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Co-opting oxylipin signals in microbial disease

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Abstract

Oxylipins, or oxygenated lipids, are universal signaling molecules across all kingdoms of life. These molecules, either produced by microbial pathogens or their mammalian host, regulate inflammation during microbial infection. In this review, we summarize current literature on the biosynthesis pathways of microbial oxylipins and their biological activity towards mammalian cells. Collectively, these studies have illustrated how microbial pathogens can modulate immune response and disease outcome via oxylipin-mediated mechanisms.

1 | INTRODUCTION

Microbes communicate with their hosts using small molecules, some unique to the microbe and some similar or even identical to host metabolites. Of the latter, oxygenated lipids called oxylipins are increasingly understood as key chemical signals that are produced and perceived by both microbe and host. These bioactive signaling molecules mediate many important biological processes, including immune homeostasis in plants and animals as well as microbial development. Despite that both microbial pathogen and the host can produce bioactive oxylipins, the role of microbial oxylipins in pathogenesis have been underappreciated. Herein we provide an overview of biosynthesis of oxylipins derived from prokaryotic and eukaryotic microorganisms that cause human infections, and the biological functions of microbial oxylipins in shaping the pathogenic relationships.

2 | MICROBIAL OXYLIPINS: ENZYMES AND PRODUCTS

Oxylipins are oxygenated derivatives of long chain mono- or poly-unsaturated fatty acids (PUFAs). Host oxylipins are mainly synthesized with 20:4 (n-6) arachidonic acid (AA), 20:5 (n-3) eicosapentaenoic acid (EPA), and 22:6(n-3) docosahexaenoic acid (DHA). Microbial pathogens can synthesize oxylipins using these PUFAs as well as other substrates such as 18:1 (n-9) oleic acid, 18:2 (n-6) linoleic acid (LA), and 18:3 (n-6) linolenic acid. Table 1 shows the enzymes and oxylipins produced by the pathogenic microbes discussed in this review. Microorganisms possess the same classes of eicosanoids biosynthesis enzymes as mammals including cyclooxygenases, lipoxygenases, and cytochrome P450s as well as

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microbial specific enzymes (Figure 1). Other microbial proteins, such as phospholipases and epoxide hydrolases, don't directly catalyze oxylipin biosynthesis but alter PUFA substrate availability and modify host oxylipins during host-microbe encounters. Although some oxylipins can be non-enzymatically derived, this review will focus on microbial enzymatic sources of these lipids.

2.1 | Cyclooxygenase (COX)-like enzymes

Filamentous and dimorphic fungi contain upwards of four enzymes with significant homologies to mammalian cyclooxygenases COX-1 and COX-2 that synthesize prostaglandin H_2 (PGH_2), the substrate for further enzymatic steps (Figure 1). The fungal COX-like oxygenases, termed Ppo proteins, have been best studied in *Aspergillus* spp. including the opportunistic pathogens *Aspergillus nidulans*, *Aspergillus flavus*, *Aspergillus fumigatus*, and *Aspergillus terreus* (Garscha et al., 2007; Hoffmann, Jernerén, & Oliw, 2013; Tsitsigiannis, Zarnowski, & Keller, 2004; Table 1). Ppo enzymes produce mono- or di-hydroxyl oxylipins derived from oleic acid and linoleic acid, and PpoA and PpoC also contribute to AA-derived prostaglandin formation (Kupfahl et al., 2012; Tsitsigiannis et al., 2005; Noverr, Toews, & Huffnagle, 2002). Ppo oxygenases contain a heme-containing oxygenase domain (similar to the vertebrate COX) and a cytochrome P450 domain, thus are also termed linoleate dioxygenase-cytochrome P450. One of these enzymes has also been biochemically characterized in the dimorphic valley fever causing fungus *Coccidioides immitis* (Oliw et al., 2016). Other fungal pathogens, including the thermal dimorphic fungus *Paracocciodiodes brasiliensis* and pathogenic yeasts *Candida albicans*, *Candida parapsilosis* and *Cryptococcus neoformans*, can produce PGE_2 and other prostaglandins, yet the responsible COX has not been identified (Bordon et al., 2007; Erb-Downward and Noverr, 2007; Erb-Downward et al., 2008; Fischer and Keller, 2016).

The intestinal amebiasis-causing agent *Entameoba histolytica* produces PGE_2 via a nuclear COX-like protein and this production is sensitive to the non-selective COX inhibitor aspirin (Dey et al., 2003). COX activity of the protease Gp63 in the Leishmania causing *Leishmania mexicana* was reported, using a chemiluminescence-based kit for COX activity (Estrada-Figueroa et al., 2018). Phylogenetic analysis revealed that the protozoan COX-like proteins, including Gp63 proteins from *L. mexicana* and the Chaga's disease agent *Trypanosoma cruzi* and the Cox-like protein of *E. histolytica,* are evolutionary distant from mammalian COXs (Estrada-Figueroa et al., 2018).

2.2 | Prostaglandin synthases and thromboxane synthase

In humans, the COX product PGH_2 serves as substrate for synthesizing various structurally similar oxylipins, including other prostaglandins PGD_2, PGE_2 and $PGF_{2\alpha}$, prostacyclin PGI_2, and thromboxane TXA_2 (Figure 1). Prostaglandin and thromboxane synthases were identified in microbial pathogens based on their biosynthetic property rather than homology to mammalian enzymes.

The African trypanosomiasis agent *Trypanosoma brucei*, the Leishmaniasis pathogen *Leishmania* spp., and malaria pathogen *Plasmodium falciparum* can produce PGD_2, PGE_2, and $PGF_{2\alpha}$ when supplemented with AA (Araújo-Santos et al., 2014; Kubata et al., 1998;

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Kubata et al., 2000; Kabututu et al., 2003). Unlike the *E. histolytica* COX activity, biosynthesis of these prostaglandins in *T. brucei* is not sensitive to COX inhibitors (Kubata et al., 2000). *Trypanosoma cruzi* produces TXA_2 as its major eicosanoid with minor amount of $PGF_{2\alpha}$ (Ashton et al., 2007). $PGF_{2\alpha}$ synthases were identified in *T. brucei* (TbPGFS), *T. cruzi* (TcOYE), and *Leishmania* spp. and reviewed in Kubata et al., (2007).

Several enzymes were found to contribute to prostaglandin production in pathogenic yeasts. *C. neoformans* laccase Lac1, a multicopper oxidoreductase, catalyzes conversion of PGG_2 to PGE_2 (Erb-Downward et al., 2008). In *C. albicans*, the oleate Δ9 fatty acid stearyl-coenzyme A desaturase Ole2 and the laccase homolog ferroxidase Fet3 contribute to PGE_2 production (Erb-Downward and Noverr, 2007). However, Ole2 of *C. parapsilosis* doesn't contribute to PGE_2 biosynthesis (Grózer et al., 2015). Three *C. parapsilosis* genes highly induced by AA were identified through RNA sequencing: CPAR2_603600 (Fet3 homolog), CPAR2_800020 (a putative thiolase) and CPAR2_807710 (a putative Acyl-CoA dehydrogenase). The CPAR2_603600 and CPAR2_800020 proteins contribute to PGE_2 and PGD_2 production while the CPAR2_807710 protein contributes to PGE_2 and 15-keto-PGE_2 production (Chakraborty et al., 2018).

2.3 | Lipoxygenases (LOXs)

A. fumigatus has two lipoxygenase homologs of human Alox15 and Alox5, denoted LoxA and LoxB (Heshof et al., 2014; Fischer et al., 2017). LoxB is secreted extracellularly and produces 13-hydroxyoctadecadienoic acid (13-HODE). A single Lox, the LoxB homolog is present in the carcinogenic fungus *Aspergillus flavus* (Horowitz Brown, 2008). Lipoxygenase activity with subsequent synthesis of leukotriene B4 (LTB_4) has been reported in *P. brasiliensis* although no associated enzyme has been characterized (Biondo et al., 2012).

Prokaryotic LOX-encoding genes are evolutionarily distant from human LOX and have been found predominantly in Gram-negative environmental species (Hansen et al., 2013). The first bacterial LOX to be identified was LoxA in the opportunistic bacterial pathogen *P. aeruginosa* (Vance et al., 2004). LoxA has multiple PUFA substrates and can convert AA and LA to 15S-hydroxyeicosatetraenoic acid (15-HETE) and 13-HODE. LoxA lacks the leukotriene synthase activity and whether it synthesize lipoxin is still debatable (Banthiya et al., 2016; Deschamps et al., 2016; Vance et al., 2004). The Toxoplasmosis causing parasite *Toxoplasma gondii* produces the anti-inflammatory lipoxin LTA_4 and the extracted soluble tachyzoites antigen (STAg) converts AA to 15-HETE (Bannenberg et al., 2004).

Biosynthesis of specialized pro-resolving mediators, such as lipoxins and resolvins, often requires multiple enzymes, sometimes in different classes (Basil and Levy, 2016). A survey of *T. cruzi* oxylipins revealed production of AA derived prostaglandins and HETE, EPA derived RvE2, and DHA derived RvD1 and RvD5 from lysates of free trypomastigotes, suggesting presence of enzymes required for biosynthesis (Colas et al., 2018). RvE1 can be produced by *C. albicans* when supplemented with EPA, suggesting that cytochrome P450 and LOX activities are present (Hass-Stapleton et al., 2007).

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2.4 | Other enzymes in oxylipin-mediated crosstalk: phospholipase and epoxide hydrolase

Human cytosolic phospholipase A_2 releases AA from plasma membrane to initiate inflammation (Dennis and Norris, 2015). Microbial phospholipases are widely present, and some can cleave host AA to mediate a host response. These studies are reviewed extensively in Ghannoum (2000) and Istivan and Coloe (2006). The most extensively characterized PLA is ExoU in *P. aeruginosa.* ExoU, a patatin-like phospholipase and cytotoxin, is injected through the Type III secretion system to the host cell (Anderson et al., 2011; Sato et al., 2003; Sawa et al., 2016). ExoU liberates AA from eukaryotic cell membrane, an activity required for its toxicity (Saliba et al., 2005; Rabin and Hauser, 2005). Other bacterial phospholipases implicated in host interaction include *Streptococcus pyogenes* phospholipase A_2 SlaA (Oda et al., 2017) and the ExoU homolog VipD in *Legionella pneumophila* (Gasper and Machner, 2014; Ku et al., 2012).

Epoxide hydrolase hydrolyzes epoxides to corresponding diols. *P. aeruginosa* secretes an epoxide hydrolase termed the CFTR inhibitory factor or Cif. Cif hydrolyzes 14,15-epoxyeicosatrienoic acid (14,15-EET) produced by epithelial cells to 14,15-dihydroxyeicosatrienoic acid (DHET; Flitter et al., 2016). Two epoxide hydrolases in *P. falciparum*, PfEH1 and PfEH2, hydrolyze epoxyeicosatrienoic acids (EETS) and epoxyoctadecenoic acids (EpOMEs) (Spillman et al., 2016). These microbial epoxide hydrolases have non-canonical active sites compared to human counterparts (Bahl et al., 2010; Spillman et al., 2016).

3 | MICROBIAL OXYLIPINS: EFFECT ON INFLAMMATION AND VIRULENCE

Pathology of microbial infections is dependent on the immunological state of the host as well as the metabolism, persistence, and growth of the pathogen. The host initiates and resolves infection through pro-inflammatory and anti-inflammatory responses mediated by AA, EPA, and DHA- derived lipid mediators and their cognate receptors (Basil and Levy, 2016; Dennis and NForris, 2015). Pro-inflammatory lipid mediators induce inflammatory cell infiltration and elevate production of chemokines and pro-inflammatory cytokines. Anti-inflammatory lipid mediators inhibit infiltration of inflammatory cells and induce anti-inflammatory cytokine production, which induces apoptosis of immune cells and resolves inflammation. Since many microbial pathogens can produce eicosanoids and other potentially immuno-modulatory oxylipins, they can significantly steer the immunological response and influence disease outcomes. Many studies – primarily with fungi - have illustrated that microbial oxylipins are also important for development and cell morphogenesis (Fischer and Keller, 2016; Deschampes et al., 2016). These effects may alter disease outcome; here we specifically focus on roles of microbial oxylipins as immune-modulators during host confrontation. Figure 2 depicts various interactions between microbial pathogens and host cells mediated by microbial oxylipins and associated enzymes.

3.1 | Fungal pathogens

Oxylipin mediated host crosstalk have been studied most predominantly in *Aspergillus*, *Candida*, and *Cryptococcus* spp., the three species that contribute to most of the fungal

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attributed mortality (Brown, 2012). These fungi can produce the same oxylipins present in the host and those unique to the microbe.

It is currently not known if *Aspergillus* LA- derived oxylipins are synthesized *de novo* in animals but the *A. fumigatus* LoxB LA-metabolite 13-HODE is also made by humans and is implicated in airway hyper-responsiveness (Mabaliraian et al., 2013). *A. fumigatus* PpoC contributes to resisting phagocytosis and killing by murine bone marrow derived macrophages (Dagenais et al., 2008). An RNAi mutant with reduced expression of *ppoA*, *ppoB*, and *ppoC* shows lower prostaglandin production *in vitro* and increased virulence in a chemotherapeutic murine model of invasive aspergillosis (Tsitsigiannis et al., 2005). The mechanism of how AA and LA-derived oxylipins catalyzed by Ppo proteins mediate macrophage interaction and virulence remains to be elucidated.

Purified *C. albicans* and *C. neoformans* PGE_2 has an anti-inflammatory effect: it reduces chemokine IL-8 and inflammatory cytokine TNF-α production but increases anti-inflammatory IL-10 production in A549 epithelial cells (Noverr et al., 2001). Further study is required to assess whether the identified oxylipin producing enzymes in these pathogens (Table 1) mediate pathogenesis through altered PGE_2 production. Deletion mutants of the three *C. parapsilosis* enzymes mentioned earlier (CPAR2_603600, CPAR2_800020, and CPAR2_807710) are more susceptible to phagocytosis and killing by human peripheral blood monocyte derived macrophages (PBMC-DM; Chakraborty et al., 2018). PBMC-DM infected by the *CPAR2_807710Δ/Δ* strain produced higher levels of IL-6, TNF-α and IL-8. All three mutants showed reduced fungal burden in various organs in a murine model of intravenous infection (Chakraborty et al., 2018).

3-HETE produced by *C. albicans* can serve as substrate for human COX-2 to synthesize 3-OH-PGE_2 (Ciccoli et al., 2005). 3-OH-PGE_2 triggers increased IL-6 expression in A549 epithelial cells and cAMP release in Jurkat T cells, mediated by the PGE_2 cognate receptors EP3 and EP4, respectively. As *C. albicans* produces RvE1 that's structurally identical to human RvE1, synthetic RvE1 was used to study neutrophil phagocytosis and pathogenesis of *C. albicans.* Treatment of low concentrations of RvE1 enhances neutrophil phagocytosis and killing of *C. albicans* and intravenous injection of RvE1 reduces *C. albicans* replication in a murine model of intravenous *C. albicans* infection (Hass-Stapleton et al., 2007). However, it's unclear whether these findings are physiologically relevant and whether RvE1 itself inhibits *C. albicans* growth.

3.2 | Bacterial pathogens

While investigations on bacteria derived oxylipins are scarce, studies on *P. aeruginosa* enzymes, including the epoxide hydrolase Cif, the phospholipase ExoU, and the lipoxygenase LoxA, have shed light on mechanisms of oxylipin-mediated host crosstalk. These studies present a view that bacterial pathogens may have evolved to manipulate host immunity in environments where oxylipins and their substrates are abundant.

Pseudomonas aeruginosa colonizes immuno-compromised individuals, such as cystic fibrosis (CF) patients. Cif, a virulence factor in *P. aeruginosa* colonization of CF lungs, degrades the potent anti-inflammatory 14,15-EET from airway epithelial cells to less potent

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14,15-DHET. This leads to reduced 15-epi LXA_4, a pro-resolving product of neutrophils, and elevated inflammation (Bahl et al., 2011; Flitter et al., 2017). Furthermore, Cif activity in CF bronchial lavage fluid is positively associated with IL-8 level, and negatively associated with lung functions and 15-epi-LXA_4 abundance (Flitter et al., 2017). Cif also inhibits mucocilliary beating and hinders mechanical clearance of *P. aeruginosa* during infection of reconstituted human bronchial epithelium and in a murine model of acute pneumonia (Hvorecny et al.,2018).

ExoU is a well-recognized virulence factor, cytotoxin, and phospholipase (Sawa et al., 2016). ExoU releases AA and increases PGE_2 and PGI_2 concentrations in culture supernatant of infected cells (Saliba et al., 2005; Plotkowski et al., 2008). ExoU expressing strains induce neutrophil production of LTB_4 and neutrophil trans-epithelial migration *in vitro*, and increase PGE_2 and LTB_4 production, innate immune cell infiltration, and myeloperoxidase activity during acute pulmonary infection in mice (Pazos et al., 2017; Saliba et al., 2005). A549 epithelial cells infected with ExoU-expressing *P. aeruginosa* have impaired antioxidant detoxification machinery and higher levels of oxidative metabolites, including lipid hydroperoxides, 8-isoprostanes, ROS, and NO (Da Cunha et al., 2015). The *L. pneumophila* homolog of ExoU, VipD disrupts endosomal membrane lipids and facilitates *L. pneumophila* escape from endosomal fusion in the Cos-1 cells (Gasper and Machner, 2014). *Streptococcus pyogenes* phospholipase A_2 SlaA increases monocyte adhesion to endothelial cells *in vitro* (Oda et al., 2017).

Recombinant *P. aeruginosa* LoxA modifies membrane phospholipids by forming 15-HETE and 13-HODE, which is associated with induction of red blood cell hemolysis (Banthiya et al., 2015). LoxA is highly expressed in *P. aeruginosa* isolated from CF lungs and is implicated in biofilm formation on biotic surfaces, such as epithelium (Deschamps et al., 2016; Starkey et al., 2009).

3.3 | Protozoan parasites

So far, all of the reported parasite derived oxylipins are present in mammals. As many of these organisms cannot grow in axenic culture, several studies have revealed parasite-host oxylipin signaling pathways by exploiting a mammalian receptor mutant. This tactic offers the additional value of insights into pharmacological control of parasite infections.

Trypanosoma cruzi produced TXA_2 and $PGF_{2\alpha}$, are important in maintaining long-term infection. TXB_2 derived from *T. cruzi*, the stable derivative of TXA_2, consists most of the circulating TXB_2 in infected mice during later stage of infection (Ashton et al, 2007). Deletion of the TXA_2 receptor TP in mice results in increased inflammatory cell infiltration, increased parasitic load in myocardium, and increased host mortality (Ashton et al, 2007). These findings suggest that *T. cruzi* exploits the TXA_2-TP signaling to prevent host from early death and maintain infection longevity. PGF_2 synthase TcOYE is important for completion and progression of its infective cycle (Díaz-Viraqué et al., 2018). The TcOYE overexpression mutant displays more aggressive parasitemia and increased parasitic load in cardiac tissue.

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The *Leishmania* spp. protein Gp63 and its product $PGF_{2\alpha}$ are implicated in mediating host responses to the parasite. Gp63 is a well-recognized virulence factor and was extensively reviewed prior to the knowledge that it possessed COX-like activity (Olivier et al., 2012). Comparison of *Leishmania amazonensis gp63* RNAi mutants expressing differential levels of Gp63 revealed that Gp63 promotes parasite binding to J774 macrophages and intracellular survival (Chen et al., 2000). Future studies on Gp63 should consider its newly identified COX activity in interpreting past studies of such mutants. The $PGF_{2\alpha}$ receptor FP of bone marrow derived macrophages localizes to the parasitophorous vacuoles when infected with *Leishmania infantum chagasi* (Araújo-Santos et al., 2014). Treatment with a FP inhibitor decreases the infection index of macrophage by various stages of *L. i. chagasi* (Araújo-Santos et al., 2014). Activation of $PGF_{2\alpha}$-FP signaling allows *L. i. chagasi* to evade the macrophage anti-parasitic activity. Therefore, blockade of this pathway may present a therapeutic avenue to manage parasitic load and treat Leishmaniasis.

Invasive infection of *E. histolytica* induces robust inflammation and tissue damage. *E. histolytica* or its secreted components induces IL-8 production by infected Caco-2 epithelial cells (Dey et al., 2008). This induction is absent using de-lipidized soluble components, aspirin treated *E. histolytica,* or Caco-2 cells with inhibited PGE_2 receptor EP4. The same group later found that the secreted components also decreases trans-epithelial resistance of the human colonic epithelial monolayer through dissociating the tight junction protein Claudin-4, which is abolished through aspirin pretreatment of *E. histolytica* or inhibition of EP4 (Lejeune et al., 2011). The role of the previously identified COX-like enzyme in these interactions is worth further investigation.

The aminopeptidase activity of PfEH2 and the epoxide hydrolase activity of PfEH1 and PfEH2 in *P. falciparum* were independently reported (Spillman et al., 2016; da Silva et al., 2016). The PfEH2 deletion mutant is more easily filtered outside of the infected erythrocytes, and the PfEH1 and PfEH2 overexpression mutants decreases abundance of several EETs and EpOMEs in infected erythrocytes.

4 | CONCLUSIONS

The critical nature of oxylipins in inflammation and infection is clear from myriad studies as reflected in the moniker ‘eicosanoid storm’ (Dennis and Norris, 2015). Yet the majority of these studies have focused solely on host oxylipins. Collectively, the studies in this review support an important but underappreciated role of microbial oxylipins in human infectious disease.

Where might the future directions microbial oxylipin research head? An increasing body of literature has reported that microbial extracellular vesicles modulate host immunological response (Joffe et al., 2016; Kuipers, et al., 2018). In mammalian systems, extracellular vesicles facilitate intercellular transport of eicosanoids and their biosynthetic machinery, mediating paracrine signaling (Boilard et al., 2018; Sagini et al., 2018). Proteins that mediate oxylipin biosynthesis and signaling, such as Cif from *P. aeruginosa* and the *Leishmania* COX Gp63 protein, are located in extracellular vesicles (Ghosh et al., 2013). Purified EVs from *C. albicans* and *C. neoformans* are internalized by macrophage and

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dendritic cells and stimulate production of nitric oxide and proinflammatory cytokine (Oliveira et al., 2010; Vargas et al., 2015). Extracellular vesicles thus can serve as a site of oxylipin biosynthesis and a vehicle in shuffling the enzymes, substrates and products between the pathogen and the host. Additionally, roles for microbial oxylipins in microbial confrontations should also be explored more thoroughly in the context of the human microbiome (Fourie et al., 2017; Krause et al., 2015).

Finally, we note that one emerging theme from the research summarized in this review is that whereas some microbial oxylipins are identical to mammalian products and impact host processes, other microbial oxylipin products and/or their synthesizing enzymes are evolutionarily distant from those in mammals (Estrada-Figueroa et al., 2018; Hansen et al., 2013). Not only is it important to investigate the potential impacts of these structurally distinct microbial oxylipins on host immunological processes but the microbial chemical signatures may be useful for molecular diagnosis of the pathogen. Furthermore, biochemical studies on microbial specific enzymes could potentially pave a way to identifying new targets for future therapies.

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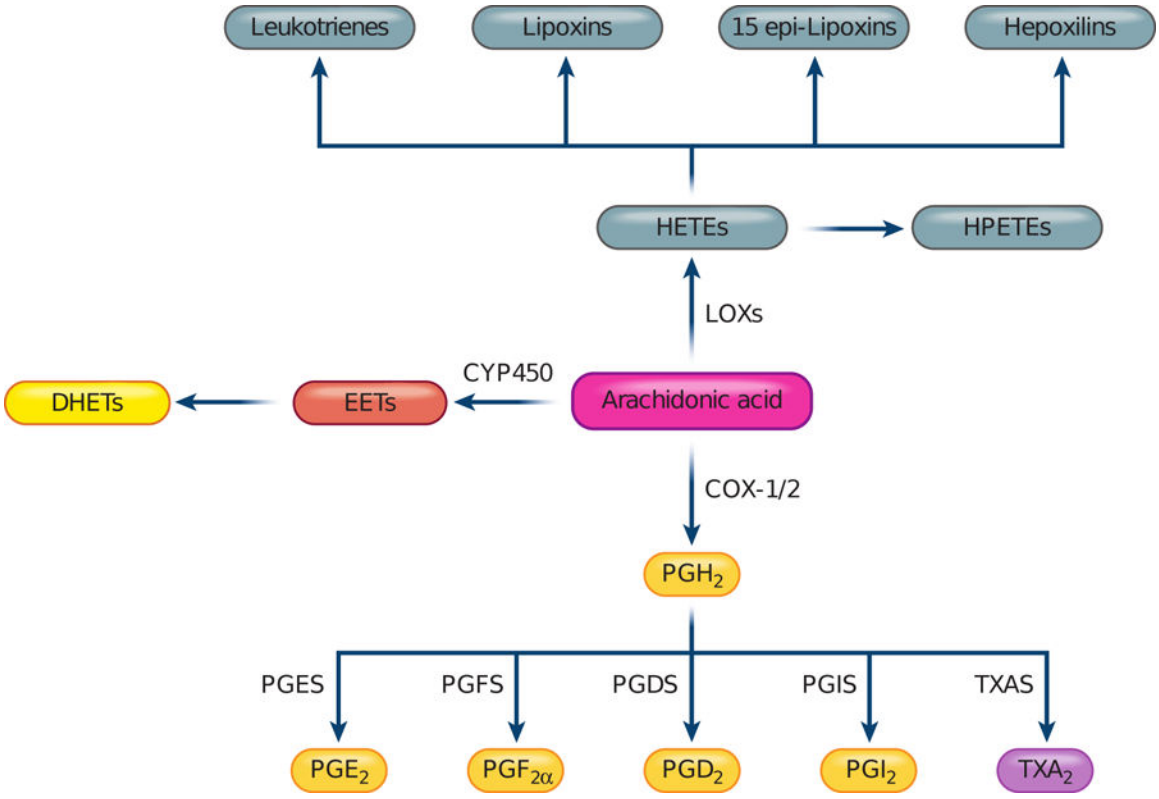

FIGURE 1.

Eicosanoid biosynthesis pathways in animals. Arachidonic acid-derived eicosanoids are biosynthesized through cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) pathways. Cyclooxygenases, including COX-1 and COX-2, produce prostaglandin H_2 (PGH_2) that is further converted by prostaglandin synthases (PGES, PGFS, PGDS), prostacyclin synthase (PGIS) and thromboxane synthase (TXAS) to prostaglandins, prostacyclin, and thromboxane respectively. Lipoxygenases, including Alox5, Alox15, Alox12, and Alox8 synthesize hydroperoxyeicosatetraenoic acids (HPETEs) that are further converted to various hydroxylated and epoxidized eicosanoids. Cytochrome P450 (CYP 450) enzymes catalyze formation of various epoxyeicosatrienoic acids (EETs), which are short-lived and rapidly converted to dihydroxyeicosatrienoic acid (DHETs). HETEs, hydroxyeicosatetraenoic acids; PGH_2, prostaglandin H_2; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGD_2, prostaglandin D_2; PGI_2, prostacyclin; TXA_2, thromboxane A_2; PGES, PGE synthase; PGFS, PGF synthase; PGDS, PGD synthase; PGIS, PGI synthase; TXA, TXA synthase

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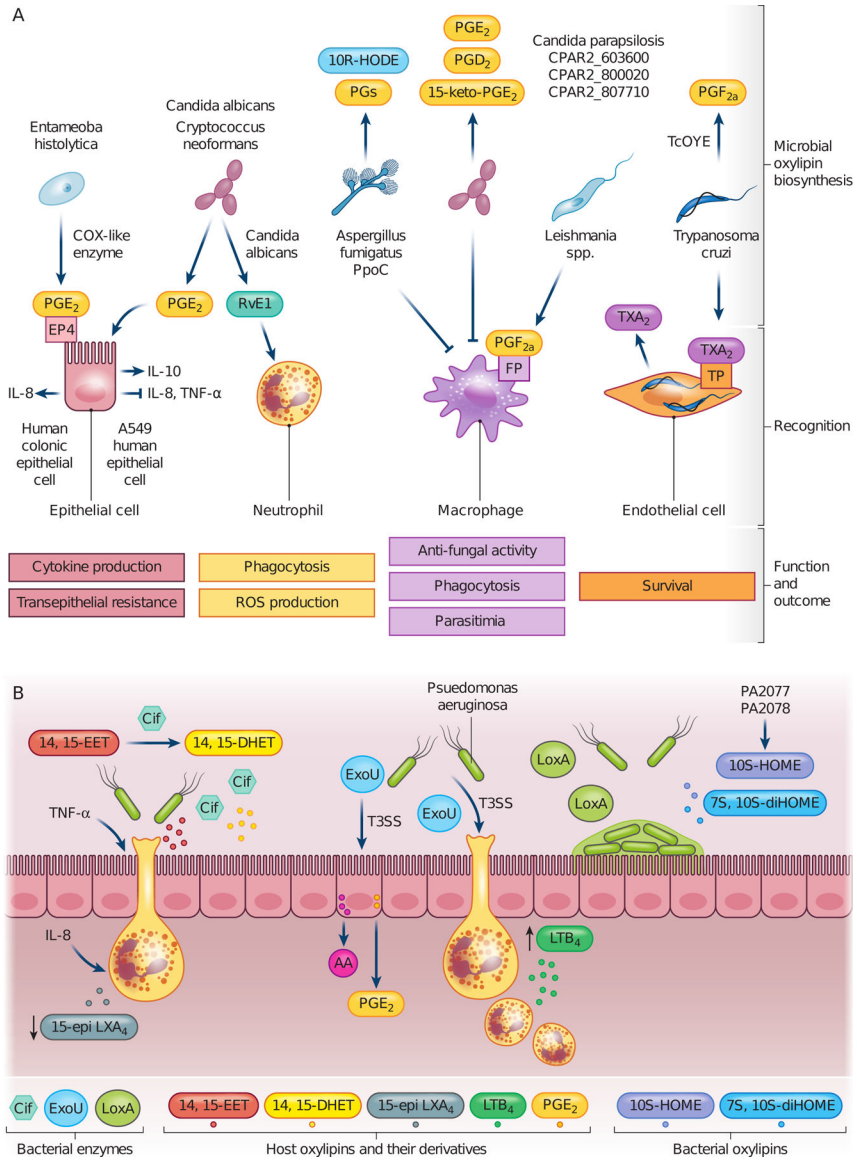

FIGURE 2.

Host-pathogen interactions mediated by microbial oxylipins and enzymes. (a) Eukaryotic microbial pathogens, predominantly pathogenic fungi and protozoan parasites, produce the same oxylipins as the host eicosanoids and those unique to microbes. Host cells in close contact with pathogens through either infection (endothelial cell and macrophage) or immune response (macrophage, neutrophil, epithelial cell) can recognize microbe-derived oxylipins and respond with altered functionality. (b) Bacterial pathogens, such as *Pseudomonas aeruginosa*, produce enzymes that influence the type and abundance of host-derived oxylipins, leading to skewed inflammatory state. These include the epoxide hydrolase Cif and the phospholipase A_2 ExoU. LoxA in *P. aeruginosa* also promotes biofilm formation on epithelial surface. IL-8, interleukin 8; IL-10, interleukin 10; TNF-α, tumor necrosis factor alpha; PGs, prostaglandins; PGE_2, prostaglandin E_2; PGD_2, prostaglandin D_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; 15-keto-PGE_2, 15-keto-prostaglandin E_2; RVE1, resolvin E1;

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10R-HODE, 10R-hydroxyoctadecadienoic acid; TXA_2, thromboxane A_2; EP4, PGE receptor; FP, PGF receptor; TP, thromboxane receptor; TcOYE, *Trypanosoma cruzi* Old Yellow Enzyme; PpoC, Psi-producing oxygenase C; 14,15-EET, 14,15-epoxyeicosatrienoic acid; 14,15-DHET, 14,15-dihydroxyeicosatrienoic acid; 15-epi-LXA_4, 15-epi-lipoxin A_4; AA, arachidonic acid; LTB_4, leukotriene B_4; T3SS, Type III Secretion System; Cif, conductance regulator inhibitory factor

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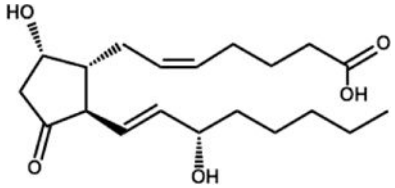
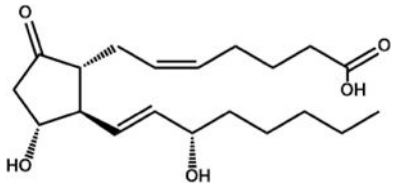
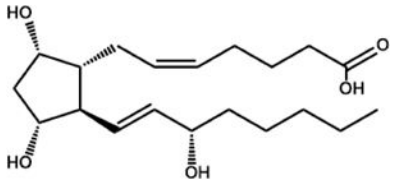
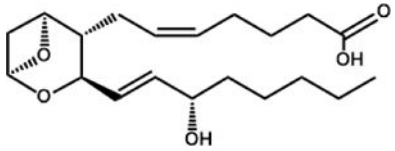
TABLE 1

List of enzyme-derived microbial oxylipins associated with pathogenesis and their microbial origin

PUFA	Oxylipin name	Chemical structure	Producer species and biosynthetic enzymes	References
Arachidonic Acid	Prostaglandin D_2 (PGD_2)		*C. albicans C. parapsilosis* (CPAR2_603600, CPAR2_800020, CPAR2_807710) *T. brucei* *P. falciparum*	Chakraborty et al., 2018; Kubata et al., 2000; Kubata et al., 1998; Noverr et al., 2001;
	Prostaglandin E2 (PGE_2)		*C. albicans* (Ole2, Fet3) *C. neoformans* (Lac1) *C. parapsilosis* (CPAR2_603600, CPAR2_800020) *P. brasiliensis* *A. fumigatus* (Ppo's) *E. histolytica* *T. cruzi* *T. brucei* *L. mexicana* *P. falciparum*	Chakraborty et al., 2018; Colas et al., 2018; Dey et al., 2003; Erb-Downward et al., 2008 Erb-Downward and Noverr, 2007; Estrada-Figueroa et al., 2018; Kubata et al., 2000; Kubata et al., 1998; Noverr et al., 2001; Tsitsigiannis et al., 2005
	Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)		*C. albicans* *C. neoformans* *T. cruzi* (TcOYE) *T. brucei* (TbPGFS) *L. major, L. donovani, L. tropica* *L.i. chagasi* *P. falciparum*	Araújo-Santos et al., 2014; Ashton et al., 2007; Colas et al., 2018; Kabututu et al., 2003; Kubata et al., 2000; Kubata et al., 1998; Noverr et al., 2001;
	Thromboxane A_2 (TXA_2)		*C. albicans* *T. cruzi*	Ashton et al., 2007; Noverr et al., 2001

Cell Microbiol. Author manuscript; available in PMC 2020 June 01.

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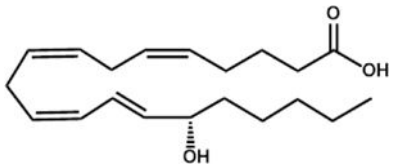
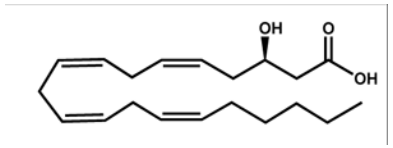
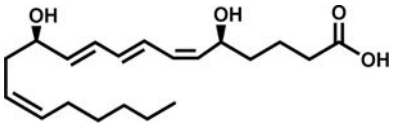
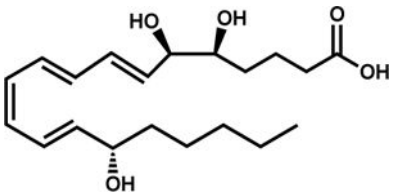
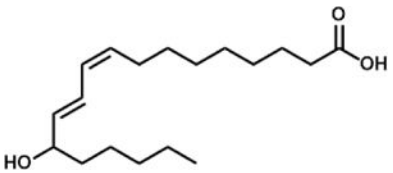
PUFA	Oxylipin name	Chemical structure	Producer species and biosynthetic enzymes	References
	15S-hydroxyeicosatetraenoic acid (15-HETE)		*P. aeruginosa* (LoxA) *T. gondii* (STAg)	Bannenberg et al., 2004; Vance et al., 2004
	3S-hydroxy eicosatetraenoic acid (3S-HETE)		*C. albicans*	Ciccoli et al., 2005
	Leukotriene B_4 (LTB_4)		*P. brasiliensis*	Bordon et al., 2007
	Lipoxin A_4 (LXA_4)		*T. gondii*	Bannenberg et al., 2004
Linoleic Acid	13-hydroxyoctadecadienoic acid (13-HODE)		*P. aeruginosa* (LoxA) *A. fumigatus* (LoxB)	Banthiya et al., 2015; Fischer et al., 2017;

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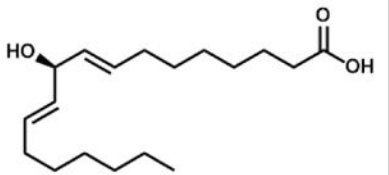
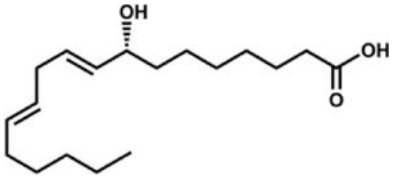
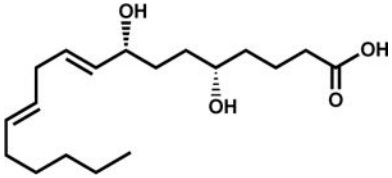
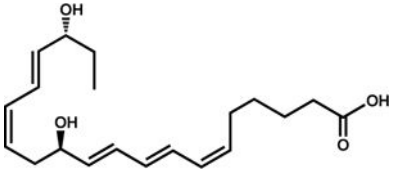
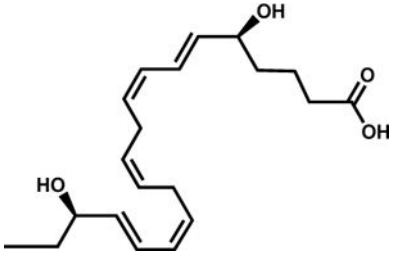
PUFA	Oxylipin name	Chemical structure	Producer species and biosynthetic enzymes	References
	10R-hydroxyoctadecadienoic acid (10R-HODE)		*A. fumigatus* (PpoC) *A. nidulans* (PpoC) *A. terreus* (ATEG_03992)	Garscha et al., 2007; Hoffmann et al., 2013
	8R-hydroxyoctadecadienoic acid (8R-HODE)		*A. nidulans* (PpoA) *A. fumigatus* (PpoA) *C. immitis* (8R-DOX-AOS)	Garscha et al., 2007; Oliw et al., 2016; Tsitsigiannis, Zarnowski, & Keller, 2004
	5S,8R-dihydroxyoctadecadienoic acid (5S,8R-diHODE)		*A. fumigatus* (PpoA)	Garscha et al., 2007
Eicosapentaenoic Acid	Resolvin E1 (RvE1)		*T. cruzi C. albicans*	Colas et al., 2018; Hass-Stapleton et al., 2007
	Resolvin E2 (RvE2)		*T. cruzi*	Colas et al., 2018

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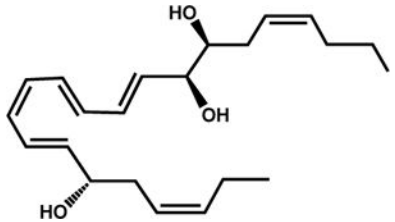
PUFA	Oxylipin name	Chemical structure	Producer species and biosynthetic enzymes	References
Docosahexaenoic Acid	Resolvin D1 (RvD1)		*T. cruzi*	Colas et al., 2018

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