Differential Effect of Lipoxygenase on Aflatoxin Production by Aspergillus spp.

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ABSTRACT

Lipoxygenase (LOX : EC 1.13.11.12) (linoleate : oxygen oxidoreductase) constitute large gene family of non heme iron containing fatty acid dioxygenases. LOXs have been hypothesized to play a role in response to many plant pathogens and significant in plant microbe interactions. Increased LOX activity and rapid lipid peroxidation are a general response to biotic and abiotic stress. The increase in LOX activity has been observed in plant tissue and cells in response to infections with bacteria, fungal and viral pathogens. Plant LOX preferentially introduce molecular oxygen in to linoleic (LA) and Linolenic Acids (ALA) either at C9 (9-LOX) or C13 (13-LOX) of the hydrocarbon backbone of the fatty acid to produce 9S or 13S-hydroperoxy octadecadienoic acid (9S- or 13S-HPODE) or 9S- or 13S- hydroperoxy octadecatrienoic acid (9S- or 13S- HPOTE). These hydroperoxides are significant in regulating Aflatoxin (AF)-a toxic secondary metabolite, biosynthesis by fungi, namely Aspergillus flavus and Aspergillus parasiticus. The 9S-HPODE promotes where as 13S-HPODE, 13S-HPOTE and down stream derivatives of 13S-HPODE as well as 13S-HPOTE inhibits aflatoxin production by A. flavus. Aldehyde products of 13S-HPODE and 13S-HPOTE have been observed to inhibit the germination of A. flavus spores and/or aflatoxin production. The differential expression of LOX and the subsequent effect of LOX metabolites on aflatoxin production in different plant varieties are presented in this review.

Key words: Lipoxygenase, hydroperoxy octadecadienoic acid, hydroperoxy octadecatrienoic acid, Aspergillus flavus, Aspergillus parasiticus, aflatoxin

INTRODUCTION

One of the most notorious mycotoxins is Aflatoxin (AF), the polyketide secondary metabolite, produced by Aspergillus flavus and Aspergillus parasiticus (Chen et al., 2004; Deepak et al., 2003; Iheshiulor et al., 2011). These two fungi causing aflaorot or yellow mold are parasitic on various oil seed crops such as peanuts, cottonseed, sunflower etc. (Liang et al., 2006; Diener et al., 1987) or on starchy seeds such as maize kernels, sorghum, corn and cereals. The fungi preferentially colonize on lipid rich parts of seed and produce AF (Alwainekel and Nasser, 2011; Brown et al., 1993; Keller et al., 1994). The mycelium grows as white to gray, tough felty mass which is submerged in seed coat. The conidial heads of fungus are in shades of green. The inoculum for fungal infection can be sclerotia, fungal hyphae or wind blown conidia. Inoculum germinates leading to fungal growth which produces aflatoxin and sporulation resulting in secondary infection (Wilson et al., 2001). Fungus requires a relative humidity of 83.3% and temperature of 30°C for
its optimum growth (Elamin et al., 1988). Aflatoxins B₁, B₂, G₁, G₂, M₁ and M₂ are the six major aflatoxins. A. flavus produce aflatoxin B₁ (AflB₁) whereas A. parasiticus produce AflB₁ and aflatoxin G₁ (AflG₁) (Payne, 1992). Among them AflB₁ is more carcinogenic and more common contaminant (Prabakaran and Dhanapal, 2009). Aflatoxins are carcinogenic to poultry when fed on contaminated meals (Okiki et al., 2010; Olsen et al., 1988). High incidence of liver cancer by hepatitis B virus was reported on continual ingestions of low level of aflatoxin (Reddy et al., 2010). Aflatoxins have been associated with various other diseases such as aflatoxicosis immunosuppression and growth reduction in animals (Hell et al., 2005). Mycotoxins in food can come directly from contaminated grains, oil seeds and other foods contaminated with toxigenic fungi e.g., contaminated meet (Biswa et al., 2010) or indirectly through food chain e.g., milk from cows fed with contaminated food.

Aflatoxin producing fungi can invade the seed before harvest, during post harvest drying, curing, during storage or during transportation (Youssef et al., 2008). The marketability of aflatoxin-contaminated products in international trade is diminished to a great extent as stringent standards of permissible limits are set by many importing countries (Shahidi Bonjar, 2004; Deepak et al., 2006). Traditional plant protection and breeding methods are not sufficient to prevent this disease. Adopting some cultural practices, curing, drying and storage practices can minimize aflatoxin contamination. But these practices are not suited to small-scale farming in developing countries. Pathogen control or removal of toxin by using chemicals have not yet been completely successful (Mehan et al., 1987). Research efforts have turned to study the molecular events regulating the Aspergillus spp. seed interaction. An emerging concept as a means to develop effective control measures is the molecular cross-talk between the two via fatty acid signaling.

Lipoxygenase (LOX) have been hypothesized to play a regulatory role in response to many plant pathogens (Doehlert et al., 1993; Kolomiets et al., 2000) and significant in plant microbe interactions (Gardner, 1991; Kolomiets et al., 2000; Devi et al., 2005). Increased LOX activity and rapid lipid peroxidation are a general response to biotic and abiotic stress. The increase in LOX activity has been observed in plant tissue and cells in response to bacterial, fungal and viral infections (Sucharita et al., 2010). LOX metabolites might be acting directly on the pathogen leading to the development of resistance (Devi et al., 2000). The function of LOX in the defense against pests seems to be related to the synthesis of a number of different compounds with signaling functions (Parchmann et al., 1997). Which include antimicrobial activity (Croft et al., 1993; Weber et al., 1999) providing building units of physical barriers against pathogen invasion, regulation of plant cell death and have a major role in the formation of phytohormones, in senescence and inhibition of aflatoxin production (Tsitsigiannis and Keller, 2007) or development of the Hypersensitive Response (HR) (Rusterucci et al., 1999). This review will focus on the plant lipoxygenase (LOX)-mediated signaling pathway in regulating aflatoxin production.

**Lipoxygenase mediated lipid metabolism:** Plant lipids consist of a large family of cell membrane components, including neutral lipids and polar lipids (Welti and Wang, 2004). Polar lipids include the major membrane lipids, in which fatty acids or other hydrocarbon moieties vary in their chain length and degree of saturation. Composition of membrane lipid species differs among cell types and is frequently altered during plant development or in response to environmental stresses (Wang, 2004). Polar lipid species are cleaved by lipases and release polyunsaturated fatty acids (PUFA). These PUFAs include linoleic acid (LA-18:2) and α-linolenic acid (ALA-18:3), the major substrates for lipoxygenase (LOX: EC 1.13.11.12) (linoleate : oxygen oxidoreductase). It
constitute large gene family of non heme iron containing fatty acid dioxygenases. LOX catalyzes the addition of molecular oxygen to PUFA containing cis, cis-1,4-pentadiene system to produce an unsaturated fatty acid hydroperoxide (Suchartha and Devi, 2010). The reaction is stereo-and regioselective (Eskin et al., 1977; Brash, 1996; Feussner and Wasternack, 2002). Distinct plant LOX isozymes catalyzes the addition of molecular oxygen to LA and ALA either at C9 (9-LOX) or C13 (13-LOX) of the hydrocarbon backbone of the fatty acid to produce 9S or 13S-hydroperoxy octadecadienoic acid (9S- or 13S-HPODE) or 9S- or 13S-hydroperoxy octadecatrienoic acid (9S- or 13S-HPOTE) (Munikumari and Uma Maheshwari Devi, 2010). Primary LOX hydroperoxide products are further metabolized to form a large class of diverse oxidized fatty acids collectively called oxylipins. The LOX metabolite biosynthesis is organized into discrete 13-LOX and 9-LOX pathways, which are divided into several sub branches with six enzymes viz., Lipoxygenase, Hydroperoxide lyase (HPL), Allene Oxide Synthase (AOS), Divinyl Ether Synthase (DES), Epoxy Alcohol Synthase (EAS) and Peroxygenase (POX) (Howe and Schilmiller, 2002). The lipoxygenase metabolites derived from branches of lipoxygenase pathway have diverse physiological functions (Feussner and Wasternack, 2002; Howe and Schilmiller, 2002). During wounding, diffusible signaling compounds such as methyl jasmonate and C6 volatiles (Bate and Rothstein, 1998) are derived from the LOX pathway initiating the plant defense response (Bohlmann et al., 1998). Several products of the LOX pathway are known to have antimicrobial-insecticidal properties. For example, in potatoes the elimination of LOX activity by antisense technology was reflected in the weight gain of insect pests feeding on the antisense potatoes (Royo et al., 1999). Antisense suppression of a LOX gene in tobacco allowed Phytophthora parasitica to successfully infect a resistant tobacco cultivar (Rance et al., 1998). Indeed, even the primary 9(S) and 13(S)-hydroperoxides have antifungal and anti-microbial properties (Devi et al., 2000). In addition, LOX gene expression in plant tissues is often important for normal plant development (Dubbs and Grimes, 2000a, b).

The 13-LOX pathway: When plants are attacked by bacterial or fungal pathogens, lipases are activated releasing the polyunsaturated fatty acids. Lipoxygenase acts on these PUFA and synthesizes a range of LOX products with diverse roles. Regulatory molecules such as traumatin (12-oxo-trans-10-dodecenolate), aldehydes and alcohols are derived from the Hydroperoxide Lyase (HPL) branch of 13-LOX pathway. C-5 aldehydes like hexenal, hexenol and C-12 omega-keto-fatty acids compounds have active role in plant defense. These are major volatile constituents of fruits, vegetables and green leaves. Other compounds like cis-3-hexenal, trans-3-hexenol and trans-2-hexenol are important in defense against microbial pathogen and insect attacks (Vancanneyt et al., 2001). They also give flavors and tastes to plants (Siedow, 1991). The C12 product derived from linolenic acid is the precursor of traumatin (12-oxo-cis-9-dodecenolic acid) or wound hormone, a compound that triggers cell division, leading to the development of a protective callus around it (Andersson et al., 2006; Siedow, 1991; Blee, 1998). Traumatin can be converted to traumatic acid non enzymatically by oxidation of the aldehydes moiety (Vick and Zimmerman, 1987). This compound was first isolated from mesocarp of wound in bean plants. It was shown to enhance cell proliferation at the wound site (Croft et al., 1993). The Short-chain aldehyde products of the 13-HPL pathway also play important roles in defenses against microbial pathogens and insects. The 13- hydroperoxy linolenic acids are converted by LOX and/or peroxygenase to epoxy and hydroxyl derivatives (Blee, 1998). Peroxygenase further reduces epoxides to corresponding alcohols (Kohlmann et al., 1999). The epoxides can also be converted to hydroxides by hydroperoxy
lyases forming toxic compounds that are involved in defense responses against fungal infection (Namai et al., 1993). Conversion of 13-hydroperoxy linolenic acid by the action of AOS leads to the biosynthesis of Jasmonate family of compounds viz jasmonic acid (JA), Methyl Jasmonate (MeJA) and their metabolic precursor, 12-oxo-phytodienoic acid (12-OPDA). Allene oxide synthase and allene oxide cyclase converts 13-HPODE to Dihydro-12-oxo-PDA and 13-HFOTE to 12-oxo-PDA these metabolic precursors in later steps leads to the formation of Dihydroepijasmonic acid and JA, respectively. The conversion of linolenate to 12-oxo-phytodienoic acid occur in chloroplast, whereas the reduction of 12-oxo-phytodienoic acid and beta-oxidation steps leading to iso-jasmonate formation occur in the peroxisome (Hoffman et al., 2005). The 13-hydroperoxides formed in potato leaf are involved in the synthesis of jasmonate (Royo et al., 1996). JA is involved in gene activation during wound response in plants as many plants respond to insect damage or wounding by the production of jasmonate. Jasmonic acid is spontaneously decomposed to form ketols and racemic 12-oxo-phytodienoic acid. JA is also a signaling molecule that mediate plant responses toward herbivory and pathogen infection, resulting in the activation of distinct sets of defense genes (Reymond and Farmer, 1998; Maleck and Dietrich, 1999). 13-LOX and 13-DES act on LA forming divinyl ethers-etheroleic and etheroleic acid. These were reported from the garlic bulbs and ranunculus leaves (Greedkin and Hamberg, 1996; Hamberg, 1998). The α-and γ-ketols are formed by hydroperoxide isomerase pathway.

**The 9-LOX pathway:** The 9-hydroperoxy fatty acids, 9-HPODE and 9-HFOTE generated by 9-LOX are further metabolised by isoforms of AOS, HPL and DES resulting in formation of 9-LOX metabolites that are structurally related to but distinct from, the 13-LOX metabolites. The 9-LOX derived divinyl ether fatty acids coeneleic and coeneleneic acids are produced in leaves of plants when infected with fungi (Stumpe et al., 2001). These products were reported to accumulate quickly in phytophthora-infected potato leaves inhibiting fungal growth (Blee, 1998). The 9-LOX derived hydroperoxide lyase aldehydes are defense compounds that also give special flavors. For example, (2E)-nonenal gives the cardboard flavor of aged beer and the off-flavor of aged milled rice. The 9-HPL activity was reported from a few plant species of rice and cucumber (Kuroda et al., 2006). The 9-hydroperoxide of linolenic acid, converting to truns-2, cis-6-nonadienal by a corresponding lyase activity was reported in bean plant (Mathew and Galliard, 1978). Short chain aldehydes have antimicrobial effect and defense roles against herbivores (Wasternack, 2007). The 9-LOX and AOS converts α-linolenic acid into metabolites viz.,(12Z, 15Z)-9-hydroxy-10-oxo-12,15-octadecadienoic acid (α-ketol) and (11E, 15Z)-10-oxo-13-hydroxy-10,15-octadecadienoic acid (γ-ketol). The α-ketol is also an endogenous flowering factor.

**Role of LOX on aflatoxin production:** A family of lipid dioxigenases known as lipoxygenases existing in many filamentous fungi are conserved to produce oxylipins. These are structurally and physiologically similar to oxylipins produced by plant lipoxygenases (Champe and El-Zayat, 1989; Champe et al., 1987; Tsitsigiannis and Keller, 2007). Several studies evidence that plant and fungal oxylipins are involved in fungus-host communications and can functionally substitute for each other. Studies have uncovered fungus-host interaction governed by oxylipins (Brodhagen et al., 2008; Devi et al., 2000). It has been proposed that A. flavus possesses a mechanism, where a sclerotia-to-conidial transition is governed by lipoxygenase activity and cell density (Brown et al., 2009). Peanut LOX expression was muted when seed were infected by Aspergillus oxylipin mutants (Brodhagen et al., 2008). Several lines of evidence suggest that host
oxylipins can mimic or interfere with endogenous fungal oxylipins, affecting fungal development. Reciprocal “cross talk” between fungus and seed was also demonstrated when plant LOX expression was altered in response to fungal infection in peanut, maize and pigeon pea (Munikumari and Uma Maheshwari Devi, 2010; Burow et al., 2000; Tsitsigiannis and Keller, 2006; Devi et al., 2000). Brown et al. (2009) presented an evidence for the involvement of four more oxylipin generating dioxygenases (PpoA, PpoB, PpoC and PpoD) in A. flavus and the effects of loss of these genes on aflatoxin production and seed colonization. They demonstrated a strain deficient in all five oxygenases (invert repeat transgene [IRT] strain IRT4 = ppoA, ppoB, ppoC, ppoD and lox) which resulted in blockage of the sclerotia-to-conidia transition and highly upregulated AF production. They propose that A. flavus Ppos and the oxylipins they produce participate in developmental shift and act in a host-fungus interaction network that affects differentiation processes. Conidiation and toxin production by A. flavus were increased during colonization of a maize lox3-4 mutant, as recently reported by Gao et al. (2009). These observations suggest that at least certain oxylipins, directly or indirectly, act to limit AF production.

Differential effect of 13-HPODE/13-HPOTE and 9-HPODE/9-HPOTE on aflatoxin production: Fatty acid derivatives of the plant lipoxygenase (LOX) pathway are implicated in the Aspergillus spp.-seed interaction, affecting the growth, development and AF production of the fungus. The LOX specific placement of the hydroperoxy moiety on the ninth or thirteenth carbon atom of linoleic acid and linolenic acid leads to the formation of 9S-HPODE and 9S-HPOTE and 13S- HPODE and 13S-HPOTE, respectively and this could account for the differential effects on AF biosynthesis by A. flavus and A. parasiticus (Brown et al., 1993; Trail et al., 1995; Yu et al., 1995, 1996; Munikumari and Uma Maheshwari Devi, 2010). These hydroperoxides are significant in regulating aflatoxin biosynthesis, 9-S HPODE promotes aflatoxin production whereas 13S-HPODE and 13S-HPOTE reduces the aflatoxin production (Burow et al., 1997). Fatty acid derivatives of seed Lipoxigenase (LOX) directly affect the production of AF in vitro. Specifically, LOX products 13S-HPODE and 13S-HPOTE reduced levels of AF gene transcripts and 9S-HPODE extended the time period in which AF gene transcripts were detected (Burow et al., 1997). Calvo et al. (1999) reported that PUFA hydroperoxides produced by LOX can affect mycotoxin biosynthesis in Aspergillus spp., by mimicking the effects of some sporulation factors. In addition 13S-HPODE induces conidial development, whereas 9S-HPODE at low concentration enhances ascospore production. It was proposed that 9S- and 13S-hydroperoxides could have different effects on mycotoxin production since 9S- stimulated whereas, 13S-hydroperoxides inhibited mycotoxin production. Furthermore, Burow et al. (2000) have shown that expression of a peanut LOX gene, pnl0x1, is stimulated by A. parasiticus infection and that levels of 9S-HPODE increased in Aspergillus spp. infected peanut seed. Downstream derivatives of 13S-HPODE and 13S-HPOTE such as methyl jasmonate inhibits aflatoxin production by A. flavus but not fungal growth on agar media (Goodrich-Tanrikulu et al., 1995). Aldehyde products of 13S-HPODE and 13S-HPOTE have been observed to inhibit the germination of A. flavus spores and/or AF production and the inhibitory effect was correlated with linoleic acid levels in maize hybrids (Zeringue et al., 1996). 13S-HPODE and 13S-HPOTE inhibit accumulation of norsolorinic acid and sterigmatocystin compounds of aflatoxin pathway. This inhibition is believed to occur by interfering with Aspergillus growth or interfering with aflatoxin (ver-1)/sterigmatocystin (steU) regulatory genes or by repressing aflatoxin/sterigmatocystin gene expression. In contrast 9S-HPODE and 9-HPOTE is believed to boost AF production by delaying the natural turning off of the genes in the pathway or by directly
depressing AF gene expression by *Aspergillus*. It was proposed that susceptible crops can develop their own defense mechanism after introduction of the 13-hydroperoxy producing lipoxygenase or antisense gene to the 9-hydroperoxy producing lipoxygenase. Resistant plant can be resulted by mutating 9-HPODE and 9-HPOTE producing lipoxygenase by physical or chemical mutagens until such lipoxygenases are non-functional (Keller, 1998). Wilson *et al.* (2001) screened LOX Expressed Sequence Tags (ESTS) in aflatoxin susceptible seed infected with *Aspergillus* spp. They identified high expression of CSSAP 92 clone which adds oxygen to carbon 9 of linoleic acid forming 9S-hydroperoxy linoleic acid. As 9S-hydroperoxy linoleic acid is aflatoxin signaling molecule they suggest that CSSAP 92 could be used as a biomarker. Gao *et al.* (2007) worked on concept that oxylipins produced by the maize 9-LOX pathway are required by pathogens to produce spores and mycotoxins and to successfully colonize the host. They tested with the Maize mutants in which the function of a 9-LOX gene, ZmLOX3, was stopped by an insertion of a Mutator transposon in its coding sequence, which resulted in reduced levels of several 9-LOX-derived hydroperoxides. In their study conidiation and production of the mycotoxin fumonisins B1 by *Fusarium verticillioides* were drastically reduced in kernels of the lox8 mutants compared with near-isogenic wild types. Similarly, conidia production and disease severity of anthracnose leaf blight caused by *Colletotrichum graminicola* were significantly reduced in the lox8 mutants. In addition, lox8 mutants displayed increased resistance to southern leaf blight caused by *Cochliobolus heterosporus* and stalk rots caused by both *F. verticillioides* and *C. graminicola*. They suggest that oxylipin metabolism mediated by a specific plant 9-LOX isoform is required for fungal pathogenesis, including disease development and production of spores and mycotoxins. These findings suggest that naturally occurring differences in oxygenase activity could explain some differences in AF production in field populations of *A. flavus* (Horn, 2007) and also support reports where high levels of AF were found despite little evidence for fungal infection (Cotty and Mellon, 2003). Downstream derivatives of 13S-HPODE and 13S-HPOTE, including methyl jasmonate (Goodrich-Tanrikulu *et al.*, 1995) and various C6-C12 alkanal and alkenal volatiles (Doehlert *et al.*, 1993; Zeringue *et al.*, 1996) can also inhibit AF production. The effects of these compounds on AF production are distinct from their effects on fungal growth and development. Therefore, the fungus appears to receive morphological and chemical developmental signals from the host plant that are a direct consequence of fungal invasion.

**Effect of methyl jasmonate on aflatoxin production:** Jasmonic Acid (JA) was isolated from culture filtrate of the fungus *Lasio diploidea* (*Botryodiplodia theobromae*), a plant pathogen and was first identified as a plant growth inhibitor (Aldridge *et al.*, 1971). Methyl Jasmonate (MeJA) inhibits spore germination, mycelial pigment and aflatoxin biosynthetic precursors like sterigmatocystin and O-methyl sterigmatocystin. The inhibition is likely to be prior to the formation of these compounds in the aflatoxin biosynthetic pathway (Goodrich-Tanrikulu *et al.*, 1995; Burow *et al.*, 1997). In one study cotton balls pretreated with MeJA accumulated lower levels of AF (Zeringue, 2002). However, when *A. parasiticus* grew in the presence of 10^{-4} M of MeJA, AF production was significantly stimulated after 7 days, whereas no significant effect on mycelial growth was observed (Vergopoulos *et al.*, 2001).

**Effect of 13-LOX volatile compounds on aflatoxin production:** Gueldner *et al.* (1985) reported the inhibitory effect of LOX volatile compounds in corn ears infected with *A. flavus*. Zeringue and McCormick (1990) reported the inhibitory effects of volatile compounds of LOX
pathway derived from cotton leaves on growth and aflatoxin production by A. flavus cultures. The gaseous C6 to C9 alkenals were found effective against aflatoxin production in corn, cotton seed and peanuts infected with toxigenic strain of A. flavus (Zeringue, 1991). In one study, hexanal, from soybean homogenate suppressed the growth of A. flavus (Doehlert et al., 1993). Zeringue and Bhatnagar (1994) reported the inhibition of spore germination and aflatoxin production by A. flavus by LOX metabolites like hexanal, trans-2-hexanal and trans-2-nonanal. When Aspergillus spp. are exposed to LOX-derived volatile organic compounds such as Green Leaf Volatiles (GLV) emitted from cotton (Green-McDowelle et al., 1999), corn (Wright et al., 2000; Zeringue, 2000) and soybean (Boue et al., 2005), fungal growth and AF production were altered in vitro. This finding is supported by another study in which a series of C5-aldehydes, including both hexanal and (E)-2-hexenal, strongly inhibited A. flavus mycelial growth and AF biosynthesis (Boue et al., 2005). In addition, AF resistant lines corn genotypes emit higher concentration of aldehyde volatiles than the susceptible ones (Zeringue, 2000). Other types of volatiles, such as octanal, n-decyl aldehyde and trans-2-nonanal from Aspergillus-resistant varieties of corn (Wright et al., 2000) and 3-methyl-1-butanol, nonanol and volatile terpenes from cotton (Greene-McDowelle et al., 1999) inhibit either radial growth of A. flavus or AF production. Thus, a number of host-derived volatile oxylipin compounds, generated through the 13-LOX pathways, contribute to the resistance to aflatoxicogenic Aspergillus, by either showing direct inhibition on fungal growth (Croft et al., 1993; Prost et al., 2005) or disrupting fungal sporulation and mycotoxin biosynthesis.

CONCLUSION

On pooling-up all the scientific reports, it can be concluded that LOX derived oxylipins, have significant inhibitory effect on fungal pathogenicity and mycotoxin biosynthesis. The oxylipin-mediated signal communication between fungus and host plants is a complex system and requires further study. To provide novel strategies to control mycotoxicogenic fungi and eliminate mycotoxin contamination of food and feed, future investigations should focus on the molecular mechanism by which host oxylipins interact with the fungal signal transduction pathway to regulate mycotoxin biosynthesis as well as sporogenesis.

REFERENCES


