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Production of cross-kingdom oxylipins by pathogenic fungi: An update on their role in development and pathogenicity

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Abstract

Oxylipins are a class of molecules derived from the incorporation of oxygen into polyunsaturated fatty acid substrates through the action of oxygenases. While extensively investigated in the context of mammalian immune responses, over the last decade it has become apparent that oxylipins are a common means of communication among and between plants, animals, and fungi to control development and alter host-microbe interactions. In fungi, some oxylipins are derived non-enzymatically while others are produced by lipoxygenases, cyclooxygenases, and monooxygenases with homology to plant and human enzymes. Recent investigations of numerous plant and human fungal pathogens have revealed oxylipins to be involved in the establishment and progression of disease This review highlights oxylipin production by pathogenic fungi and their role in fungal development and pathogen/host interactions.

Keywords

oxylipins; fungi; microbial interactions

Introduction

Communication is key in all aspects of life processes. Organisms must be able to sense their surrounding environment and adapt accordingly depending on appropriate cues. It is becoming increasingly clear that plants, animals, and fungi all utilize oxygenated polyunsaturated fatty acids (oxylipins) as a common communication currency to elicit biological responses. In recent years, it has become apparent that fungi not only produce oxylipins to coordinate their developmental program, but to modify plant and mammalian host responses.

Oxylipins are produced by the incorporation of molecular oxygen into polyunsaturated fatty acids (PUFAs), and occasionally monounsaturated fatty acids, by the action of oxygenases. PUFAs vary by the length of the carbon chain and by the location/number of double bonds within the carbon chain. A list of unsaturated fatty acids and their corresponding oxylipin

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classes are listed in Table 1. C_{18} PUFAs such as linoleic, α-linolenic, and the monounsaturated oleic acid are classified as omega-6 fatty acids and are the predominant oxygenase substrates used in plants and fungi, specifically basidiomycetes and ascomycetes (Stahl and Klug, 1996). A C_{20} PUFA known as arachidonic acid (AA) is utilized by mammals to produce a class of oxylipins known uniquely as the eicosanoids (Fig. 1A). Most fungi only produce minor amounts of AA, however the zygomycete *Mortierella alphina* synthesizes large quantities of AA (Samadlouie *et al.*, 2014; Li *et al.*, 2015). Those fungi that do not produce significant amounts of AA readily utilize and oxygenate AA from environmental sources (Stahl and Klug, 1996) to generate various bioactive oxylipins implicated in disease development (Ells *et al.*, 2013).

Oxygenases are predominantly classified into three major categories in plants, animals, and fungi: cyclooxygenases (COX), including the α-dioxygenases which share common catalytic features with cyclooxygenases (Goulah *et al.*, 2013), lipoxygenases (LOX), and monooxygenases. The cyclooxygenase and lipoxygenase classes are well-known for their role in the synthesis of the AA-derived eicosanoids (Fig. 1A) that are regulators of mammalian immune responses, particularly with inflammation and allergy (Noverr *et al.*, 2003). Eicosanoids are potent and short-lived, usually being synthesized *de novo* and exerting their effects locally at nanomolar concentrations (Marks, 1999; Funk, 2001). Monooxygenases are a broader class of specialized cytochrome P450 enzymes that are responsible for downstream processing of many oxylipins, particularly in plants (e.g. allene oxide synthases, hydroperoxide lyases, divinyl ether synthases, and peroxygenases, Griffiths, 2015). While knowledge of oxylipin function in plants and animals has been known for several decades, the idea that host-pathogen “cross-talk” occurs and contributes to infection has only emerged in the last ten years since discovering that many microbes, including some fungi, produce prostaglandins and prostaglandin-like molecules (Noverr *et al.*, 2003). As a result, examples of inter-kingdom signaling molecules that are perceived between animals, plants, and fungi are now well documented (Table 2).

Here we present a summary of the oxylipins produced by each class of oxygenase in fungi, focusing on oxylipins that also have functions in plants and mammals. Recent examples of fungi responding to plant oxylipin defense molecules are provided as well as cases where the fungal oxylipins affect the mammalian host. Understanding what fungal species produce oxylipins and the mechanism by which they are perceived as cross-kingdom signaling molecules will have implications on both human health and global food production as fungi are intimately linked with both topics.

Fungal oxygenases and their corresponding oxylipins

Sequencing of fungal genomes has revealed putative homologs of canonical oxylipin-producing enzymes found in plants and mammals (Brodhun and Feussner, 2011). In some cases, biochemical analyses have determined oxylipins produced by particular oxygenases, some of which are already known to regulate biological responses in plants and animals. For example, eicosanoids derived from environmental or host AA have been identified in several pathogenic species of *Candida*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Epidermophyton floccosum*, *Fusarium dimerim*, *Microsporum audiouinii*, *Microsporum*

canis, *Trichophyton rubrum*, *Sporotrix schenkii*, *Absidia corymbifera*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Penicillium* spp., *Rhizopus* spp., *Rhizomucor pusillus*, and numerous *Aspergillus* species (Noverr et al., 2001, 2002, 2003).

Fungal cyclooxygenases

Prostaglandins were first identified in environmental yeasts of the Lipomycetaceae family (*Dipodascopsis*, *Lipomyces*, *Zygozyma*, and *Myxozyma*) and *Saccharomyces cerevisiae* in the early 1990s (Kock *et al.*, 1991; Noverr *et al.*, 2003). Since then, prostaglandins have been identified in *C. neoformans*, several pathogenic species of *Candida, P. brasiliensis*, and several *Aspergillus* spp. (Noverr *et al.*, 2002; Tsitsigiannis *et al.*, 2005a; Bordon *et al.*, 2007; Biondo *et al.*, 2010).

The psi factor-producing oxygenases (Ppo proteins), first described in the genus *Aspergillus* but found in most fungi, are a well characterized class of cyclooxygenase-like enzymes. These enzymes and their cognate oxylipins were initially investigated in the fungus *A. nidulans* with regard to their impact on asexual or sexual spore development (Champe *et al.*, 1987; Champe and El-Zayat, 1989; Tsitsigiannis *et al.*, 2004a, 2005c).

Aspergillus species contain between 3–4 Ppo enzymes (Tsitsigiannis *et al.*, 2004a, 2005c; Horowitz *et al.*, 2008; Brown *et al.*, 2009; Wadman *et al.*, 2009; Jernerén *et al.*, 2010a). Although chemical characterization has been assessed primarily with linoleic acid as a substrate, additional work suggest that Ppo proteins also oxidize oleic, linolenic, and arachidonic acids (Champe and El-Zayat, 1989; Mazur *et al.*, 1991; Calvo *et al.*, 2001; Tsitsigiannis *et al.*, 2005a) and may synthesize certain prostaglandins (Tsitsigiannis *et al.*, 2005a; Brown *et al.*, 2009).

PpoA in *A. nidulans* is well-characterized and contains two heme domains each of which catalyze specific reactions (Brodhun *et al.*, 2009). The N-terminal heme peroxidase domain predominantly oxidizes linoleic acid to 8(R)-hydroperoxyoctadecadienoic acid (8(R)-HPODE) which can be reduced to 8-hydroxyoctadecadienoic acid (8(R)-HODE), or further isomerized by the C-terminal P450 heme thiolate domain to 5,8-dihydroxyoctadecadieonic acid (5,8-DiHODE) (Garscha *et al.*, 2007; Brodhun, *et al.*, 2009; Fielding *et al.*, 2011). Studies with GFP-tagged forms of PpoA reveal that PpoA localizes to lipid bodies within the reproductive structures of *A. nidulans*, including the metulae of the asexual conidiophore and the Hülle cells and young cleistothecia of the sexual structures. Bioinformatic analysis of PpoA confirmed the presence of a proline knot motif essential for targeting proteins to lipid bodies (Tsitsigiannis *et al.*, 2004b). Thus, PpoA is localized within the reproductive tissues of *A. nidulans* (such as phialides, metulae, cleistothecia, and Hülle cells) with large quantities of fatty acid substrate in close proximity for conversion to oxylipins.

Other Ppo proteins are also involved in sporulation processes as determined by overexpression of, or deletion of, *ppo* genes or exogenous application of the oxylipins and their substrate produced by these (and host) enzymes affects sporulation in *Aspergillus* spp. (Calvo *et al.*, 1999; Tsitsigiannis *et al.*, 2005c). Detailed work with *A. nidulans* showed deletion of either *ppoA* or *ppoB* results in increased production of asexual spores with a corresponding decrease in sexual spore production whereas loss of *ppoC* yields the opposite

phenotype (Tsitsigiannis *et al.*, 2004a, 2004b, 2005c). In *A. flavus* where there are four *ppo* genes, disruption of both *ppoA* and *ppoC* resulted in decreased asexual sporulation whereas disruption of *ppoD* resulted in increased asexual sporulation in a density-dependent fashion (Brown *et al.*, 2009). In *A. fumigatus* deletion of *ppoC* significantly reduced spore numbers but resulted in enlarged spore size (Dagenais *et al.*, 2008). In addition to sporulation processes, Ppo proteins have an impact on diverse processes such as production of toxic secondary metabolites and degradative enzymes as will be discussed in greater detail in the fungal/plant interaction section below.

Several studies have focused on characterizing Ppo homologs (also known as linoleate diol synthases, linoleate dioxygenases, or LDSs) in fungi other than aspergilli. LDS-encoding genes have been identified in both pathogenic and non-pathogenic fungi including *Magnaporthe oryzae* (Cristea *et al.*, 2003; Jerneren *et al.*, 2010b), *Cercospora zeae-maydis* (Shim and Dunkle, 2002), *Ustilago maydis* (Huber *et al.*, 2002), and the cereal pathogen *Fusarium verticillioides* (Scala *et al.*, 2014). *Fusarium verticillioides* contains an LDS termed Fv*lds1* that produces oxylipins that regulates fungal development. Oxylipin profiling of a Fv*lds1* deletion strain identified reduced levels of 11-HPODE, 12,13-diHOME, 12-epoOME (epoxy-octadecenoic acid), 9,10-diHOME, 9-epoOME, 8,13-diHODE, 8-HPODE, and 8-HODE (Scala *et al.*, 2014).

The dimorphic fungus *C. neoformans* produces prostaglandin E_2 (PGE_2) that is identical to human PGE_2 even though a canonical cyclooxygenase is not present in the genome (Fig. 2). Mass spectrometry of *C. neoformans* lysate with exogenous AA identified PGE_2 production which could not be inhibited by the additions of aspirin or indomethacin, known inhibitors of cyclooxygenase enzymes (Erb-Downward and Huffnagle, 2007). Further studies identified that a *C. neoformans* laccase (*lac1*) was necessary to synthesize PGE_2 from exogenous AA. Recombinant Lac1 did not convert AA to PGE_2, but could convert a prostaglandin intermediate PGG_2 to PGE_2 and 15-keto-PGE_2, suggesting additional enzymes participate in *C. neoformans* prostaglandin production (Erb-Downward *et al.*, 2008).

Fungal lipoxygenases

Reports of fungal lipoxygenase activity were published as early as the 1950s. The first partially purified lipoxygenase was reported in *Fusarium oxysporum* in 1975 through the detection of linoleic acid-derived hydroperoxides with similar R*f* values to linoleic acid hydroperoxides from a soybean lipoxygenase (Satoh *et al.*, 1975). Since, LOX activity has been documented in the fungus *Pityrosporum orbiculare* (the causative agent of the skin disorder, pityriasis versicolor) (Nazzaro-Porro *et al.*, 1986; De Luca *et al.*, 1996), *Gaeumannomyces graminis* (the causative agent of take-all root rot disease) (Su and Oliw, 1996), *A. fumigatus* (Heshof *et al.*, 2014), and *A. flavus* (Horowitz Brown *et al.*, 2008).

The most recent comprehensive analysis of fungal lipoxygenases has been carried out by Heshof *et al.* (2014) who phylogenetically describe the relation of fungal LOXs with respect to their ability to be secreted (signal peptide sequence), their carboxy-terminal amino acid, oxylipin stereochemistry, and metal ion cofactor. Heshof *et al.* (2014) divided fungal LOXs into two groups: those that encode a C-terminal isoleucine (Ile-group) or valine (Val-group).

The Ile-group LOXs all contain a conserved WRYAK motif whereas the Val-group contain a conserved WL-L/F-AK sequence found in plant and mammalian lipoxygenases. The Val-group LOXs have signal peptide sequences suggesting the proteins are secreted extracellularly. Biochemical analysis of a Val-group LOX from *A. fumigatus* identified manganese as the cofactor and the predominant oxylipin product to be 13-HPODE, derived from linoleic acid (Heshof *et al.*, 2014).

In the plant pathogen *A. flavus*, the sole lipoxygenase (Lox) along with the Ppo proteins is involved in quorum sensing (Fig. 2). Disruption of either Lox or PpoC alters the density-dependent production of sclerotia and conidia: specifically, an increase in sclerotia and a decrease in conidia at high cell densities ($>10^5$ spores/plate) compared to increased conidia and decreased sclerotia in wild type (Horowitz *et al.*, 2008; Brown *et al.*, 2009). Mutants where all four *ppo* genes and *lox* were down-regulated together resulted in up to a 500-fold increase in the sexual stage and 100-fold decrease in the asexual stage (Brown *et al.*, 2009).

Fungal monooxygenases

Monooxygenases are much more prevalent in fungi than lipoxygenase or cyclooxygenase homologs. Only recently has a monooxygenase been definitively linked to oxylipin production in fungi, specifically with the production of 12-OH-jasmonic acid (12-OH-JA) in the rice blast fungus, *M. oryzae* (Fig. 1B) (Patkar *et al.*, 2015). A possible connection has been inferred with the dimorphic fungus *C. albicans*. Lipidomic studies of *C. albicans* cultures show that the fungus is capable of producing Resolvin E1, a potent anti-inflammatory oxylipin identified in mammals and derived from the modification of eicosapentaneoic acid (EPA) (Arita *et al.*, 2005) by a cytochrome P450 monooxygenase (CYP450s) and neutrophil 5-lipoxygenase in mammals (Arita *et al.*, 2005; Tjonahen *et al.*, 2006). *C. albicans* grown in the presence of EPA produces significant amounts of Resolvin E1 (Fig. 2). Furthermore, canonical mammalian LOX inhibitors, such as esculetin (12/15-LOX) and zileuton (5-LO inhibitor) inhibit the production of *C. albicans* RvE1 by 91% and 53%, respectively, yet a lipoxygenase is not present in the genome of the fungus. However, the genome encodes at least fifteen CYP450s that the authors speculate participate in one or multiple biosynthetic steps in Resolvin E1 production (Haas-Stapleton *et al.*, 2007).

Oxylipin perception

In mammals, eicosanoid oxylipins are detected by different G-protein coupled receptors (GPCRs) which vary depending on the cell type (Funk, 2001; Noverr *et al.*, 2003). Nine prostaglandin receptors have been identified in humans and mice: four of the receptors (EP_1-EP_4) bind PGE_2, two (DP_1 and DP_2) bind PGD_2, and PGF_2, PGI_2, and TxA_2 via FP, IP, and TP, respectively. Most of the prostaglandin receptors are localized at the plasma membrane, but some are also found in the nuclear envelope (Bhattacharya *et al.*, 1998; Funk, 2001). Cysteinyl leukotrienes are also perceived via two subtypes of GPCRs, $CysLT_1$ which is expressed on smooth muscle cells and vascular endothelial cells, and $CysLT_2$ which is expressed on spleen, Purkinje fibers of the heart, and regions of the adrenal gland. $CysLT_1$ activation promotes bronchoconstriction and up-regulation of cell adhesion molecules whereas the role of $CysLT_2$ is less clear. G2A is a GPCR expressed in lymphoid tissues that induces cell cycle arrest during the G_2/M transition and on macrophages near atherosclerotic

lesions. Oxylipins derived from linoleic and arachidonic acid including 9(S)-HPODE, 13(S)-HPODE, 5-HETE, 8-HETE, 8-HETE, 11-HETE, 12-HETE, 15-HETE, and 9(S)-HODE are recognized by G2A (Obinata *et al.*, 2005).

Interestingly, two of the G2A ligands, 13(S)-HPODE and 9(S)-HPODE, affect sporulation and mycotoxin production in *Aspergillus* (Burow and Nesbitt, 1997; Calvo *et al.*, 1999), suggesting that fungal GPCR receptors might also recognize and respond to these oxylipins. To query this possibility, Affeldt *et al.* (2012), characterized 10 *A. nidulans* GPCR disruption mutants and found that GprD was responsible for perception of 13(S)-HPODE, 9(S)-HPODE, 13(S)-HODE, and 9(S)-HODE (Affeldt *et al.*, 2012). Since then, a deletion library for GPCRs was developed in *A. flavus* and responses to PUFAs and oxylipins characterized (Affeldt *et al.*, 2014). Strains where *gprA*, *gprB*, *gprF*, *gprG*, *gprM*, *gprO*, *gprP*, or *gprR* are deleted are non-responsive to exogenous methyl jasmonate – a potent plant defense oxylipin (Fig. 1B and Table 2). Mutants where *gprA*, *gprC*, *gprD*, *gprF*, *gprG*, *gprJ*, *gprO*, or *gprP* are disrupted still sporulate in response to linoleic acid, but are non-responsive to the sporulation inducing oxylipin 13(S)-HPODE, suggesting that the lack of sporulation is specific to the inability to detect 13(S)-HPODE (Affeldt *et al.*, 2014).

Oxylipin signaling in fungal/host interactions

Fungi and plants

Jasmonic acid (JA) is a plant signaling molecule that is involved in plant responses to desiccation, ozone, UV, osmotic, cold and light stresses, and regulation of seasonal and circadian rhythms (Wasternack, 2014) (Table 2). Upon wounding, α-linolenic acid is liberated from chloroplast membranes via phospholipase A1 and is oxygenated by a 13-lipoxygenases (13-LOX), modified by a 13-allene oxide synthase (AOS) and allene oxide cyclase (AOC), and undergoes β-oxidation in peroxisomes to yield JA (Fig. 1B) (Wasternack, 2014). JA is only active when conjugated to an amino acid [valine, leucine, or isoleucine (Kang *et al.*, 2006; Wang *et al.*, 2007)] or methylated (Griffiths, 2015). Jasmonyl-isoleucine is formed specifically upon wounding or attack by fungi, leading to the production of toxic compounds that deter further damage and initiate plant defense responses. JA may impact aflatoxin production, a mycotoxin produced by *A. flavus*, during fungal invasion of seed although the literature supports cases for JA inhibition (Goodrich-Tanrikulu *et al.*, 1995), JA induction (Vergopoulou *et al.*, 2001), and no impact of JA (Burow and Nesbitt, 1997) on aflatoxin synthesis (Fig. 2).

Disrupting JA biosynthesis in *Arabidopsis* and in rice increases susceptibility to *F. oxysporum* and *M. oryzae* infection, respectively (Thatcher *et al.*, 2009; Riemann *et al.*, 2013). Specifically, the loss of allene oxide cyclase increases rice susceptibility to *M. oryzae* strains that are normally unable to cause virulence (Riemann *et al.*, 2013). A recent investigation by Patkar *et al.* (2015) identified a *M. oryzae* monooxygenase (referred to as antibiotic biosynthesis monooxygenase, or *abm*) that specifically modifies JA in rice. *M. oryzae* strains that lack *abm* grow like wild type with respect to appressorium formation, vegetative growth, and asexual development. However, the strains are severely attenuated in their ability to penetrate the rice cell wall. Only 35% of appressoria penetrate the rice sheath when *abm* is disrupted, compared to 70% in the wild type. When appressoria formation is

induced artificially on a glass surface, extracellular fluid from the wild type and the *Δabm* strains reveals a striking difference in the jasmonates produced by *M. oryzae*: wild type extracellular fluid contained JA and a hydroxylated derivative 12-OH-JA (Fig. 2), whereas *Δabm* fluid only contained JA and methyl-jasmonate (MeJA). Interestingly, addition of increasing concentrations of exogenous MeJA to the wild type strain reduce the number of invading appressoria in a dose-dependent fashion. Alternately, exogenous 12-OH-JA *increases* the number of *Δabm* invading appressoria in a dose-dependent fashion. The authors went on to identify that Abm is secreted from both the biotrophic interfacial complex (BIC) and the appressorium of *M. oryzae* during pathogenic growth, providing evidence that Abm hydroxylates not only *M. oryzae* JA, but plant-derived JA as well (Patkar *et al.*, 2015).

As mentioned earlier, *A. flavus* contains a single lipoxygenase that produces oxylipin products that influence host responses in maize and peanut. Lipidomic approaches to characterize the oxylipin profile of wild type and *lox* mutants on maize kernels show increased levels of diHODES and HPODE oxylipins in maize inoculated with the *Δlox* strain, suggesting that *A. flavus* Lox produces compounds that suppress maize kernel oxylipin production. Furthermore, the *lox* (also called *Δ*Af*lox1*) disruption strain is unable to produce aflatoxin in axenic culture under inducing conditions, but produces slightly more aflatoxin when grown on maize kernels (Scarpari *et al.*, 2014). The Lox product, 13-HPODE and its stable surrogate, 13-HODE have been well characterized as an important mediator of mammalian, plant, and fungal biological responses (Table 2). Seeds produce 13-HPODE and 9-HPODE, both lipoxygenase products, when subjected to abiotic or biotic stresses such as fungal infection. Both oxylipins alter secondary metabolism in *Aspergillus parasiticus* and *A. nidulans* (Gardner, 1995; Burow and Nesbitt, 1997), increase levels of asexual spores in *A. flavus* and *A. nidulans*, and increase cAMP levels in *A. nidulans* (Fig. 2) (Calvo *et al.*, 1999; Affeldt *et al.*, 2012). Experiments done with *F. verticillioides* infection of maize have revealed similar results: when inoculated on maize, LOX-derived products from linoleic acid (9- and 13-HODE) and linolenic acid (9- and 13-Hydroxy-octadecatrienoic acid or HOTE) were significantly up-regulated when compared to levels found in *F. verticillioides* or maize grown independently (Ludovici *et al.*, 2014).

Aspergillus infection alters plant *LOX* gene expression in corn (Wilson *et al.*, 2001) and in peanut (Burow *et al.*, 2000; Tsitsigiannis *et al.*, 2005b) through the action of *ppo* genes (Fig. 2) (Brodhagen *et al.*, 2008). Infection of peanut seeds with *A. nidulans* strains with defects in one or more *ppo* genes decreases peanut *13-LOX* (*pnlox2* and *pnlox3*) expression, specifically when inoculated with Δ*ppoAC* and Δ*ppoABC* strains (Brodhagen *et al.*, 2008). A *ppo* homolog in *F. verticillioides* (Fv*lds1*) influences plant *LOX* expression as well. Virulence assays on maize cobs revealed that a Fv*lds1* deletion strain is more virulent than wild type, and does not trigger the expression of *ZmLOX3* and *ZmPR4* as vigorously in maize as wild type (Scala *et al.*, 2014). *ZmLOX3* is a maize lipoxygenase that is induced upon interaction with mycotoxin-producing fungi (Gao and Kolomiets, 2009) and *ZmPR4* is a chitinase that helps degrade the invading fungal cell wall (Wang *et al.*, 2011). Interestingly, *ZmPR4* is known to be regulated through the action of ethylene- and jasmonic acid pathways in *Arabidopsis* (van Loon *et al.*, 2006). Maize strains where lipoxygenases are deleted (*lox3-4*) are more susceptible to *A. flavus* and *A. nidulans* infection. These fungi

produced more spores and increased amounts of mycotoxins when maize *lox3-4* are disrupted (Gao *et al.*, 2009).

Fungi and mammals

Higher eukaryotes rely heavily on oxylipins to respond to environmental factors and cue responses. Eicosanoids are derived from AA and include leukotrienes and prostanoids (prostaglandins, thromboxanes, and prostacyclins) (Fig. 1A). Leukotrienes (LTs including LTB_4 LTC_4, LTD_4, and LTE_4) are lipoxygenase derived and play an important signaling role in inflammation and bronchial smooth muscle contraction (Ford-Hutchinson, 1985; Henderson, 1994) (for review, see Singh *et al.*, 2013). Prostaglandins are cyclooxygenase-derived and have widespread roles in numerous diseases, with implications in bronchodilation, pain signaling, innate and adaptive immune responses, arthritis, atherosclerosis, and cancer (Simmons *et al.*, 2004; Park *et al.*, 2006).

Paracoccidioides brasiliensis evades dendritic cell recognition by inhibiting the production of PGE2 by immature dendritic cells, as their maturation is PGE2-dependent (Fig. 2) (Fernandes *et al.*, 2015). A potent derivative of PGE_2, 3-hydroxy-PGE_2, is produced by the yeast *Dipodascopsis uninucleata* and the commensal dimorphic fungus, *C. albicans* from the incomplete β-oxidation of exogenous arachidonic acid into 3-HETE (van Dyk *et al.*, 1991; Ciccoli *et al.*, 2005). Oxygenation of 3-HETE by purified COX-2 enzymes leads to the production of a milieu of 3-HETE-derived compounds, one of which (3-hydroxy-PGE_2, Fig. 1A) induces elevated expression of IL-6 mRNA in A549 cells when compared to PGE_2.) (Fig. 2). Co-incubation of *C. albicans* (which lacks a canonical COX-2 enzyme to produce 3-hydroxy-PGE_2) with HeLa cells led to the production of 3-hydroxy-PGE_2. Thus fungal derived oxylipin products can be modified by host cells into compounds that modify host cellular responses (Fig. 2) (Ciccoli *et al.*, 2005). Oxylipin transcellular biosynthesis is well documented in different cell types of mammals, particularly for leukotrienes (Fabre *et al.*, 2002; Folco and Murphy, 2006; Gijon *et al.*, 2007; Zarini *et al.*, 2009).

ppoC has been extensively studied in the context of pathogenicity for *A. fumigatus*. In addition to the reduction in asexual spores upon *ppoC* deletion, disruption alters conidial shape, germination rate, hydrogen peroxide susceptibility, and spore neutralization by alveolar macrophages (Dagenais *et al.*, 2008). Interestingly, even though Dagenais *et al* observed an increase in hydrogen peroxide resistance in the *ΔppoC* strain, spores were *more* susceptible to killing by alveolar macrophages, which carry out their killing via the production of superoxide anion. Thus, while catalase activity may be greater than or equal to that of wild type spores, the activity of superoxide dismutase is diminished when PpoC is absent.

Conclusion

Oxylipins are intimately linked to basic fungal development as demonstrated by alterations in the ratio of sexual to asexual structures, spore shape, germination rate, quorum sensing and mycotoxin (e.g. secondary metabolite) synthesis upon loss of oxylipin generating oxygenases or application of exogenous oxylipins. Fungal oxylipins can also modulate host oxygenase expression as illustrated by mRNA levels of peanut seed lipoxygenases in

response to *A. nidulans* oxylipin production. Fungal modification of plant oxylipins is also a crucial component of niche establishment since tissue invasion is severely compromised when an oxylipin producing monooxygenase is deleted in *M. oryzae*. In co-culture with mammalian cells, oxylipins that are unique to fungi can be modified by host cells yielding potent immune system-modulating oxylipins. Immune clearance of certain fungi can be enhanced by targeting the oxylipin-dependent development of dendritic cells. Thus oxylipins are central to many host-pathogen interactions. As more and more fungal genomes become available, it will be necessary to develop high-throughput screening platforms to identify oxylipins profiles for many organisms. Already rapid quantification schemes for oxylipin profiling have been described (Yang *et al.*, 2009), which will be useful for both *in vivo* and *in vitro* studies of oxylipin production in axenic or host-pathogen cultures.

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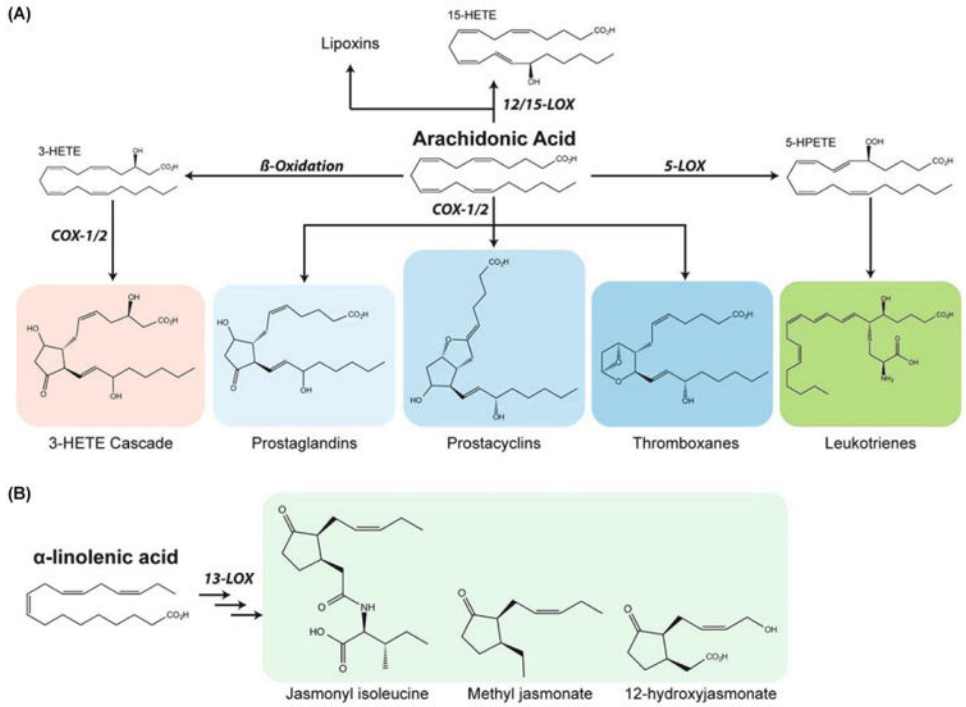


Fig. 1. Partial eicosanoid and jasmonic acid pathways and oxylipin products with biological activities

(A) Arachidonic acid (AA) can be modified by lipoxygenases (LOXs) or cyclooxygenases (COX-1/2) to yield different eicosanoids (prostanoids: blue boxes, leukotrienes: green box). A prostaglandin intermediate can be modified into thromboxanes or prostacyclins. Incomplete β-oxidation of AA by several fungi in co-culture with mammalian cells produces 3-HETE, that upon further modification by host COX enzymes yields a potent prostaglandin derivative, 3-OH-PGE2 (red box) (Ciccoli *et al.*, 2005). 5-LOX is the first committed step to leukotriene production, yielding the unstable intermediate, 5-hydroperoxyeicosatetraenoic acid (5-HPETE), from AA. 12- and 15-LOXs produce other immune-modulating compounds including lipoxins, which resolve inflammation, and 15-hydroxyeicosatetraenoic acid (15-HETE), a MAP kinase and PPAR-γ pathway activator (Kuhn and O'Donnell, 2006). (B) α-Linoleic acid is modified by a 13-lipoxygenase enzyme yielding 13(S)-HPOTE (13(S)-hydroperoxyoctadecatrienoic acid) that after additional modification yields jasmonic acid (JA). JA is further modified into several compounds including jasmonyl isoleucine (JA-Ile), methyl jasmonate (MeJA), and 12-hydroxyjasmonate (12-OH-JA) all of which are implicated in host-pathogen interactions.

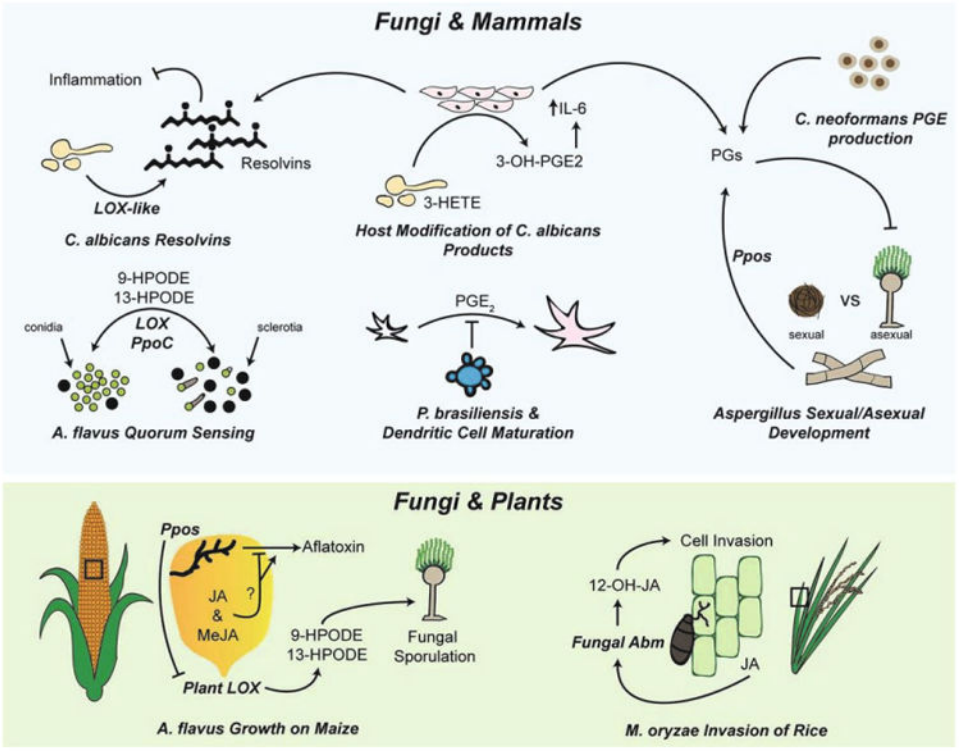


Fig. 2. Cross-species oxylipin signaling between plants, animals, and fungi

Oxylipins produced by fungi are documented in mammals and mediate important immunological responses and promote cell maturation. *Candida albicans* and *Paracoccidioides brasiliensis* both produce compounds that can impact host immunological responses, such as resolution of inflammation or immune cell maturation, respectively. Prostaglandins are central to many mammalian immune responses, but are also produced by many fungi and have been shown to impact sporulation. Fungal LOX activity is implicated in sporulation, but has been investigated more extensively in the plant context. Both fungal Ppos and LOXs can impact plant LOX expression through oxylipin production, inducing fungal sporulation in the plant host. A secreted *M. oryzae* monooxygenases modifies endogenous and plant jasmonic acid (JA) into 12-OH-JA greatly, increasing the efficiency at which the fungus infiltrates the plant cell.

Table 1
Polyunsaturated fatty acids and their cognate oxylipins

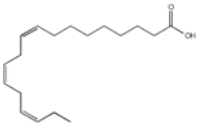
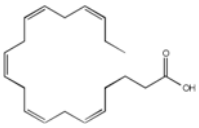
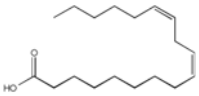
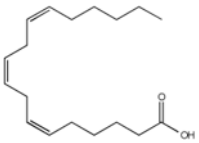
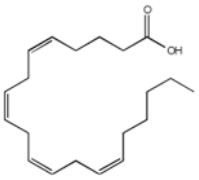
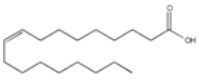
Fatty acid	Lipid name	Structure	Oxylipins
α-Linolenic acid	18:3 (n-3)		Hydroperoxyoctadecatrienoic acid (HPOTEs), Hydroxyoctadecatrienoic acid (HOTEs), di-hydroxyoctadecatrienoic acid (diHOTES)
Eicosapentaenoic acid	20:5 (n-3)		Resolvin E1
Linoleic acid	18:2 (n-6)		Hydroperoxyoctadecadienoic acid (HPODES), Hydroxyoctadecadienoic acid (HODES), di-hydroxyoctadecadienoic acid (diHODES)
δ-Linolenic acid	18:3 (n-6)		Hydroperoxyoctadecatrienoic acid (HPOTEs), Hydroxyoctadecatrienoic acid (HOTEs), di-hydroxyoctadecatrienoic acid (diHOTES)
Arachidonic acid	20:4 (n-6)		Hydroperoxyeicosatetraenoic acid (HPETE), Hydroxyeicosatetraenoic acid (HETEs), di-hydroxyeicosatetraenoic acid (diHETEs), Leukotrienes (LTs), Prostaglandins (PGs), Lipoxins, Thromboxanes
Oleic acid	18:1 (n-9)		Hydroperoxyoctanoic acid (HPOMES), Hydroxyoctanoic acid (HOMEs), di-hydroxyoctanoic acid (diHOMEs)

Table 2

Oxylipins with cross-kingdom roles in mammals, plants, and fungi

Oxylipin	Full name	PUFA	Enzyme	Mammals	Plants	Fungi
9-HODE (9-HPODE)	9S-Hydroxyoctadecadienoic acid	Linoleic acid	LOX	Induce Ca^{2+} mobilization via G2A GPCR receptor (Obinata *et al.*, 2005).	Induce programmed cell death in tomato protoplasts (Knight *et al.*, 2001).	Altered *A. nidulans* sporulation (Calvo *et al.*, 1999). Promote cAMP production via fungal GPCR signaling (Affeldt *et al.*, 2012).
13-HODE (13-HPODE)	13S-Hydroxyoctadecadienoic acid	Linoleic acid	LOX	Airway hyperresponsiveness (Henricks *et al.*, 1995; Cooper *et al.*, 2010) and disruption of Ca^{2+} homeostasis in airway epithelial cells and bronchial cell injury (Ng *et al.*, 2007; Spears *et al.*, 2009).	Produced as product of lipid body mobilization during cucumber germination (Feussner *et al.*, 1995). Proposed to be “labeled form” of lipid stores for β-oxidation during germination (Feussner *et al.*, 1997, 2001).	Suppress mycotoxin production (Burow and Nesbitt, 1997) and promote asexual spore production (Calvo *et al.*, 1999). Promote cAMP production via fungal GPCR signaling (Affeldt *et al.*, 2012).
5-HETE (5-HPETE)	5-Hydroxyeicosatetraenoic acid	Arachidonic acid	LOX	Precursor to leukotriene biosynthesis. Potent survival factor that inhibits apoptosis of human prostate cancer cells (Ghosh and Myers, 1998).	Induce programmed cell death in tomato protoplasts (Knight *et al.*, 2001).	-
15-HETE (15-HPETE)	15-Hydroxyeicosatetraenoic acid	Arachidonic acid	LOX	Precursor to lipoxin biosynthesis. Induces constriction of pulmonary arteries in response to hypoxia (Zhu, 2003). Modulate vascular smooth muscle and endothelial cell function (Campbell and Gauthier, 2013) and cell proliferation (Schneider and Pozzi, 2011).	Induce programmed cell death in tomato protoplasts (Knight *et al.*, 2001).	-
JA	Jasmonic acid	α-Linolenic acid	LOX/Allene Oxide Synthase	Suppresses proliferation and induces apoptosis in human lymphoblastic	Global plant stress, defense, and	JA and numerous analogs produced by *F. oxysporum*

Oxylipin	Full name	PUFA	Enzyme	Mammals	Plants	Fungi
				leukemia cells (Fingrut and Flescher, 2002).	developmental processes (Wasternack, 2014).	(Miersch *et al.*, 1999a) and *A. niger* (Miersch *et al.*, 1999b).
MeJA	Methyl jasmonate	α-Linolenic acid	LOX/Allene Oxide Synthase/Others	Membrane depolarization and cytochrome C release of human leukemic cancer lines (Rotem *et al.*, 2005). Suppress proliferation and induces apoptosis in human lymphoblastic leukemia cells (Fingrut and Flescher, 2002).	Global plant stress, defense, and developmental processes (Wasternack, 2014; Patkar *et al.*, 2015).	Secondary metabolite induction (Ren *et al.*, 2010).
12-OH-JA	12-Hydroxy-jasmonic acid	α-Linolenic acid	Monooxygenase	-	Promotes flower and tuber development, suppresses plant defense responses (Patkar *et al.*, 2015).	Produced during host penetration and suppresses methyl jasmonate formation (Patkar *et al.*, 2015).
8-HODE	8-Hydroxyoctadecadienoic acid	Linoleic acid	COX-like	-	-	*Aspergillus* fungal sporulation factor (Champe and El-Zayat, 1989; Mazur *et al.*, 1990). Secreted by *Laetisaria arvalis* and is antifungal to plant pathogenic strains of *Pythium ultimum* (Bowers *et al.*, 1986).
5,8-diHODE	5,8-Dihydroxyoxctadecadienoic acid	Linoleic acid/8-HODE	COX-like	-	-	Inducer of sexual development in *A. nidulans* and regulates ratio of asexual to sexual spores (Champe and El-Zayat, 1989; Mazur *et al.*, 1990, 1991; Tsitsigiannis and Keller, 2007; Horowitz Brown *et al.*, 2008).
PGs	Prostaglandins (PGD_2, PGE_2, PGF_2)	Arachidonic acid	COX/COX-like	Central role in initiation of inflammatory responses. For review,	-	Produced by COX-like enzymes Ppos in *A. fumigatus*

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Oxylipin	Full name	PUFA	Enzyme	Mammals	Plants	Fungi
				see (Ricciotti and Fitzgerald, 2011). PGE_2 enhances Thl7 host defenses of mucosa (Valdez *et al.*, 2012).		(Tsitsigiannis *et al,* 2005a) and produced by *C. neoformans* and *C. albicans* (Noverr *et al.*, 2001). Production of PGE_2 by *C. neoformans* suppresses IL-17-dependent antimicrobial responses (Valdez *et al.*, 2012).
LTs	Leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4)	Arachidonic acid	LOX	Induce bronchial smooth muscle contraction (Barnes *et al.*, 1984), promote mucus secretion in airway (Henderson, 1994), and promote recruitment of leukocytes (Ford-Hutchinson, 1985). For review, see (Singh *et al.*, 2013).	-	Produced by pathogenic fungi (Noverr *et al.*, 2002). No documented response on fungi.
3-HETE	3-Hydroxyeicosatetraenoic acid	Arachidonic acid	Unclear/Monooxygenase	Affects signal transduction in human neutrophils and tumor cells (Nigam *et al.*, 1999; Kock *et al.*, 2003).	-	Regulatory role of sexual cycle in *D. uninucleata* (Kock *et al.*, 1998). Associated with proper aggregation of ascospores in *D. uninucleata* (Kock *et al.*, 1999).