

OPDA, more than just a jasmonate precursor

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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 OPDA protein interactome and biological roles of OPDA conjugates.

1. OPDA metabolism

The fatty acid (FA) derivative 12-oxo-phytodienoic acid (OPDA) belongs to a large group of natural compounds collectively called oxylipins, which are produced through oxygenation of polyunsaturated FAs (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 thaliana* (Arabidopsis) (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) (Fig. 1). Lipase-mediated liberation of α -LA is also a major regulatory step in OPDA synthesis, and activity of the lipases is subjected to 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 OPDA 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). Moreover, 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).

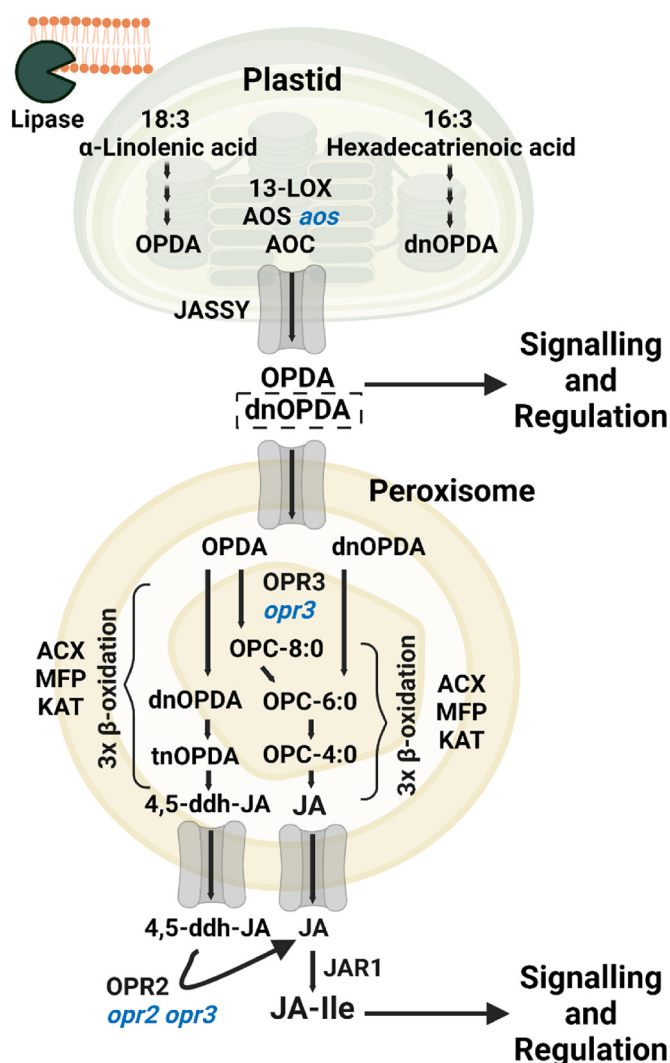
OPDA accumulates upon several environmental cues and can be

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metabolized to (–)-7-iso-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, 1997) 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,

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 esterase(s) 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.

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 (Fig. 1). JA-Ile binds to a coreceptor complex composed of the F-box protein coronatine insensitive 1 (COI1) and a jasmonate zim-domain (JAZ) protein, which, in the resting state, represses transcription factors of the MYC family (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 on-off switches 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 (Ferne 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, developmental and defense plant responses.

3. 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 JA-Ile precursor. 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 or JA identified approximately 150 transcripts, including multiple heat shock proteins and glutathione-S-transferases (Taki et al., 2005), that exhibit stronger responses to the 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 hyper-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 OPDA 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 folia 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 OPR2 (Chini et al., 2018) (Fig. 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 brassicola* (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 deplete and 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 insect pathogens described above, OPDA was also associated with the regulation of seed germination (Dave et al., 2011, 2016), 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) (Fig. 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 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 (Kourtschenko 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 chitoooligosaccharide-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;

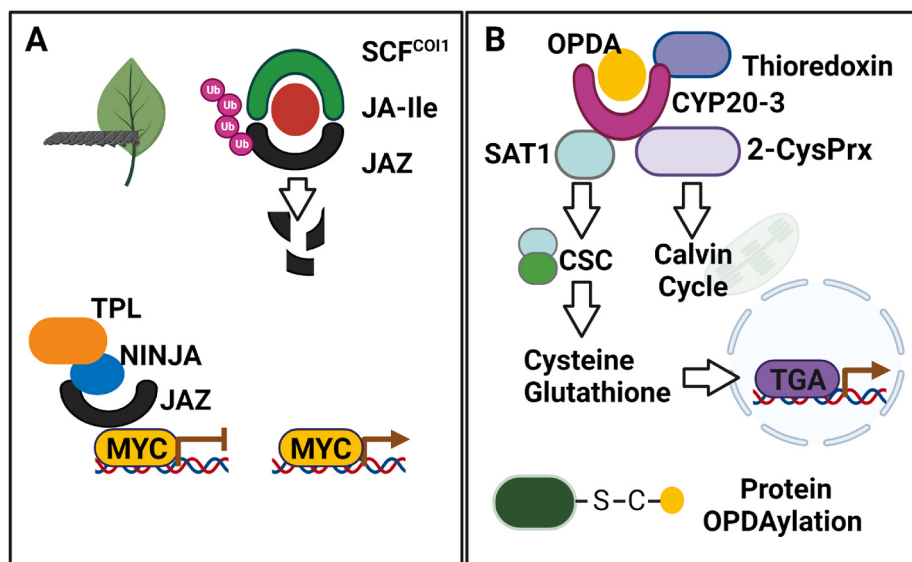


Fig. 2. Schematic representation of jasmonoyl-L-isoleucine (JA-Ile) and 12-oxo-phytodienoic acid (OPDA) signaling. A) JA-Ile binding to the SCF^{COI1} receptor complex induces ubiquitination and subsequent degradation of the JAZ repressors and activates gene expression. B) OPDA binding induces the formation 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. OPDA can also covalently modify protein cysteinyl thiols, which is referred to as OPDAylation, affecting protein activities.

Wasternack and Feussner, 2018). Therefore, it is difficult to rule out a JA-Ile-dependent activity in this experiment. Indeed, the typical JA-Ile concentration is approximately 10–100 fold lower than that of JA, and 100–1000 fold, or more, lower than that of 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.

4. OPDA, a 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 (Altioek et al., 2008). Moreover, among several tested jasmonates including, JA, 12-OH-JA, MeJA, and JA-Ile, only OPDA suppressed H₂O₂-induced cytotoxicity. OPDA pretreatment inhibited the H₂O₂-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.

5. 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., 2018, 2020; Soriano et al., 2022; Kneeshaw 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 *MpAOC* (Yamamoto et al., 2015). Conversely, the loss of OPDA production by *MpAOS1/2* 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 in *Marchantia* (Monte et al., 2019; Peñuelas et al., 2019). Moreover, transcriptional analysis of wild-type and *Mpcoi1* 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).

6. 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 on 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.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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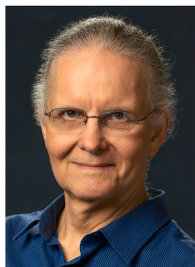


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