# Chapter 6
# Host Defense Peptides and the Eicosanoid Cascade

**Min Wan, Xiao Tang and Jesper Z. Haeggström**

**Abstract** Host defense peptides (HDPs) and eicosanoids are two important families in host defense and inflammation. Most of the naturally occurring HDPs are cationic and amphipathic short polypeptides with typical length between 15 and 40 amino acid residues. HDPs not only possess potent antimicrobial activity against a variety of pathogens, they are also widely recognized for their multifunctional roles in both the innate and adaptive immune responses. On the other hand, arachidonic acid-derived eicosanoids, including prostaglandins, thromboxanes, leukotrienes and lipoxins, are small lipid molecules with a 20-carbon backbone, which possess potent biological properties and participate in regulation of physiological and pathophysiological processes. In this article, we discuss the biosynthesis and functions of eicosanoids with emphasis on the roles of eicosanoids in host defense and regulation of HDP production. Moreover, we review how HDPs regulate eicosanoid metabolism and conclude that there are positive feedback circuits between HDP and eicosanoid signaling with implications for certain pathological conditions, such as infection and allergy.

## 6.1 Introduction

Arachidonic acid (AA) is released from phospholipids by phospholipases $A_2$ ($PLA_2$), and metabolism of AA leads to several families of lipid mediators collectively known as eicosanoids, including prostaglandins (PGs), thromboxanes, leukotrienes (LTs), and lipoxins (LXs), along two major pathways, the lipoxygenase (LOX) and the cyclooxygenase (COX) pathways (Haeggstrom and Funk

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2011). Eicosanoids are secreted and act locally in an autocrine or paracrine fashion through interaction with specific G-protein coupled receptors (GPCR) to exert their biological effects (Back et al. 2011; Woodward et al. 2011; Serhan 2014). They possess potent biological activities and are involved in fever, pain, maintenance of normal hemostasis, regulation of blood pressure, renal function, and reproduction as well as host defense (Haeggstrom and Funk 2011).

Host defense peptides (HDPs), also known as antimicrobial peptides (AMPs), are evolutionarily conserved molecules of the innate immune system. Their widespread distribution throughout the animal and plant kingdoms suggests that HDPs have served a fundamental role in the successful evolution of complex multicellular organisms (Zasloff 2002). They are not only important molecules in host defense against a very broad spectrum of microorganisms, such as gram negative and gram positive bacteria, fungi, parasites, and viruses, via various mechanisms of action, but also possess diverse immunomodulatory capabilities (Mansour et al. 2014).

Several studies have indicated that inhibition of eicosanoid biosynthesis lethally impairs insect immune reactions (Stanley-Samuelson et al. 1991) and also that eicosanoids play an important role in regulating innate immunity and host defense of mammals (Peters-Golden et al. 2005; Dennis and Norris 2015). The first suggestion that eicosanoids are involved in signaling pathways that lead to HDP production came from a study demonstrating that an eicosanoid biosynthesis inhibitor suppressed two HDP gene expressions in response to bacterial challenge in the fat body of the silkworm, *Bombyx mori* (Morishima et al. 1997). Accumulating evidence from the studies on insects suggested a direct induction of HDPs by AA (Morishima et al. 1997; Sun and Faye 1995), and also a direct functional link between eicosanoids and the production of HDPs induced by LPS (Yajima et al. 2003) or peptidoglycan (Morishima et al. 1997). Interestingly, the studies from our research group and others have also suggested positive feedback loops between eicosanoids and HDP production in mammalian leukocytes (Wan et al. 2011; Sun et al. 2013; Kanda et al. 2010; Bernard and Gallo 2010; Niyonsaba et al. 2001; Kase et al. 2009; Chen et al. 2007).

In this chapter, we will discuss the role of eicosanoids in host defense, and how HDPs and eicosanoids, two important families of innate immunity interact and cooperate to regulate the innate immunity and control infections.

## 6.2 Eicosanoids in Host Defense

$PLA_2$ enzymes are crucial for increasing the levels of free AA for eicosanoid biosynthesis under most physiological conditions, but particularly following inflammatory cell activation (Dennis and Norris 2015). Three members of the $PLA_2$ superfamily have been implicated most strongly in cellular eicosanoid production: cytosolic calcium-dependent $PLA_2$ ($cPLA_2$), cytosolic calcium independent $PLA_2$ ($iPLA_2$) and secreted $PLA_2$ ($sPLA_2$) (Dennis and Norris 2015). Among them, $cPLA_{2\alpha}$ is the only $PLA_2$ that exhibits preference for hydrolysis of AA from

phospholipid substrates that occurs in cells stimulated with diverse agonists (Leslie 2015). The observation that mice lacking $cPLA_2$ are profoundly depleted of all eicosanoids indicates that this enzyme is indispensable for the liberation of AA in vivo (Fujishima et al. 1999). Because AA is the precursor of eicosanoids, it is generally accepted that $cPLA_{2\alpha}$ plays a major role in inflammatory diseases (Dennis et al. 2011).

Early studies on insects demonstrated that eicosanoids play an important role in bacterial infection by using $PLA_2$ inhibitor, and the functions suppressed by $PLA_2$ inhibitor can be rescued by adding exogenous AA (Stanley-Samuelson et al. 1991, 1997; Yajima et al. 2003; Miller et al. 1994). Subsequent studies further showed that AA and eicosanoids promote HDP expression in insects (Morishima et al. 1997; Sun and Faye 1995; Yajima et al. 2003; Hwang et al. 2013). Studies in humans and mammals demonstrated that eicosanoids affect the immune response by modulating cellular differentiation, migration, phagocytosis, and cytokine/chemokine production, and also play an important role in connecting innate and adaptive immunity by acting on cells of both systems (Harizi and Gualde 2005). It has been reported that zymosan and *Candida albicans* induce $cPLA_2$ activation and eicosanoid production in macrophages via different signaling mechanisms (Gijon et al. 2000; Suram et al. 2006, 2010). Moreover, a recent report investigated the functional consequences of $cPLA_{2\alpha}$ activation and the effect of endogenously produced eicosanoids on gene expression in response to *C. albicans* by comparing $cPLA_{2\alpha}^{+/+}$ and $cPLA_{2\alpha}^{-/-}$ resident mouse peritoneal macrophages (RPM), and the results revealed that *C. albicans* killing was impaired in $cPLA_{2\alpha}$ deficient RPM, and *C. albicans*-stimulated $cPLA_{2\alpha}$ activation and the early production of prostanoids promote an autocrine pathway in RPM that affects the expression of genes involved in host defense to dampen inflammation (Suram et al. 2013). In addition, it has also been shown that AA stimulates human neutrophils to release HDPs to strongly impair bacterial growth (Chouinard et al. 2013). Interestingly, evidence has been provided that eicosanoids are involved in lactose and phenylbutyrate (PBA)-induced human cathelicidin expression in human epithelial cell line HT-29 since a $PLA_2$ inhibitor significantly suppressed lactose/PBA-induced peptide expression (Cederlund et al. 2014).

We will discuss more details on LTs, PGs and LXs in host defense and infections.

### *6.2.1 Prostanoids*

Prostanoids are lipid mediators derived from AA via the COX pathway. COX exists as two isoforms referred to as COX-1 and COX-2. COX-1 is expressed constitutively in most tissues, whereas COX-2 is not detectable in most normal tissues or resting immune cells, but its expression can be induced by factors such as endotoxins, cytokines, growth factors, and carcinogens (Smith et al. 2011). COX enzymes convert AA to the unstable endoperoxide $PGH_2$, which can be

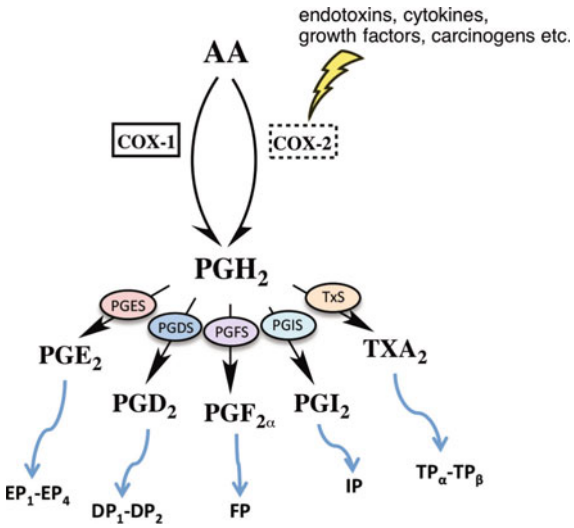


**Fig. 6.1** Biosynthesis of prostanoids. Arachidonic acid (AA) can be metabolized by cyclooxygenase (COX) isoforms known as COX-1 and COX-2. Unlike COX-1, which is constitutively expressed in most tissues and cells, COX-2 remains at low expression in resting cells. However, COX-2 can be activated by factors such as endotoxins, cytokines, growth factors and carcinogens. COX isozymes convert AA to the unstable endoperoxide prostaglandin (PG)$H_2$, which is further metabolized to $PGE_2$, $PGD_2$, $PGF_{2\alpha}$, $PGI_2$ (prostacyclin), and thromboxane $A_2$ ($TXA_2$) by specific terminal synthases, in a cell-type restricted fashion. PGs exert their functions via specific G-protein coupled receptors (GPCR), i.e., EPs, DPs, FP, IP and TPs in an autocrine or paracrine manner

metabolized by the actions of specific terminal synthases that are expressed in a cell type-selective fashion to produce $PGE_2$, $PGD_2$, $PGF_{2\alpha}$, $PGI_2$ (prostacyclin), and thromboxane $A_2$ ($TXA_2$), which are collectively called prostanoids (Hirata and Narumiya 2012). The biosynthesis of prostanoids is summarized in Fig. 6.1.

$PGE_2$ is the most abundant prostanoid in the inflammatory milieu, and it is one of the best known and most well-characterized prostanoids in terms of immunomodulation. $PGE_2$ exerts its biological functions through four distinct G protein–coupled receptors called E prostanoid (EP) receptors, which are numbered EP1–4 (Woodward et al. 2011). Although $PGE_2$ has myriads of immunomodulatory effects and induces both pro- and anti-inflammatory effects, the immunosuppressive actions of $PGE_2$ to limit both the amplitude and duration of immune responses have been extensively studied and reported (Kalinski 2012; Agard et al. 2013). For example, $PGE_2$ suppresses macrophage phagocytosis (Aronoff et al. 2004; Lee et al. 2009; Serezani et al. 2012), restrains bacterial killing in alveolar macrophages by inhibiting NADPH oxidase (Serezani et al. 2007), exacerbates intrauterine group A *Streptococcal* infections (Mason et al. 2013), dampens antifungal immunity by inhibiting interferon regulatory factor 4 functions and interleukin-17 expression in

T cells (Valdez et al. 2012). Moreover, $PGE_2$ suppresses antiviral immunity through induction of type I interferon and apoptosis in macrophages (Coulombe et al. 2014), and blockade of $PGE_2$ signaling improves viral control (Chen et al. 2015). However, it has also been reported that $PGE_2$ induces resistance to HIV-1 infection by downregulation of the chemokine receptor CCR5 expression to suppress HIV-1 entry into macrophages (Thivierge et al. 1998). Several studies also demonstrate that $PGE_2$ plays an important role to inhibit *Mycobacterium tuberculosis* replication in vitro and in vivo (Chen et al. 2008; Kaul et al. 2012; Mayer-Barber et al. 2014).

Several lines of evidence indicate that PGs are involved in host defense by modulating HDP expression. Studies from insects have demonstrated that PGs induce the expression of humoral immune-associated genes, including HDP cecropin in the beet armyworm, *Spodoptera exigua* (Shrestha and Kim 2009). In another study on mosquito *Anopheles albimanus* has shown that $PGE_2$ reduces mRNA synthesis of HDP ambicin and attacin in cultured midguts and fat bodies, while enhancing the cecropin mRNA (Garcia Gil de Munoz et al. 2008). Studies have also demonstrated that $PGD_2$ induces human β-defensin (hBD)-3 production in human keratinocytes (Kanda et al. 2010), and one possible mechanism for the antimicrobial effects of the antimycotic drugs itraconazole and terbinafine hydrochloride could be to induce hBD-3 in keratinocytes by increasing $PGD_2$ release from keratinocytes (Kanda et al. 2011). Consistently, Bernard et al. also found that $PGD_2$ and 15-deoxy-$D^{12,14}$-$PGJ_2$ (a dehydration product of $PGD_2$) induces the production of hBD-2 and hBD-3 by human keratinocytes (Bernard and Gallo 2010). However, $PGE_2$ dramatically suppresses hBD-1 expression in human uterine epithelial cells, and also moderates TNF-α-induced hBD-2 expression in human uterine epithelial cells (Aronoff et al. 2008).

It is well-established that non-steroidal anti-inflammatory drugs (NSAIDs) block prostanoid synthesis by inhibiting COX enzymes and are widely used to treat both acute and chronic inflammation. Some evidence suggests that NSAID use is also linked to modulation of HDP expression. One report showed that the COX inhibitor etodolac enhanced hBD-2 mRNA levels in *Actinobacillus actinomycetemcomitans* infected human gingival epithelial cells (HGEC) (Noguchi et al. 2003). Since etodolac almost suppressed the production of $PGE_2$ by *A. actinomycetemcomitans* in HGEC, this result indicated that endogenous $PGE_2$ produced by *A. actinomycetemcomitans* in HGEC suppresses hBD-2 expression (Noguchi et al. 2003). In another report, Bernard et al. demonstrated a critical role for COX-2 in hBD production by human keratinocytes and treatment with a COX-2 inhibitor led to reduced antibacterial activity in these cells (Bernard and Gallo 2010). Interestingly, one recent report also describes that COX inhibitors aspirin or etoricoxib significantly suppress lactose/PBA-induced cathelicidin expression in the human epithelial cell line HT-29 (Cederlund et al. 2014). All these evidences suggest that prostanoid signaling is involved in the regulation of HDP expression.

### 6.2.2 *Leukotrienes (LTs)*

LT biosynthesis from free unesterified AA is catalyzed by a series of enzymes, starting from 5-lipoxygenase (5-LOX). Upon an increase in intracellular calcium, 5-LOX translocates to the nuclear membrane and associates with 5-LO-activating protein (FLAP) to promote dioxygenation and dehydration of AA (Dixon et al. 1990). This process gives rise to the unstable epoxide $LTA_4$, the key intermediate in leukotriene biosynthesis, which is converted to $LTB_4$ through the action of $LTA_4$ hydrolase (Samuelsson and Funk 1989). $LTA_4$ can also be conjugated with GSH by $LTC_4$ synthase to produce $LTC_4$, which constitutes the parent compound of the cysteinyl LTs (cys-LTs) also including $LTD_4$ and $LTE_4$ (Samuelsson et al. 1987). The biosynthesis of LTs is summarized in Fig. 6.2. LT production is cell type specific and largely limited to cells of the myeloid lineage. LT signaling is achieved through a family of GPCR. So far, it has been found that $LTB_4$ binds to two GPCRs, BLT1 and BLT2 with high and low affinity. Likewise, CysLT1, CysLT2

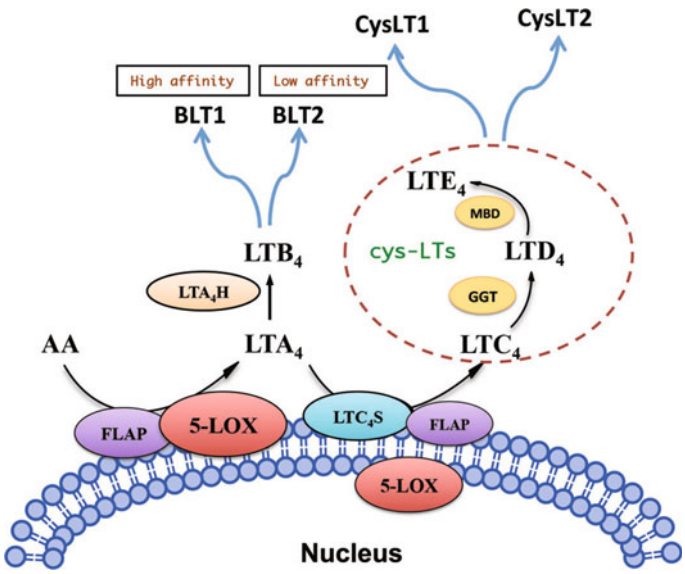


**Fig. 6.2** Biosynthesis of leukotrienes (LTs) at the nuclear membrane. Upon certain stimuli, intracellular calcium level increases, leading to the translocation of 5-LOX from cytosol to the nuclear membrane (not depicted in figure). Free AA is presented to 5-LOX by the nuclear membrane integral protein 5-LO-activating protein (FLAP) and converted to $LTA_4$, the key intermediate in LT biosynthesis. $LTA_4$ is further converted to $LTB_4$ by $LTA_4H$, and the released $LTB_4$ acts via its high affinity receptor BLT1 or low affinity receptor BLT2 on target cells. Meanwhile, $LTA_4$ can also be metabolized to $LTC_4$ by the integral membrane enzyme $LTC_4s$. $LTC_4$ is further transformed by extracellularly localized γ-glutamyl transpeptidase (GGT) to $LTD_4$, and further into $LTE_4$ by membrane-bound dipeptidase (MBD). $LTC_4$, $LTD_4$ and $LTE_4$, together known as cys-LTs, can activate and bind to two main receptors CysLT1 and CysLT2 for their bioactivities

and a putative receptor for $LTE_4$ (CysLT3) have been reported to transduce cys-LT signaling (Back et al. 2011).

$LTB_4$ is best known for its role as a neutrophil chemoattractant, and cys-LTs are famous for their ability to induce bronchoconstriction in asthma (Peters-Golden and Henderson 2007). However, LTs are now recognized as important participants in the host response and they are produced at sites of infection by phagocytes, which promotes killing of microbes, including bacteria (Bailie et al. 1996; Mancuso et al. 1998, 2010; Serezani et al. 2005; Soares et al. 2013), mycobacteria (Peres et al. 2007; Tobin et al. 2010; Peres-Buzalaf et al. 2011; Tobin et al. 2012), fungi (Medeiros et al. 2008; Morato-Marques et al. 2011; Secatto et al. 2012, 2014), parasites (Talvani et al. 2002; Machado et al. 2005; Serezani et al. 2006; Morato et al. 2014; Canavaci et al. 2014) and virus (Flamand et al. 2004; Gosselin et al. 2005; Gaudreault and Gosselin 2008; Bertin et al. 2012).

Accumulating evidence has clearly demonstrated that LTs, particularly $LTB_4$, plays a significant role in the control of microbial infections through its ability to activate host immunity, for instance by promoting HDP release (Peters-Golden et al. 2005; Le Bel et al. 2014). A study on insects showed that $LTB_4$ induced expression of humoral immune-associated genes, including HDP cecropin in the beet armyworm, *S. exigua* (Shrestha and Kim 2009). Moreover, studies on human neutrophils demonstrated that $LTB_4$ induces the release of human HDP, including α-defensins, cathepsin G, elastase, lysozyme C, and LL-37 from human neutrophils via the BLT1 receptor (Wan et al. 2007; Flamand et al. 2007). Furthermore, it has been shown that *i.v.* injection of $LTB_4$ to monkey and human (Flamand et al. 2004, 2007) induces a dose-dependent plasmatic increase in α-defensins. Meanwhile, evidence has been provided that $LTB_4$-induced HDP production by neutrophils, transduced via BLT1, plays a role in $LTB_4$-mediated antiviral activity in vitro and in vivo (Gaudreault and Gosselin 2007, 2008). Recently, it was also reported that AA induces the release of HDPs (α-defensins and LL-37) from human neutrophils through metabolism into $LTB_4$ and the activation of BLT1 (Chouinard et al. 2013). All these studies further support the notion that $LTB_4$-induced HDPs play an important role in host defense.

### *6.2.3 Lipoxins (LXs)*

In 1984, Serhan and colleagues discovered a new family of eicosanoids called lipoxins (LXs) (Serhan et al. 1984a, b). $LXA_4$ and $LXB_4$ are positional isomers that each possesses potent cellular and in vivo actions, whereas $LXA_4$ has been more widely studied for its functions. The LXs are generated from AA via sequential action of two or more LOXs during cell–cell interactions by transcellular biosynthetic routes that occur in inflammation and disease pathogenesis (Serhan 2005). Three transcellular pathways for biosynthesis of $LXA_4$ in human cells are depicted

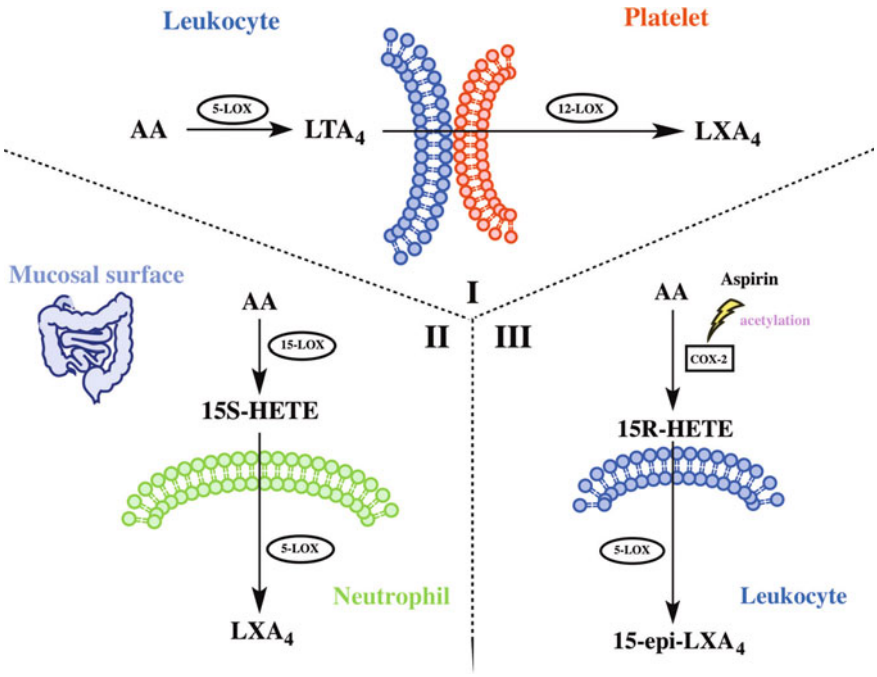


**Fig. 6.3** Transcellular biosynthesis of lipoxins (LXs). (**I**) 5-LOX in leukocytes converts AA to $LTA_4$, which is released from leukocytes and further transformed to $LXA_4$ via the enzyme 12-LOX in adherent platelets. (**II**) On mucosal surfaces, AA can be transformed via 15-LOX to 15S-hydroxy-eicosatetraenoic acid (15S-HETE), which is rapidly taken up by neutrophils and converted to $LXA_4$ via 5-LOX. (**III**) aspirin-acetylated COX-2 transforms AA to 15R-HETE, which is taken up by leukocytes and converted via 5-LOX to 15-epi-$LXA_4$, a product that is also called aspirin-triggered lipoxins (ATL)

in Fig. 6.3. The first pathway involves peripheral blood leukocyte–platelet interactions. The enzyme 5-LOX in leukocytes converts AA to $LTA_4$, which is released from leukocytes and further transformed by adherent platelets to $LXA_4$ via 12-LOX (Edenius et al. 1988; Romano and Serhan 1992). The second biosynthetic route is initiated at mucosal surfaces by 15-LOX that transforms AA to 15S-hydroxy-eicosatetraenoic acid (15S-HETE), which is rapidly taken up by neutrophils and subsequently converted via 5-LOX to $LXA_4$ (Serhan 1997). In addition to these two main routes, it has been discovered that aspirin-acetylated COX-2 can transform AA to 15R-HETE, which is taken up by leukocytes and converted via 5-LOX to 15-epi-$LXA_4$, also called aspirin-triggered lipoxins (ATL) (Claria and Serhan 1995).

LXs and ATL act at both temporal and spatially distinct sites from other eicosanoids produced during the course of inflammatory responses to actively participate in anti-inflammation and resolution of inflammation (Serhan 2005). LXs and

n-3 polyunsaturated fatty acid (PUFA) eicosapentaenoic acid and docosahexaenoic acid-derived resolvins, protectins and maresins are collectively termed specialized proresolving mediators (SPM). Recent studies demonstrated that SPMs are temporally and differentially regulated during infections (Chiang et al. 2012), and they potently stimulate cessation of PMN infiltration and enhance macrophage uptake of apoptotic cells, debris and microbes (Serhan 2014), aiding a return to tissue homeostasis. Accumulated evidence demonstrated that SPM including $LXA_4$ play an important role in infectious diseases. Thus, it has been reported that $LXA_4$ displays protective effects on host defense against fungal pathogen *Cryptococcus neoformans* (Colby et al. 2015), parasite *Toxoplasma gondii* (Aliberti et al. 2002) and *Trypanosoma cruzi* (Molina-Berrios et al. 2013), respiratory viruses (Kim 1990; Shirey et al. 2014) and influenza A virus (Cilloniz et al. 2010), and cerebral malaria (Shryock et al. 2013). Moreover, $LXA_4$ exhibits beneficial effects on bacteria *Porphyromonas gingivalis*-induced periodontitis (Serhan et al. 2003) and LPS-induced preterm birth (Rinaldi et al. 2015). Interestingly, ATL combined with antibiotics protects mice from *Escherichia coli*-induced sepsis (Ueda et al. 2014). In contrast, $LXA_4$ seems to exert detrimental effects on *Mycobacterium tuberculosis* infection (Chen et al. 2008; Bafica et al. 2005).

Interestingly, it has been demonstrated that $LXA_4$ and other SPM also can regulate HDP expression. We have shown that resolvin E1 (RvE1) dampens $LTB_4$-induced human cathelicidin LL-37 release from human neutrophils via binding to BLT1 (Wan et al. 2011). On the other hand, ATL induces the expression of an antimicrobial peptide/protein called bactericidal permeability-increasing protein in epithelial cells (Canny et al. 2002). Campbell et al. concluded that generation of SPM in the resolution phase elicits the induction of "nonclassical" AMPs to accelerate return to homeostasis via continued bacterial killing, and inhibition of LPS signaling; meanwhile, SPMs can block and/or counteract the release of "classical" AMPs from leukocytes, dampening the proinflammatory signals (Campbell et al. 2011).

It is noteworthy that LXs act as agonists at specific GPCRs, in particular FPR2/ALX, to regulate cellular responses in inflammation and resolution (Fiore et al. 1994). Actually, FPR2/ALX binds both protein and lipid ligands that evoke opposing biological responses. For example, ALX mediates the proinflammatory actions of LL-37 (Wan et al. 2011) and the acute-phase protein serum amyloid A (SAA) (Bozinovski et al. 2012). In contrast, ALX also mediates the anti-inflammatory actions of the lipid $LXA_4$ (Fiore et al. 1994) and protein annexin A1 (AnxA1) (Perretti and D'Acquisto 2009). Actually, lipid and peptide ligands act with different affinities and bind to distinct pockets on the receptor, thus making a direct competition unlikely (Filep 2013). In one recent report, Cooray et al. identified that AnxA1, but not SAA, stimulated ALX homodimerization and activated the p38 MAPK/MAPKAPK/Hsp27 signaling cascade (Cooray et al. 2013).

## 6.3 HDPs and Eicosanoid Productions

Although first studied for their antimicrobial activity, HDPs are now widely recognized for their multifunctional roles in both the innate and adaptive immune responses. Their diverse immunomodulatory capabilities include the modulation of pro- and anti-inflammatory responses, chemoattraction, enhancement of extracellular and intracellular bacterial killing, cellular differentiation and activation of the innate and adaptive compartments, wound-healing, and modulation of autophagy as well as apoptosis and pyroptosis (Mansour et al. 2014). Increasing evidence demonstrate that HDPs also promote eicosanoid productions in various cell types to form a positive feedback loop between HDP and eicosanoid production, which plays an important role in several pathophysiological conditions.

### *6.3.1 Positive Feedback Loops Between HDPs and Eicosanoids*

#### 6.3.1.1 HDPs and $LTB_4$ in Host Defense

Human α-defensins, also known as human neutrophil peptides (HNP), are a major product of activated neutrophils. HNP types 1–4 are abundant in human neutrophils, constituting 5 % of all neutrophil proteins and 30–50 % of the total protein content of the azurophilic granules in neutrophils (Ganz et al. 1985). It has been shown that $LTB_4$ triggers the release of α-defensins from circulating neutrophils (Flamand et al. 2004; Gaudreault and Gosselin 2008; Flamand et al. 2007). Moreover, HNP promote $LTB_4$ production in human alveolar macrophages in a dose-dependent manner (Spencer et al. 2004), suggesting α-defensins and $LTB_4$ could interact through a positive feedback loop. In addition, our research group and others have demonstrated that $LTB_4$ also induces hCAP18/LL-37 release from neutrophils via the BLT1 receptor (Wan et al. 2007; Flamand et al. 2007). LL-37 is present at high concentrations as the inactive proform hCAP-18 in the secondary granules of neutrophils (Sorensen et al. 1997). Once hCAP18 is secreted from neutrophils, it is processed into the active LL-37 peptide by proteinase 3 that is present in the primary granules of these cells (Gudmundsson et al. 1996; Sorensen et al. 2001). Interestingly, we also identified that LL-37 induces intracellular calcium mobilization, activates p38 MAP kinase, promotes phosphorylation of $cPLA_2$ and translocation of 5-LOX, which promotes $LTB_4$ release from human neutrophils via the GPCR FPR2/ALX (Wan et al. 2007, 2011), and from human macrophages via $P2X_7R$ (Wan et al. 2014), indicating that a positive feedback loop exists between cathelicidin and $LTB_4$ production as well.

Considering the importance of $LTB_4$-induced HDPs from neutrophils in antiviral activity in vitro and in vivo (Flamand et al. 2004, 2007; Gaudreault and Gosselin 2008), the positive feedback loop between $LTB_4$ and HDPs could be vital to

amplify the host antiviral activity. Recently, Chaves et al. provided evidence that $P2X_7R$ activation in macrophages leads to $LTB_4$ formation, which is required for *L. amazonensis* elimination (Chaves et al. 2014). In our recent studies, we further demonstrate that LL-37 promotes $LTB_4$ production in human macrophage via $P2X_7R$ (Wan et al. 2014) and that LL-37 enhances bacterial clearance by macrophages (Wan et al. 2014). Macrophages can also import LL-37 released from $LTB_4$-challenged neutrophils to promote intracellular bacterial clearance (Tang et al. 2015). All these evidences suggest the presence of positive feedback circuits between HDPs and $LTB_4$ that are important in host defense against various pathogens.

Intriguingly, we have also shown that anti-inflammatory lipid mediators $LXA_4$ and RvE1 might counteract the proinflammatory circuit between LL-37 and $LTB_4$ in human neutrophils by blocking the receptors FPR2/ALX and BLT1, respectively, that signal in a $LTB_4$/LL-37 positive feedback loop in neutrophils (Wan et al. 2011). It is noteworthy that both $LTB_4$ and LL-37 are involved in many chronic inflammatory diseases, such as atherosclerosis (Funk 2005; Qiu et al. 2006; Edfeldt et al. 2006), inflammatory bowel diseases (Hawthorne et al. 1992; Schauber et al. 2006) and cancers (Satpathy et al. 2015; von Haussen et al. 2008). Therefore, it appears essential to interfere with and dampen $LTB_4$/LL-37 co-driven inflammatory responses.

#### 6.3.1.2 HDPs and $PGD_2$/cys-LTs in Allergy

Human β-defensins (hBDs) are mainly produced by epithelia of several organs including skin, and participate in host defense by killing invading pathogens, as well as promoting both innate and adaptive immune responses (Yang et al. 1999). Among four hBDs identified in epithelium so far, hBD-1 is generally constitutively produced by various epithelial tissues such as those in the urogenital and respiratory tracts, and skin (Valore et al. 1998), whereas the expressions of hBD-2, hBD-3, and hBD-4 are inducible (Singh et al. 1998).

It has been reported that $PGD_2$ induces hBDs including hBD-2 and hBD-3 production in human keratinocytes (Kanda et al. 2010; Bernard and Gallo 2010). $PGD_2$ is the major prostaglandin produced by mast cells and is involved in allergic diseases such as asthma (Matsuoka et al. 2000). Interestingly, it has been reported that hBD-2 works as a chemotaxin for mast cells (Niyonsaba et al. 2002), and induces intracellular calcium mobilization, AA release and $PGD_2$ production in rat peritoneal mast cells via COX-1 (Niyonsaba et al. 2001; Kase et al. 2009). Furthermore, hBD-3 and hBD-4 also act on mast cells and enhances their chemotaxis and degranulation, which results in the release of $PGD_2$ (Chen et al. 2007). Moreover, cathelicidins can activate mast cells as well. For example, LL-37 was shown to induce intracellular calcium mobilization, AA release and $PGD_2$ production in rat peritoneal mast cells via COX-1 (Niyonsaba et al. 2001). Furthermore, rat cathelicidin rCRAMP and human cathelicidin LL-37 trigger generation and release of cys-LTs and other pro-inflammatory mediators in mast

cells (Babolewska et al. 2014; Babolewska and Brzezinska-Blaszczyk 2015). Work in our laboratory has also revealed that LL-37 induces synthesis and release of cys-LTs from human eosinophils via FPR2/ALX by enhancing $cPLA_2$ activity and inducing intracellular translocation and assembly of 5-LOX and $LTC_4S$ at perinuclear locations and lipid bodies (Sun et al. 2013). In addition, we could observe that eosinophils from asthmatics express significantly higher hCAP18 protein levels compared with those from healthy subjects, and eosinophils isolated from asthmatics released more hCAP18 upon leukotriene stimulation than did cells from healthy subjects (Sun et al. 2013). Hence, this study suggested that a positive feedback loop also exists between leukotrienes and LL-37 in eosinophils, which might contribute to asthma progress. The results from all these studies indicate that the proinflammatory circuit between HDPs and eicosanoids in mast cells and eosinophils may be undesirable for the host during an antimicrobial process, and could be a potential therapeutic target for allergic diseases, such as asthma.

### *6.3.2 Other HDPs and Eicosanoid Production*

One early study investigated the effects of two magainin peptides originally isolated from the skin of the African claw toad (*Xenopus laevis*) on eicosanoid synthesis by rat peritoneal macrophages stimulated with LPS and lipid A from *Salmonella*. The results showed that depending on the type of peptide used and on its concentration, these two magainin peptides exhibited different effects on LPS or lipid A-induced macrophage eicosanoid synthesis ($TXB_2$ and 6-keto-$PGF_{1\alpha}$) (Matera et al. 1993). Another family of α-helical HDPs, pleurocidins, originate from fish and are structurally and functionally similar to cathelicidins (Cole et al. 1997; Patrzykat et al. 2003). Chiou et al. demonstrated that cecropin and pleurocidin induce gene expression of IL-1β and COX-2 in a trout macrophage cell line (Peter Chiou et al. 2006), suggesting a proinflammatory role of pleurocidin in the vertebrate immune system. One recent report illustrated that pleurocidins activated human mast cells to induce intracellular calcium mobilization and production of cys-LTs and $PGD_2$ in human mast cells through the FPR2/ALX receptor (Pundir et al. 2014). Moreover, catestatin, a neuroendocrine antimicrobial peptide, can also activate human mast cells to induce intracellular calcium mobilization and the production of cys-LTs, $PGD_2$ and $PGE_2$ (Aung et al. 2011). Another report revealed that hBD-3 and LL-37 function as proinflammatory mediators to up-regulate COX-2 expression and $PGE_2$ synthesis in human gingival fibroblasts (Chotjumlong et al. 2010, 2013). Furthermore, we also identified that LL-37 elicited a biphasic release of eicosanoids in macrophages with early, $Ca^{2+}$-dependent formation of $LTB_4$ and $TXA_2$ (measured as $TXB_2$) followed by a late peak of $TXA_2$ (measured as $TXB_2$), generated via induction of COX-2 by internalized LL-37 (Wan et al. 2014). Importantly, our findings provide evidence that LL-37 is an endogenous regulator of eicosanoid-dependent inflammatory responses in vivo, since intraperitoneal injection of mice with murine cathelicidin-related antimicrobial peptide (mCRAMP) induces significantly higher levels of $LTB_4$ and

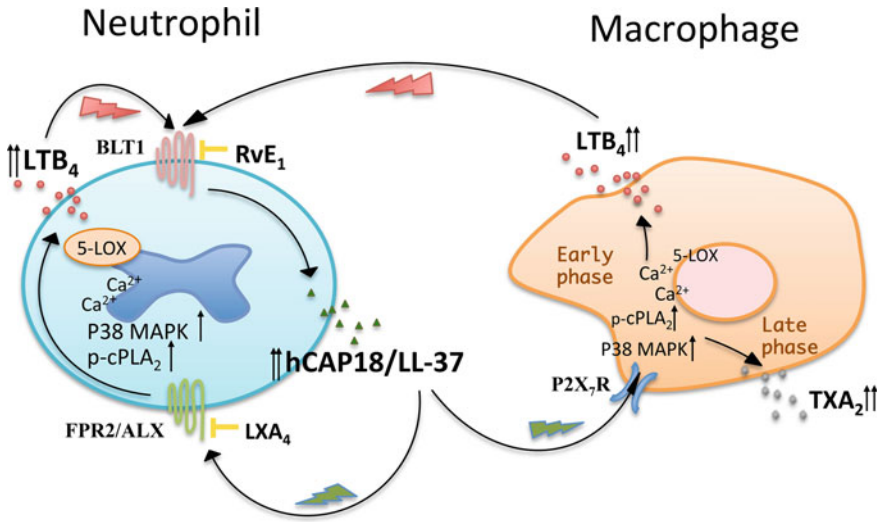


**Fig. 6.4** The crosstalk between LL-37, a human HDP, and eicosanoids in leukocytes. Inflammation is induced (e.g., by microbes), and neutrophils are recruited to the sites of inflammation guided by chemoattractants, such as $LTB_4$. $LTB_4$ can trigger the release of hCAP18/LL-37 via BLT1. The released LL-37 conversely induces $LTB_4$ production from neutrophils via FPR2/ALX, or from macrophages via $P2X_7R$, by triggering intracellular calcium mobilization, activating p38 MAP kinase, promoting phosphorylation of $cPLA_2$ and translocation of 5-LOX. Similarly, the released LL-37 also induces $LTB_4$ production from macrophages. Therefore, there is a positive feedback loop between LL-37 and $LTB_4$ production in leukocytes, which can be blocked by the anti-inflammatory lipid mediators $LXA_4$ and $RvE_1$ by competition with LL-37 or $LTB_4$ for binding at FPR2/ALX or BLT1, respectively. Moreover, the neutrophil-released LL-37 can also be taken up by macrophages, leading to further eicosanoid production such as $TXA_2$ or facilitated intracellular bacterial killing

$TXA_2$ in mouse ascites rich in macrophages. Conversely, cathelicidin-deficient ($Cnlp^{-/-}$) mice produce much less $LTB_4$ and $TXB_2$ in vivo in response to TNF-α compared with control mice (Wan et al. 2014). Additionally, we also found that LL-37 induces angiogenesis via $PGE_2$–EP3 signaling in endothelial cells, and mCRAMP also induced prostaglandin-dependent angiogenesis in vivo, which could be blocked by aspirin (Salvado et al. 2013).

## 6.4 Conclusion

As two important components in innate immunity and inflammation, plenty of studies on HDPs and eicosanoids have been undertaken. Accumulated evidence demonstrates that HDPs not only kill pathogens directly, but also possess potent immunoregulatory activities including regulation of eicosanoid production. Meanwhile, eicosanoids participate in host defense via various mechanisms, one of

which is to modulate HDP production. The crosstalk between these two families of molecules has been concluded in Fig. 6.4. Considering the involvement of these two families of peptides and lipids in several pathophysiological situations, such as infections and allergy, intervention in positive cross-signaling loops has become a potential strategy for treatments against infection, allergy, and other inflammatory diseases.

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