas, C., García-Mina, J.M., Solano, R., 2022. An evolutionarily ancient fatty acid desaturase is required for the synthesis of hexadecatrienoic acid, which is the main source of the bioactive jasmonate in Marchantia polymorpha. New Phytol. 233, 1401–1413.

Stelmach, B.A., Müller, A., Hennig, P., Laudert, D., Andert, L., Weiler, E.W., 1998. Quantitation of the octadecanoid 12-oxo-phytodienoic acid, a signalling compound in plant mechanotransduction. Phytochemistry 47, 539–546.

Stenzel, I., Otto, M., Delker, C., Kirmse, N., Schmidt, D., Miersch, O., Hause, B., Wasternack, C., 2012. ALLENE OXIDE CYCLASE (AOC) gene family members of Arabidopsis thaliana: tissue- and organ-specific promoter activities and in vivo heteromerization*. J. Exp. Bot. 63, 6125–6138.

Stintzi, A., Browse, J., 2000. The Arabidopsis male-sterile mutant, opr3, lacks the 12-oxophytodienoic acid reductase required for jasmonate synthesis. Proc. Natl. Acad. Sci. U. S. A. 97, 10625–10630.

Stintzi, A., Weber, H., Reymond, P., Browse, J., Farmer, E.E., 2001. Plant defense in the absence of jasmonic acid: the role of cyclopentenones. Proc. Natl. Acad. Sci. U. S. A. 98, 12837–12842.

Taki-Nakano, N., Ohzeki, H., Kotera, J., Ohta, H., 2014. Cytoprotective effects of 12-oxo phytodienoic acid, a plant-derived oxylipin jasmonate, on oxidative stress-induced toxicity in human neuroblastoma SH-SY5Y cells. Biochim. Biophys. Acta 1840, 3413–3422.

Taki, N., Sasaki-Sekimoto, Y., Obayashi, T., Kikuta, A., Kobayashi, K., Ainai, T., Yagi, K., Sakurai, N., Suzuki, H., Masuda, T., Takamiya, K.-I., Shibata, D., Kobayashi, Y., Ohta, H., 2005. 12-oxo-phytodienoic acid triggers expression of a distinct set of genes and plays a role in wound-induced gene expression in Arabidopsis. Plant Physiol. 139, 1268–1283.

Varsani, S., Grover, S., Zhou, S., Koch, K.G., Huang, P.-C., Kolomiets, M.V., Williams, W.P., Heng-Moss, T., Sarath, G., Luthe, D.S., Jander, G., Louis, J., 2019. 12-Oxo-Phytodienoic Acid Acts as a Regulator of Maize Defense against Corn Leaf Aphid. Plant Physiol. 179, 1402–1415.

Venegas-Molina, J., Molina-Hidalgo, F.J., Clicque, E., Goossens, A., 2021. Why and How to Dig into Plant Metabolite-Protein Interactions. Trends Plant Sci. 26, 472–483.

Veyel, D., Sokolowska, E.M., Moreno, J.C., Kierszniowska, S., Cichon, J., Wojciechowska, I., Luzarowski, M., Kosmacz, M., Szlachetko, J., Gorka, M., Méret, M., Graf, A., Meyer, E.H., Willmitzer, L., Skirycz, A., 2018. PROMIS, global analysis of PROtein–metabolite interactions using size separation in Arabidopsis thaliana. J. Biol. Chem. 293, 12440–12453.

Vick, B.A., Zimmerman, D.C., 1983. The biosynthesis of jasmonic acid: a physiological role for plant lipoxygenase. Biochem. Biophys. Res. Commun. 111, 470–477.

Wagner, M., Zhang, B., Tauffenberger, A., Schroeder, F.C., Skirycz, A., 2021. Experimental methods for dissecting the terra-incognita of protein-metabolite interactomes. Current Opinion in Systems Biology 100403.

Wang, K., Guo, Q., Froehlich, J.E., Hersh, H.L., Zienkiewicz, A., Howe, G.A., Benning, C., 2018. Two Abscisic Acid-Responsive Plastid Lipase Genes Involved in Jasmonic Acid Biosynthesis in Arabidopsis thaliana. The Plant Cell. https://doi.org/10.1105/tpc.18.00250

Wasternack, C., 2017. A plant's balance of growth and defense--revisited. New Phytol. 215, 1291–1294.

Wasternack, C., 2014. Action of jasmonates in plant stress responses and development--applied aspects. Biotechnol. Adv. 32, 31–39.

Wasternack, C., 2007. Jasmonates: an update on biosynthesis, signal transduction and action in plant stress response, growth and development. Ann. Bot. 100, 681–697.

Wasternack, C., Feussner, I., 2018. The Oxylipin Pathways: Biochemistry and Function. Annu. Rev. Plant Biol. 69, 363–386.

Wasternack, C., Hause, B., 2013. Jasmonates: biosynthesis, perception, signal transduction and action in plant stress response, growth and development. An update to the 2007 review in Annals of Botany. Ann. Bot. 111, 1021–1058.

Wasternack, C., Strnad, M., 2018. Jasmonates: News on Occurrence, Biosynthesis, Metabolism and Action of an Ancient Group of Signaling Compounds. Int. J. Mol. Sci. 19. https://doi.org/10.3390/ijms19092539

Weber, H., Vick, B.A., Farmer, E.E., 1997. Dinor-oxo-phytodienoic acid: a new hexadecanoid signal in the jasmonate family. Proc. Natl. Acad. Sci. U. S. A. 94, 10473–10478.

Yamamoto, Y., Ohshika, J., Takahashi, T., Ishizaki, K., Kohchi, T., Matusuura, H., Takahashi, K., 2015. Functional analysis of allene oxide cyclase, MpAOC, in the liverwort Marchantia polymorpha. Phytochemistry 116, 48–56.

Yan, Y., Christensen, S., Isakeit, T., Engelberth, J., Meeley, R., Hayward, A., Emery, R.J.N., Kolomiets, M.V., 2012. Disruption of OPR7 and OPR8 reveals the versatile functions of jasmonic acid in maize development and defense. Plant Cell 24, 1420–1436.

Zhang, Y., Turner, J.G., 2008. Wound-induced endogenous jasmonates stunt plant growth by inhibiting mitosis. PLoS One 3, e3699.

Figures

Figure 1. Simplified scheme of the OPDA and JA biosynthesis (LOX pathway). LA (18:3n3) is released from the glycerolipids by phospholipases in the chloroplast. The action of LOX results in the conversion of α-LA into the hydroperoxide 13-hydroperoxyoctadeca-9,11-dienoic acid (13-HPOT). Following this step, AOS transforms 13- HPOT into the unstable allene oxide 12,13(S)-epoxylinolenic acid (12,13-EOT), which is further converted to OPDA by the AOC enzyme. OPDA translocation into the peroxisomes is mediated by JASSY, and once there is reduced to OPC-8:0 by OPR3, although this step may be bypassed (dashed line). OPC-8:0 is activated to the corresponding CoA ester by OPCL1 (OPC-8:0-CoA ligase 1). This is the entry-point of three β-oxidations carried out by ACX (acyl-CoA oxidase), MFP (multifunctional protein) and KAT (L-3- ketoacyl CoA thiolase). Jasmonoyl-CoA, is likely cleaved by a thioesterase to produce (+)-7-*iso*-JA, which can epimerize to the more stable (-)-JA. Finally, JAR1 conjugates JA to Ile in the cytoplasm resulting in JA-Ile. Arabidopsis mutants discussed in the review are indicated in blue for the particular step. Dashed lines and bonds indicate the existence of an OPR3-independent pathway and compounds, respectively.

Commented [GJ1]: It is not immediately obvious what this is referring to in the figure.

Also, in the figure, it is not clear which reaction is catalyzed by OPR2

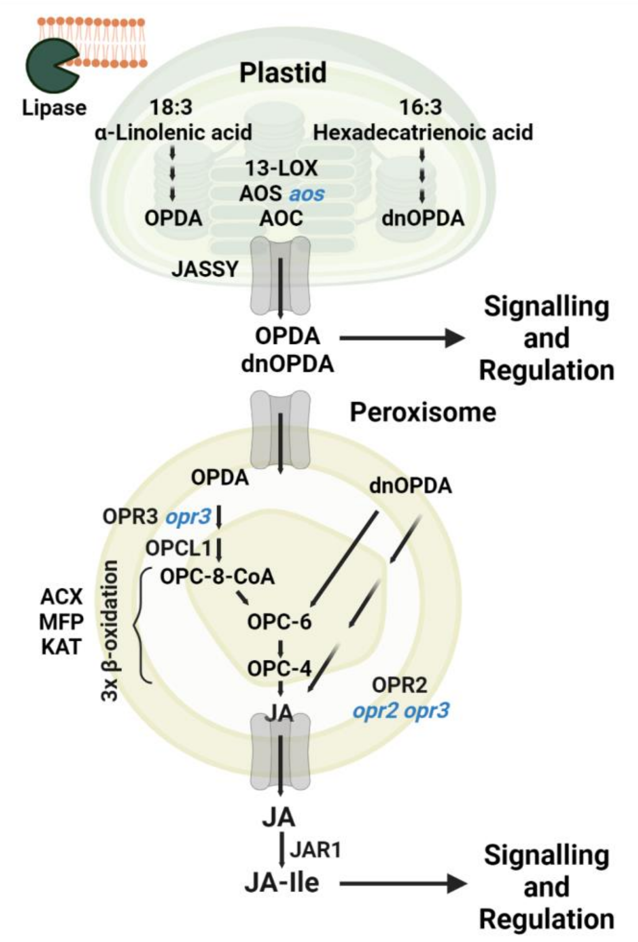
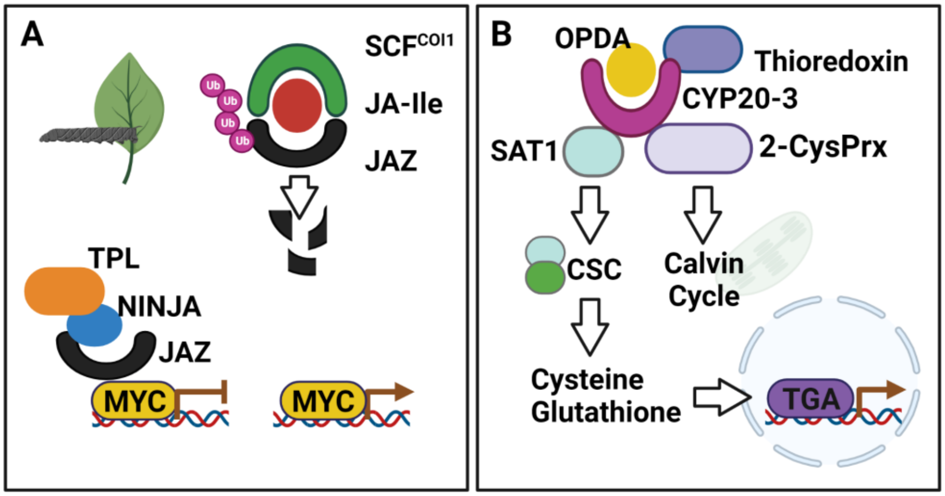

Lipase
Plastid
18:3
α-Linolenic acid
16:3
Hexadecatrienoic acid
13-LOX
AOS aos
AOC
OPDA
dnOPDA
JASSY
OPDA
dnOPDA
Signalling and Regulation
Peroxisome
OPDA
dnOPDA
OPR3 opr3
OPCL1
OPC-8-CoA
ACX
MFP
KAT
3x β-oxidation
OPC-6
OPC-4
JA
OPR2
opr2 opr3
JA
JAR1
JA-Ile
Signalling and Regulation

Figure 2. Schematic representation of jasmonoyl-L-isoleucine (JA-Ile) and 12-oxo-phytodienoic acid (OPDA) signaling. A) JA-Ile binding to the SCF^{COI1} receptor complex induces ubiquitination and subsequent degradation of the JAZ repressors and activates gene expression. **B)** OPDA binding induces the formation of the cysteine synthase complex (CSC) composed of serine acetyltransferase1 (SAT1), and *O*-acetylserine(thiol)lyase. Consequent changes to the redox status drive gene expression. OPDA also promotes activation of the peroxiredoxin, 2-CysPrx, directly impacting Calvin Cycle enzymes.



Graphic Abstract