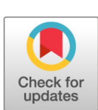
MINIREVIEW



Roles of Eicosanoids in Regulating Inflammation and Neutrophil Migration as an Innate Host Response to Bacterial Infections

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ABSTRACT Eicosanoids are lipid-based signaling molecules that play a unique role in innate immune responses. The multiple types of eicosanoids, such as prostaglandins (PGs) and leukotrienes (LTs), allow the innate immune cells to respond rapidly to bacterial invaders. Bacterial pathogens alter cyclooxygenase (COX)-derived prostaglandins (PGs) in macrophages, such as PGE2 15d-PGJ_2, and lipoxygenase (LOX)-derived leukotriene $LTB_{4,}$ which has chemotactic functions. The PG synthesis and secretion are regulated by substrate availability of arachidonic acid and by the COX-2 enzyme, and the expression of this protein is regulated at multiple levels, both transcriptionally and posttranscriptionally. Bacterial pathogens use virulence strategies such as type three secretion systems (T3SSs) to deliver virulence factors altering the expression of eicosanoid-specific biosynthetic enzymes, thereby modulating the host response to bacterial lipopolysaccharides (LPS). Recent advances have identified a novel role of eicosanoids in inflammasome activation during intracellular infection with bacterial pathogens. Specifically, PGE_2 was found to enhance inflammasome activation, driving the formation of pore-induced intracellular traps (PITs), thus trapping bacteria from escaping the dying cell. Finally, eicosanoids and IL-1β released from macrophages are implicated in the efferocytosis of neighboring neutrophils. Neutrophils play an essential role in phagocytosing and degrading PITs and associated bacteria to restore homeostasis. This review focuses on the novel functions of host-derived eicosanoids in the host-pathogen interactions.

KEYWORDS bacterial infection, inflammasome, inflammation, lipid metabolism, prostaglandins

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most taken over-the-counter pain relievers. While these medications are taken to alleviate the symptoms of viral and bacterial infections (1, 2), NSAIDs can have severe side effects, including gastrointestinal and cardiovascular complications (3–6). Many NSAIDs act by inhibiting cyclooxygenase (COX)-1/-2 enzymes, which biosynthesize prostaglandins (PGs) and other bioactive lipids that downstream trigger pain or elevated temperature (1, 2, 5). PGs belong to the class of eicosanoids, which are immunomodulatory lipids generated via the oxidation of arachidonic acid (AA) or other polyunsaturated fatty acids (PUFAs) (7). Eicosanoids vary in function and structure and act on discrete cellular receptors designated EP receptors (8, 9). As a result, a wide variety of physiological responses are possible depending on the generation of specific eicosanoids and the expression of individual eicosanoid receptors (10–14). Eicosanoids have a complex function in the innate immune response: in some cases, eicosanoids support inflammation, such as enhancing pro-interleukin-1β (pro-IL-1β) biosynthesis, and in others, eicosanoids block inflammatory processes, for instance, by destabilizing tumor necrosis factor alpha (TNF-α) transcripts (15–19). Despite what is known, eicosanoid functions in bacterial infections remain elusive, and it appears that depending on the pathogen, unique mechanisms lead to the perturbations of the eicosanoid metabolism in the host cell. This review focuses on the

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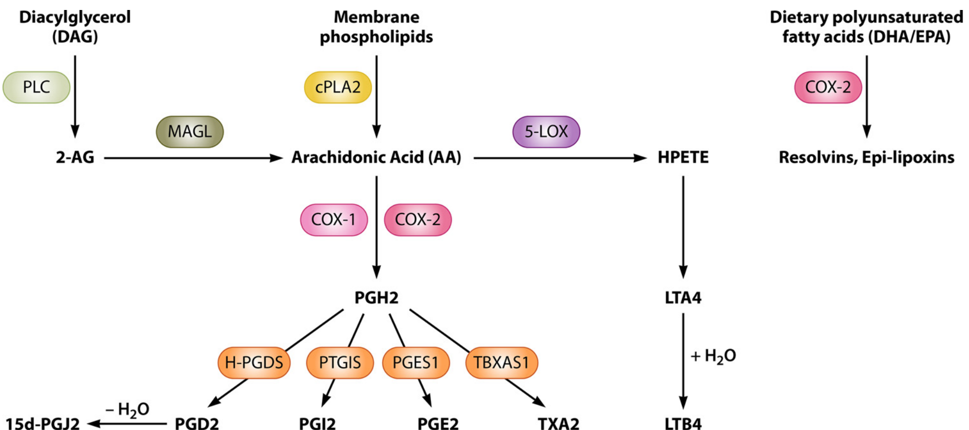

FIG 1 Biosynthesis of various prostaglandins and leukotrienes. Membrane phospholipids are converted to AA by the PLA2 enzyme. Alternatively, AA can be synthesized from diacylglycerol (DAG), where DAG is converted by PLC to 2-AG intermediate, followed by MAGL degradation of 2-AG to AA. AA serves as a substrate of COX-1 and COX-2, which convert AA to PGH_2. Alternatively, AA is used by the 5-LOX enzyme to produce leukotrienes. PGH_2 is converted to PGE_2 by prostaglandin E synthase 1 (PGES-1) or PGD2 by hematopoietic prostaglandin D synthase (H-PGDS). PGD2 undergoes a dehydration reaction to form 15d-PGJ_2. LTA4 is derived from 5-LOX generated HPETE. LTA_4 can be processed further to LTB_4 via a hydrolysis reaction. Various other eicosanoids, such as resolvins and other lipoxins, are generated from the oxidation of polyunsaturated fatty acids other than AA, such as DHA and EPA.

function of distinct classes of eicosanoids such as PGE_2, 15d-PGJ_2, and LTA_4/LTB_4 in the conserved host response to bacterial LPS.

REGULATION OF EICOSANOID BIOSYNTHESIS

Arachidonic acid, AA, is a 20-carbon fatty acid, and it serves as a primary eicosanoid precursor in the cells. AA is not freely available in the cell, and it is instead associated with cellular membranes. However, under activation of Toll-like receptor 4 (TLR4) by bacterial LPS and other stimuli, membrane phospholipids are cleaved by cPLA2 to produce free AA (20–22) (Fig. 1). Host mitogen-activated protein kinases (MAPK) are rapidly phosphorylated in response to lipid-A of bacterial LPS binding to host TLR4, leading to activation of transcription factors such as nuclear factor-κB (NF-κβ) that drives pro-inflammatory cytokine biosynthesis (22, 23). The cPLA2 enzyme is activated via phosphorylation by host MAPKs at serine 505 residue, leading to activation of cPLA2 and consequent AA liberation (20, 24, 25). Cytosolic AA can then be further metabolized to oxygenated derivatives, eicosanoids, which include prostanoids (prostaglandins, PGs, and thromboxanes), leukotrienes (LTs), lipoxins (LXs), and epoxyeicosatrienoic acids (EETs) (26). In addition to AA, other PUFAs can also be used as eicosanoid precursors, including ω6-derived PUFAs from dihomo-γ-linolenic acid (DGLA) or ω3-derived PUFAs from α-linolenic acid (ALA), for instance, eicosapentaenoic acid (EPA). PGs and LTs are generated via the oxidation of AA by cyclooxygenase (COX) or lipo-oxygenase (LOX) enzymes, respectively.

Two different cyclooxygenase enzymes are responsible for converting AA into the various prostaglandins, COX-1 and COX-2. Human COX-1 and COX-2 are homodimers and share 60% sequence similarity (27). These enzymes contain two different active sites, a peroxidase and a cyclooxygenase active site, flanking a central heme group (27, 28). The peroxidase center catalyzes the removal of two electrons from Tyr-385 residue in the cyclooxygenase active site to produce a tyrosyl radical that can catalyze the cyclooxygenase reaction. Due to their functions in regulating inflammation, COX enzymes are targets of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen, which function by inhibiting pro-inflammatory PG synthesis and thus result in decreased pain, inflammation, and fever (29). Different NSAIDs have distinct selectivity for COX isoenzymes. For example, aspirin covalently modifies Ser-530 residue in the active site of both COX isoenzymes, preventing PG synthesis, while other COX inhibitors such as

ibuprofen are reversible inhibitors of both COX enzyme functions (reviewed in reference 30). In addition, while aspirin and ibuprofen are nonselective COX inhibitors, celecoxib and etoricoxib have high selectivity toward COX-2 and therefore have reduced adverse effects related to gastrointestinal tract (31, 32). Under biological conditions, AA is first reduced to the hydroperoxy arachidonate metabolite PGG_2 (33) and then further reduced to PGH_2 by the peroxidase activity of COX-1/2 (34). PGH_2 is converted rapidly to biologically active prostanoids by specific synthases and acts on discrete receptors designated EP receptors, which exist at various levels in particular tissues (35–38). These prostanoids include prostaglandin E_2 (PGE_2) synthesized by prostaglandin E synthase (PGES), prostacyclin (PGI_2) synthesized by prostaglandin I synthase (PGIS), prostaglandin D_2 (PGD_2) synthesized by prostaglandin D synthase (PGDS), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) synthesized by prostaglandin F synthase (PGFS), and thromboxane A2 (TXA_2) generated by thromboxane A synthase (TXAS) (7). Further, an anti-inflammatory prostaglandin 15d-PGJ_2 is synthesized from PGD_2 via its dehydration to PGJ2, which is also converted to 15d-PGJ_2 or Δ-12-PGJ_2 (7).

Leukotrienes are generated from 5-lipoxygenase (arachidonate-5-lipoxygenase; 5-LOX)-mediated conversion of AA to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) intermediate (39), which is then rapidly reduced to 5-hydroxyeicosatetraenoic acid (5-HETE) (Fig. 1). However, 5-HPETE can be alternatively converted by 5-LOX to an unstable structure called leukotriene A_4 (LTA_4), which can be further modified to generate leukotriene B_4 (LTB_4) by LTA_4 hydrolase, or to leukotriene C_4 (LTC_4) by LTC_4 synthase, respectively. LTB_4 and LTC_4 molecules are mainly produced by immune cells. Following the export of these LTs, LTC_4 is metabolized to LTD_4 by gamma-glutamyl transpeptidase, while LTD_4 can be modified to LTE_4 by cysteinyl glycinase.

The availability of AA and the cell's physiological state dictate the LT and PG levels at the same time since COX and LOX enzymes both utilize AA as a substrate for PG and LT biosynthesis, respectively. Hence, a delicate balance between PG and LT synthesis is maintained upon various stimuli, resulting in specific physiological responses. Bacterial LPS and subsequent inflammation associated with these infections serve as such stimuli contributing to COX and LOX activation. During bacterial infection, pathogen-associated molecular patterns (PAMPs) are recognized by membrane-bound Toll-like receptors (TLRs) or other pattern recognition receptors (PRRs), as well as by intracellular cytosolic nucleotide oligomerization domain (NOD)-like receptors (NLRs) (40). Pro-inflammatory signaling is not always desirable for a pathogen. Certain bacteria aim to evade the immune system by inducing changes to the bacterial lipopolysaccharide (LPS), a component of Gram-negative bacteria's outer membrane, impairing TLR signaling (41–44). LPS is a potent inducer of PGE2 biosynthesis and is involved in a wide variety of bacterial infections (Table 1). Gram-negative bacterial LPS comprises multiple elements, including lipid-A, inner core, outer core, and O antigen components. Lipid-A is a potent endotoxin that binds specifically to TLR4 and, along with the help of MyD88, activates transcriptional factors such as NF-κB to upregulate pro-inflammatory cytokine production as well as COX-2 expression, the major biosynthetic enzyme of PGE_2 (21–23). The binding of lipid-A to TLR4 activates MyD88, which results in phosphorylation of host mitogen-activated protein kinases (MAPKs), resulting in the subsequent phosphorylation of IκB kinase (IKK), which results in derepression of NF-κB, allowing its translocation to the nucleus to upregulate gene transcription (23). It is unclear if PGE_2 biosynthesis in response to LPS-TLR4 is due to lipid-A or other parts of bacterial LPS since rough or smooth mutants of *Salmonella enterica* serovar Typhimurium lacking O antigen or characterized by an impaired lipid-A biosynthesis all induce PGE_2 biosynthesis (19). Chemical inhibitors of the MAPK cascade during LPS treatment alone or several Gram-negative bacterial infection models have been reported to abrogate PGE_2 biosynthesis, potentially indicating a conserved host response mechanism of PGE_2 biosynthesis in response to Gram-negative bacterial infection (45). In contrast, Gram-positive bacteria lack LPS, but they contain teichoic and lipoteichoic acids as well as a thick peptidoglycan layer, and these pathogens

TABLE 1 The effect of bacterial infections on eicosanoid production and function of eicosanoids in bacterial infections

Organism	The effect of infection on eicosanoids	The effect of eicosanoids on infection	Reference(s)
Burkholderia pseudomallei	Increase in PGE_2	PGE_2 has detrimental effects on the survival of infected mice	155
Campylobacter jejuni	Increase in PGE_2		156
Escherichia coli	Increase in PGE_2	PGE_2 increase by colibactin-producing *E. coli* functions in colon cancer tumorigenesis; inhibition of COX-2 enhances infection with extraintestinal *E. coli*	51, 134, 137
Francisella tularensis	Increase in PGE_2	PGE_2 has detrimental effects on the infected host via downregulation of Th1 immunity	157, 158
Helicobacter pylori	Increase in PGE_2	PGE_2 contributes to chronic inflammation but also cancer cell growth and proliferation	130, 131, 133
Klebsiella pneumoniae		LTB_4 promotes phagocytosis, enhances ROS-dependent NADPH oxidase activation	111
Legionella pneumophila	Increase in PGE_2		159
Mycobacterium tuberculosis	Degradation of LTB_4 to its inactive form 12-oxo-LTB_4; decrease in PGE_2	LTA_4H deficiency downregulates TNF-α; COX-2 inhibition leading to reduced PGE_2 enhances phagocytosis of *M. tuberculosis*	109, 124, 125
Pseudomonas aeruginosa	Increase in PGE_2	COX-2-deficient mice have increased survival rates during infection	160–162
Salmonella enterica	Increase in PGE_2 by SPI-2 T3SS factors	PGE_2 affects macrophage polarization	19, 57, 123
Shigella flexneri	PGE_2 levels are elevated in the stool of infected patients and in rabbit ileal loops		52, 148, 149
Staphylococcus aureus	Increase in PGE_2	PGE_2 promotes the growth and biofilm formation of *S. aureus* and enhances the attachment of bacterium to the human fibronectin	47
Yersinia enterocolitica	Increase in PGE_2 but downregulation of PGE_2 by T3SS virulence factors	PGE_2 affects macrophage polarization	19

typically do not induce large levels of PGE_2 biosynthesis except for *Staphylococcus aureus* infection (46, 47).

The immunomodulatory effects of PGs and LTs depend on the expression of cognate receptors on recipient cells, which varies depending on the cell population and the cells' physiological state. For example, macrophages generate a wide variety of PGs and LTs in response to TLR stimuli, but the biosynthesized levels of specific eicosanoids change across macrophages from different sources and under distinct physiological states (12). While COX-1 is constitutively expressed in almost all tissue types, COX-2 is inducible by inflammatory cytokines and TLR activation (48). The 5′-UTR (untranslated region) of the COX-2 gene includes binding sites for several transcription factors such as NF-κB, AP-1, CRE, and others (49). COX-2 is also regulated by posttranscriptional processes due to instability sequences in the 3′-UTR. RNA-binding proteins that recognize AU-rich elements (AREs) are hypothesized to control COX-2 mRNA stability, such as CUGBP2 or HuR, which binds to COX-2 mRNA and prevents translation (50). Mitogenic inhibitors can also influence COX-2 expression in a protein kinase C-p38 MAPK (mitogen-activated protein kinase)-dependent manner (41–44). TLR4 signaling is in particular essential for COX-2 upregulation. COX-2 and PGE2 biosynthesis is upregulated in response to a wide variety of Gram-negative pathogens, including *Salmonella enterica* serovar Typhimurium, *Shigella flexneri*, *Helicobacter pylori*, *Yersinia enterocolitica*, and *Escherichia coli*, which will be covered in following sections (14, 19, 50–53).

The leukotriene biosynthesis is also enzymatically controlled by several proteins. Specific LOX enzymes are present in different cells to metabolize AA, including 5-LOX in leukocytes, 12-LOX in platelets, or 15-LOX in endothelial cells. LTB_4 is a chemoattractant for polymorphonuclear leukocytes (PMNs), such as neutrophils and eosinophils (54, 55). Accordingly, 5-LOX and LTB_4 are heavily regulated in immune cells. For instance, pro-inflammatory or M1 macrophages secrete high levels of LTB_4, whereas

anti-inflammatory M2 macrophages express lipoxins, which aid in immune suppression. 5-LOX is inactive in resting cells and becomes activated by increasing intracellular calcium or phosphorylation (56, 57).

THE FUNCTION OF EICOSANOIDS IN THE REGULATION OF INFLAMMATORY PROCESSES IN RESPONSE TO BACTERIAL INFECTIONS

Eicosanoids regulate pro-inflammatory processes, often associated with bacterial infections. Bacterial products (PAMPs) and danger-associated molecular patterns (DAMPs) are recognized by both intracellular and extracellular receptors expressed by the host cell, such as macrophages. PAMPs include LPS, flagellin, and the needle and rod protein of the bacterial T3SS, while DAMPs include elevated ATP levels or K^+ influx (58–60). These components are recognized by typically extracellular membrane-bound TLRs or cytosolic NOD-like receptors (NLR). The initial stimulus triggers the oligomerization of NLRs with an adapter protein, ASC, to form the inflammasome (61). Five well-studied receptors capable of creating inflammasomes in response to bacterial infection and noncanonical inflammasomes that detect bacterial LPS and activate caspase-11 are NLRP1, NLRP3, NLRC4, AIM2, and pyrin (61). For example, during *S.* Typhimurium infection, NLRP3 and NLRC4 inflammasomes are upregulated and activated to produce a large quantity of IL-1β (62).

In contrast, other pathogens such as *Mycobacterium tuberculosis* and *Yersinia pestis* actively repress inflammasome formation by employing virulence factors and impairing IL-1β signaling during infection (63, 64). Inflammasomes are a hallmark of pyroptosis, a form of pro-inflammatory programmed cell death that leads to the rapid clearance of bacteria by removing intracellular replication niches and enhancing chemotaxis of neutrophils to the site of infection (51). Recent studies have investigated PGs' role in modulating the activity of inflammasomes and will be discussed below. Relatively few categories of eicosanoids have been extensively studied in the context of infections, whereas PGs and LTs are some of the best-characterized eicosanoids due to their roles in inflammatory conditions, such as arthritis and bacterial sepsis (65). Below, we will discuss specific functions of eicosanoids in inflammasome activation, phagocytosis, and efferocytosis, giving specific examples of bacteria that modulate the biosynthesis of eicosanoids. Finally, we will review the outcomes of eicosanoid biosynthesis changes in these infections, focusing on gastrointestinal pathogens.

The role of PGE_2 and 15d-PGJ_2 during inflammasome activation and inflammation. PGE_2 is one of the most significant eicosanoids released during infection with Gram-negative pathogens (Table 1). PGE_2 stimulates the production of pro-inflammatory cytokines such as IL-1β, IL-23/17, or IL-8 while limiting inflammation by controlling TNF-α levels and inducing IL-10 secretion (19, 66). These unique functions of PGE_2 in the stimulation of specific cytokine profiles emphasize the importance of this molecule in maintaining homeostasis during infection. Bacterial components such as LPS or virulence factors can induce transcriptional changes that enhance COX-2 expression, resulting in the biosynthesis and secretion of PGE_2 (19, 21). PGE_2 acts on neighboring immune cells by binding to discrete G-protein coupled receptors, designated EP receptors 1 to 4, each with different downstream consequences in response to activation (as extensively reviewed in reference 8). Once bound, the G-linked receptors control levels of secondary messengers in the cell, such as cAMP, IP3, and Ca^{2+}, which induce transcriptional changes via NF-κB or C-JUN (67–70). Gene regulation by EP receptor signaling has a wide range of effects on host cells, including shifts in macrophage polarization or downregulation of bactericidal capabilities in neutrophils by downregulating NADPH oxidase and reducing the generation of reactive oxygen species (ROS) (19, 71–73).

PGE_2 has also been reported as having a pro-inflammatory role in inflammasome activation in pyroptosis that is often present during bacterial infections. For instance, PGE_2 increases inflammation by leading to an elevated IL-1β expression, which is subsequently cleft by caspase-1 and secreted and in this way can reach neighboring cells (15, 74). The binding of IL-1β to IL-1R also increases the expression of the COX-2 enzyme, creating a positive feedback loop by stimulating host MAPK-extracellular signal-regulated kinase (ERK)

signaling-mediated transcriptional changes (15). Additionally, increased PGE_2 biosynthesis is associated with decreased phagocytosis (67). The killing ability of macrophages is also reduced by PGE_2, for instance, by diminished nitric oxide synthesis in macrophages, leading to larger bacterial loads during some infections, such as *Mycobacterium tuberculosis* (75). As such, PGE_2 has become increasingly acknowledged as an essential factor in determining the fate of the host during bacterial infection and has made PGE_2 an appealing option for antimicrobial treatments targeting COX-2 or EP receptor inhibition (76–79). PGE_2 signaling via the EP3 receptor increases activation of inflammasome in some infections. Specifically, PGE_2 signaling through the EP3 receptor leads to activation of the NLRC4 inflammasome during infection with *Anaplasma phagocytophilum*, a bacterium that causes anaplasmosis (80).

Although EP2 and EP4 receptors also have been shown to be involved in inflammasome activation, reports of PGE_2 function in mediating inflammasome activation through EP2 and EP4 have been conflicting. For example, PGE2 inhibits NLRP3 inflammasome by signaling through the EP4 receptor (69). The EP4 receptor activates adenylate cyclase, increasing intracellular cAMP levels via phosphoinositide 3-kinase (PI3K), leading to the downregulation of NLRP3 (16). Interestingly, EP2 receptor agonists failed to produce a similar result in dampening NLRP3 activation, even though PGE_2 has a much stronger affinity for the EP2 receptor. The EP2 receptor is more strongly associated with the cAMP production by adenylate cyclase than is the EP4 receptor, thus leading to more considerable changes in cAMP intracellular concentrations (81). In zebrafish, macrophage uptake of apoptotic neutrophils was found to be required for the resolution of inflammation. In this model, PGE2 acts via EP4 receptors to drive inflammation resolution by reverse migration (82). Other reports have suggested that PGE_2 and IL-1β form a positive feedback loop, which may be downstream of EP2 or EP4 (79). A receptor-specific response to PGE_2 has been reported multiple times, emphasizing that the functions of EP2 and EP4 receptors have to be studied more extensively (70, 79, 83, 84).

Apart from PGE_2, there are other PGs that affect inflammasome activity and inflammation, such as 15d-PGJ_2. 15d-PGJ_2 is a cyclopentane prostaglandin formed via the dehydration of PGD2 and has been shown to activate PPARγ promoting adipocyte and monocyte differentiation (85–87). 15d-PGJ_2 also inhibits inflammatory gene expressions such as inducible NO synthase and tumor necrosis factor α (TNF-α) (88–90). Additionally, 15d-PGJ_2 inhibits multiple steps in the NF-κB signaling pathway by directly modifying critical cysteine residues in IKK-β kinase and the DNA-binding domains of NF-κB subunits (91). 15d-PGJ_2 also inhibits inflammasome activation by inhibiting caspase-1 activation by the NLRP1 and NLRP3 inflammasomes in response to anthrax lethal toxin in a murine infection model (92). The negative effect of 15d-PGJ_2 on inflammasome activation is independent of canonical signaling pathways activated by 15d-PGJ_2. Instead, 15d-PGJ_2 induces a cell state that does not process caspase-1 to its active form, indicating a unique form of inflammasome inhibition (92). Additionally, exogenous administration of 15d-PGJ_2 appears to be anti-inflammatory in additional mouse models by inhibiting NLRP3-dependent peritonitis (93).

The function of 15d-PGJ_2 during bacterial infection models has become a new interest among researchers considering its ability to interact with PPARγ. In a brain abscess inflammation model, microglial activation by *Staphylococcus aureus* (*S. aureus*), one of the main etiologic agents of brain abscess in humans, was selectively attenuated by 15d-PGJ_2 (94). 15d-PGJ_2 inhibited increases in pro-inflammatory cytokines IL-1β and TNF-α, immunological markers such as TLR2, CD14, MHC class II, CD40 expression, and a variety of chemokines in microglial infected with *S. aureus* (94). Another study found similar anti-inflammatory effects for 15d-PGJ_2 in an astrocyte infection model of *S. aureus* but interestingly was able to function independently of PPARγ since inhibition of inflammation was still observed in PPARγ-deficient astrocytes (95). 115d-PGJ_2 also has been reported to play an anti-inflammatory role in several sepsis models, including *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) and *Escherichia coli* infections (96–98). *In vivo* infection with *S.* Typhimurium led to increased 15d-PGJ2 biosynthesis in the spleen and livers of infected mice (99), and follow-up studies using RAW macrophages, bone marrow-derived macrophages, and J774 cells indicate that 15d-PGJ2 is essential for

reducing bacterial colonization (100). 15d-PGJ_2 suppresses RANTES expression by inhibited NADPH oxidase activation in *Helicobacter pylori*-infected gastric epithelial cells (101). Ultimately, these studies suggest an important anti-inflammatory role for 15d-PGJ_2 during inflammasome activation and inflammation, which indicates a potential use of 15d-PGJ_2 in a variety of infectious diseases.

Functions of LTs in phagocytosis and efferocytosis. Among the LTs, LTB_4 is most involved in the early phases of inflammation during infection. For instance, these eicosanoids act as factors that recruit neutrophils to phagocytize and degrade invading pathogens (102). LTB_4 is a potent activator and chemoattractant of neutrophils and is biosynthesized and secreted primarily by polymorphonuclear leukocytes in macrophages and monocytes in response to bacterial infection (103, 104). LTB_4 works with other chemokine gradients such as C5a to attract neutrophils to the site of infection (105). LTB_4 signaling, through its cognate receptor BLT1, is critical for neutrophil migration to the foci of damage (106). For example, in Wistar rats, neutrophil migration induced by IL-1β is lost when animals are treated with MK866, a LOX-5 inhibitor (107). In a methicillin-resistant *S. aureus* (MRSA) skin infection model, LTB_4 promotes cutaneous abscess formation absent in LTB4R1-deficient mice (108). Interestingly, an ointment containing LTB_4 acted synergistically with the antibiotic mupirocin in lowering MRSA bacterial numbers in cutaneous abscesses, thereby indicating LTB_4 as a novel potential therapeutic option (108). In the zebrafish model of *Mycobacterium tuberculosis* infection, LTB_4 appears to be detrimental to host defense (109). LTA_4H (which converts LTA_4 to LTB_4) overexpression results in increased TNF-α secretion and increased *M. tuberculosis* bacterial numbers (110). LTB_4 also plays an important role in promoting phagocytosis (14, 104). Exogenous LTB_4 restores the phagocytic ability of 5-LOX-deficient neutrophils for serum opsonized *Klebsiella pneumoniae* (111). Once phagocytized, neutrophils utilize reactive oxygen species (ROS) to kill invading pathogens. LTB_4 enhances ROS-dependent NADPH oxidase activation via phosphorylation of the cytosolic subunit p47phox (112). LTB_4 also enhances MyD88 expression, which is required for NF-κB-mediated activation of pro-inflammatory cytokines (23). Upon PAMP or DAMP recognition, TLRs recruit Toll/IL-1R domain (TIR) adaptor molecules such as MyD88 or TRIF to initiate downstream signaling events, dictating the type of host response. LPS recognition and binding to TLR4 induce MyD88- and TRIF-dependent signaling pathways involving multiple host-activated mitogen kinases (MAPKs) such as MEK, JNK, and p38 kinases, which function by altering translocation of transcription factors to the nucleus to bind to and alter gene transcription during MyD88-dependent responses. For example, activation of host MyD88-dependent MAPKs results in derepression of NF-κB signaling by inhibiting IKK repression of NF-κB by direct phosphorylation of IKK, allowing NF-κB to migrate to the nucleus and initiate transcription of pro-inflammatory cytokines such as IL-1β and TNF-α (NF-κB has been extensively reviewed, e.g., see reference 113). These cytokines are important for the host immune response to invasive pathogens.

LTs are critical for efferocytosis of neutrophils to resolve inflammation, but paradoxically high levels of LTB_4 are associated with chronic inflammatory disorders such as type-1 and type-2 diabetes or arthritis (114–116). Paradoxically, LTB_4 plays a critical role in bacterial clearance but also contributes to long-term inflammatory disorders. Aberrant leukotriene production is hypothesized to alter immune cell function, which results in the hyperproductivity of inflammatory cytokines such as TNF-α, IL-8, and Il-6 during chronic inflammation (117–119). A genetic screen discovered that mutants of the lta4h locus in zebrafish resulted in altered LT4AH expression, which caused increased susceptibility to *Mycobacterium marinum* infection (120). LTA4H deficiency leads to anti-inflammatory activity in the host, which happens due to aberrant TNF-α production, damaging the host since a moderate level of inflammation is typically required to resolve infection (120). Accordingly, bacterial numbers were lower in wild-type zebrafish than in LTA4H-deficient zebrafish (120). In an additional study, *Streptococcus iniae* infection of zebrafish with deficiencies in LTB_4 production due to loss of LTB4H expression resulted in a loss of macrophage aggregation and increased susceptibility to disease (121). The resulting phenotype was reversible when

exogenous LTB_4 was restored, indicating the importance of functional LTB_4 during bacterial infection (120). LTB_4 signaling also contributes to bacterial sepsis during endotoxic shock (122). For instance, BLT1/2-dependent signaling pathways mediated the expression of IL-17, IL-6, and IL-1β, key cytokines for the development of this endotoxic shock, via NF-κB activation in the LPS-induced endotoxic shock mouse model (122).

Modulation of host eicosanoids by bacterial agents causing gastrointestinal diseases. PGE2 is rapidly generated in response to infections with Gram-negative bacteria such as *Salmonella enterica*, *Escherichia coli*, *Chlamydia trachomatis*, *Legionella pneumophila* (19, 46, 51, 57, 123), acid-fast bacterium *Mycobacterium tuberculosis* (109, 124), and the Gram-positive bacteria *Staphylococcus aureus* (46, 47). Some pathogens,0 such as *Yersinia enterocolitica* and *Mycobacterium tuberculosis*, have mechanisms to counteract PGE_2 biosyntheses, (19, 125). While mounting evidence suggests that bacteria can use virulence factors to increase or decrease PGE_2 production, specific mechanisms that regulate eicosanoid levels are mostly unknown. Although several pathogens have been reported to stimulate eicosanoid biosynthesis during infection (Table 1), in this review, we focus on pathogens that primarily cause gastrointestinal diseases (124).

***Helicobacter pylori*.** *Helicobacter pylori* is among the most prevalent infectious disease-causing pathogens, being present in approximately half of the world population, although this microorganism often persists in the host without inducing disease (126). *H. pylori* uses a variety of virulence factors, including outer membrane proteins (OMPs) such as OipA, toxins like CagA, and a type 4 secretion system (T4SS), and thus induces severe inflammation and damage in the host (127). However, *H. pylori* is also proposed to have favorable immunomodulatory properties in the case of asthma and skin allergies by reducing inflammation (128). *H. pylori* has recently been postulated to activate the NLRP3 inflammasome in murine bone marrow-derived dendritic cells (129). *H. pylori* LPS signals through the TLR4-MyD88 axis to drive IL-1β transcription, which in turn results in increases IL-1β secretion upon inflammasome activation in macrophages. In dendritic cells, *H. pylori* urease B subunit (UreB) mutant was unable to trigger inflammasome activation (129). What triggers the oligomerization of the NLRs to form the inflammasome in *H. pylori* infection is still unclear. *H. pylori* infection also induces COX-2 expression in gastric epithelial cells, where it first comes in contact with the stomach by activating the epidermal growth factor receptor (130) in a T4SS-dependent fashion, leading to robust production of PGE_2, which contributes to chronic inflammation. PGE_2 supports cancer cell growth and proliferation, which are associated with *H. pylori* infection. Treatment with COX-2/EGFR inhibitors leads to a decrease in gastric tumorigenesis (131). Moreover, 15d-PGJ_2 is reportedly downregulated upon infection with *H. pylori* and even more so in gastric tumors associated with *H. pylori* infection (132). These observations suggest that control of homeostatic imbalance between the PGE_2 and 15d-PGJ_2 levels could counteract gastric cancer tumorigenesis. Other studies in monocytes and macrophages have indicated an important role of host microRNA-155 in increasing COX-2, TNF-α, and IL-23 during *H. pylori* infection (133). The mechanism by which *H. pylori* induces miRNA-155 is unknown.

***Escherichia coli*.** *E. coli* is one of the most abundant species of bacteria found in the gut of mammals. Depending on the species, *E. coli* has various pathogenicity levels, from the highly pathogenic pedestal-forming *E. coli* (EPEC) or uropathogenic *E. coli* (UPEC) to commensal *E. coli* found in the gut of most mammals. EPEC, UPEC, and commensal *E. coli* induce PGE_2 secretion, but more invasive strains contribute a more robust PGE_2 response (134). Using a T3SS, EPEC induces COX-2 expression via the virulence protein EspT independent of LPS or passive recognition by the host in an ERK1/2-dependent manner (51). Some *E. coli* strains belonging to the B2 phylogroup and producing colibactin are capable of inducing COX-2 and are hypothesized to have a role in colon cancer tumorigenesis (135). Macrophages are heavily involved in tumor infiltration and removal (136). Macrophages affected by colibactin-producing *E. coli* enhance the tumorigenesis of colon cancers and are more resistant to killing by THP-1 macrophages (135).

Extraintestinal pathogenic *Escherichia coli* (ExPEC) can colonize sites outside the gastrointestinal tract, and as a comparison to EPEC, ExPEC infection also upregulates COX-2, which happens in the TLR4-dependent manner (137). However, in ExPEC infection, COX-2 inhibition enhances the infection, leading to an increased bacterial burden in blood, liver, lung, spleen, and brain (137). The mechanism by which COX-2 downregulation has a deleterious effect on the host depends on autophagy, which is a process that the host can direct against bacterial pathogens, such as *Salmonella* (138). In ExPEC infection, COX-2 inhibition leads to a decrease in macrophage autophagy, and inhibition of the autophagy process leads to increased bacterial survival in the cells. In contrast, enhanced autophagy leads to decreased bacterial survival in macrophages. Hence, COX-2 upregulation can prime the activation of autophagy in macrophages, thereby facilitating clearance of this bacterium (137).

Uropathogenic *E. coli* also increases COX-2 transcription and secretion of PGE2 during urinary tract infections (UTIs) (139). The type 1 fimbriae of uropathogenic *Escherichia coli* (UPEC) have been described as important for establishing bladder infections and urinary tract infections (UTI) (139). Induction of COX-2 in infected human bladder 5637 cells by UPEC is mediated via host TLR4-dependent activation of MAPKs such as JNK, p38, and ERK, and inhibition of transcription factors AP-1 and NF-κB resulted in abrogation of COX-2 promoter activity and expression (139).

Salmonella enterica. *S. enterica* Typhimurium is a foodborne pathogen which causes severe inflammation upon infection. *Salmonella*'s virulence originates in at least two different *Salmonella* pathogenicity islands (SPI) designated SPI-1 and SPI-2, which control the infection process by encoded protein effectors. The T3SS of *S.* Typhimurium injects host macrophages with virulence factors that induce COX-2 expression. For example, individual deletions of genes carried by the SPI-2 revealed SpiC as a significant contributor to COX-2-based prostaglandin biosynthesis via activation of the ERK1/2 pathway (57). Interestingly, COX-2 inhibition does not impair *Salmonella*'s ability to invade and replicate in host cells, but it enhances host survival during later infection stages. Our group identified an essential role for PGE_2 production in inflammasome activation with *S.* Typhimurium (19). Consistent with other studies, infection with wild-type *S.* Typhimurium leads to an increase in PGE2 biosynthesis and upregulation of COX-2 compared to infection with ssaV-deficient mutant, which has an impaired SPI-2. PGE_2 priming of macrophages results in a robust inflammasome upregulation in macrophages infected with *S.* Typhimurium, signified by an enhanced IL-1β secretion. This PGE_2-mediated effect on inflammasome in infected cells is most likely a result of PGE_2 signaling via EP4 receptor, which effectively leads to increased transcription of IL-1β in human THP-1 macrophages. Following the inflammasome oligomerization, a greater pool of immature IL-1β is converted to mature IL-1β, which drives the inflammation and may play a beneficial role for the pathogen during later stages of infection (19). As another outcome, PGE_2 also alters macrophage polarization following the infection with *Salmonella*, suggesting that other functions of macrophages are also changed by PGE_2 (19).

Another PG that is enhanced by *Salmonella* Typhimurium infection is 15-deoxy-PGJ_2 (15d-PGJ_2). This lipid is released from macrophages during infection with *Salmonella* Typhimurium and exerts anti-inflammatory effects. 15d-PGJ_2 acts on two different PDG_2 receptors, DP1 and DP2, with a preference for the DP2 receptor (140), which is found primarily on Th2 cells, T cytotoxic cells, eosinophils, and basophils and plays a role in chemotactic migration (141). Interestingly, 15d-PGJ_2 is known to be active in the cytosol, binding to the intranuclear receptor PPARγ leading to reduced inflammatory cytokine gene expression (142). Many of the effects attributed to PPARγ activation contribute to the production of anti-inflammatory cytokines in macrophages. For example, 15d-PGJ_2 inhibits TNF-α, IL-1β, and inducible nitric oxide synthase *in vitro* (88).

Yersinia enterocolitica. *Y. enterocolitica* is a foodborne pathogen that resides almost exclusively in the lymphoid tissue. This bacterium resists the host immune system's activation by virulence factors encoded within its 70-kb virulence plasmid designated pYV. *Yersinia*'s T3SS encodes several adhesins, including YadA and virulence proteins designated Yops (143). Elevation of the temperature to 37°C increases the expression of genes

involved in pathogenesis such as the T3SS, loss of motility by flagellar downregulation, and upregulation of Yops (144).

The pYV virulence plasmid plays a crucial role in modulating eicosanoid responses to infection (19). While COX-2 is slightly increased upon infection with *Y. enterocolitica*, the *Y. enterocolitica* devoid of pYV virulence plasmid leads to an extensive induction of COX-2 mRNA in infected macrophages, suggesting that some yet unidentified effectors encoded by *Yersinia* play a role in COX-2 downregulation (19). The function of this downregulation of COX-2 signaling by *Y. enterocolitica* is unclear. The baseline activation of COX-2 by wild-type *Y. enterocolitica* may be due to LPS-TLR-4 signaling, which is reduced in the case of *Y. pestis* infection due to changes in LPS composition but appears active in *Y. enterocolitica* infection (145). PGE_2 is also secreted from macrophages in response to *Y. enterocolitica*, which depends on the presence or absence of the pYV virulence plasmid (19). Triple-quadruple mass spectrometry analysis of media from macrophages infected with *Y. enterocolitica* revealed large quantities of PGE_2 in response to a pYV mutant compared to those in response to the wild type. Exogenous addition of PGE_2 before infection with *Y. enterocolitica* resulted in a strong inflammasome response via EP4 stimulation and decreased bacterial load 2, 24, and 48 h postinfection (19). In summary, *Y. enterocolitica* downregulated PGE_2 biosynthesis, which might be a possible pathogen strategy to skew the macrophage function.

***Shigella flexneri*.** Another pathogen proposed to alter eicosanoid biosynthesis upon infection is *Shigella flexneri*. *S. flexneri* is a highly inflammatory intracellular pathogen that tends to cause bloody stool and diarrhea during shigellosis. *S. flexneri* expresses virulence genes from a conserved virulence plasmid and encodes multiple secretion systems, including the T3SS (146). Both pathogens activate the inflammasome and are known to release IL-1β and IL-18. However, *S. flexneri* is also known to inhibit the release of pro-inflammatory cytokines, such as IL-8, by inhibiting the NF-κB pathway (147). Due to the conserved nature of the T3SS and inflammasome activation, it is unsurprising that PGE_2 levels are elevated in the stools of patients suffering from shigellosis T3SSs (146). Both pathogens activate the inflammasome and are known to release IL-1β and IL-18. However, *S. flexneri* is also known to inhibit the release of pro-inflammatory cytokines, such as IL-8, by inhibiting the NF-κB pathway (147). Due to the conserved nature of the T3SS and inflammasome activation, it is unsurprising that PGE_2 levels are elevated in the stool of patients suffering from shigellosis (148). Another study performed by Sansonetti et al. also indicated that COX-2 transcripts are strongly induced in the rabbit ileal loops infected with *S. flexneri* (149). It has also been shown that *S. flexneri* leads to the upregulation of COX-2 transcription in Peyer's patches of the infected rabbit ligated intestinal loops and that this upregulation of COX-2 mRNA is abrogated by secretory IgA (SIgA) (52). HeLa cells infected with Δ*ospF S. flexneri* exhibit increased COX-2 mRNA compared to that of cells infected with wild-type strains (150). OspF/OspB are involved in the activation and sustained phosphorylation of host MAPKs, including p38, JNK, and ERK signaling pathways, in response to LPS-TLR4 interactions during infection, which lead to cPLA2 activation. cPLA2 activation is the first step in PGE2 biosynthesis and is necessary for AA synthesis prior to conversion to PGE_2 by COX-2 (151).

NOVEL ROLES FOR PGE_2 AND LTB_4 DURING BACTERIA-DRIVEN PYROPTOSIS: PORE-INDUCED INTRACELLULAR TRAPS

During pyroptosis, the inflammasome activates caspase-1, which activates other enzymes via proteolytic cleavage. One such target, gasdermin D (GSDMD), is cleaved to produce an N-terminal product that triggers inflammatory cell death. The N-terminal product oligomerizes into the cell membrane to form pores visible by microscopy (152). High affinity for negatively charged lipid heads allows the pore to be formed via binding of GSDMD and subsequent insertion. The pore formation disrupts the sodium-potassium gradient across the plasma membrane, resulting in a massive influx of sodium into the cell, causing intracellular changes and eventual cell death.

One of the most recent discoveries pertaining to pyroptosis is that this form of cellular death is associated with the formation of cell corpse consisting of insoluble

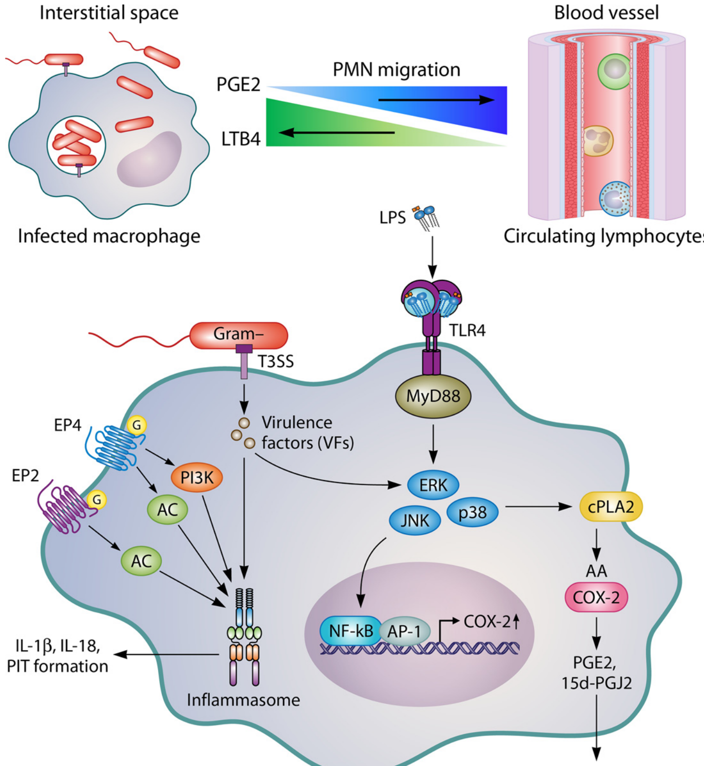

FIG 2 Gram-negative pathogens such as *S.* Typhimurium and EPEC use T3SS to inject virulence factors such as EspT and SpiC that activate NF-κB to induce COX-2 expression. This activation of COX-2, in turn, leads to the production of prostaglandins, such as PGE_2, which act via discrete EP receptors EP2 and EP4 to enhance inflammasome activation during pyroptosis. Inflammasome activation further drives the formation of PITs, which trap live bacteria. Neutrophils are recruited to the site of infection via eicosanoids and phagocytize PITs to clear the invaders.

components, which trap bacteria inside the macrophage. The formation of these pore-induced intracellular traps (PITs) is hypothesized to destroy the replicative niche the pathogen is trying to use and immobilize the invading bacteria. Neutrophils are then recruited via PGs and LTs to phagocytize and degrade the dead cell, including the trapped bacteria (153). It appears that pyroptosis damages the bacteria but is not sufficient for the complete clearance of the pathogens. The efferocytosis of neighboring neutrophils by PGs and LTs is critical in controlling bacterial escape from PITs.

While undergoing pyroptosis, large amounts of eicosanoids are released from cells, such as PGE_2 (7) and the chemotactic leukotriene LTB_4, hypothesized to play a role in neutrophil migration toward newly formed PITs. Studies done by Jorgenson et al. have demonstrated that neutrophil migration is influenced by inflammasome activation products like IL-1β and IL-18 (154). By using an engineered strain of *S.* Typhimurium expressing flagellin during intracellular infection, it was determined that IL-1β and IL-18 work cooperatively to clear the bacterium *in vivo*. Interestingly, inhibition of individual COX enzymes or leukotriene generating lipooxygenases (LOXs) did not affect bacterial clearance, while simultaneous inhibition of both enzymes resulted in impaired clearance. It is possible that optimal neutrophil migration is not specific to essential prostaglandins or leukotrienes and that the loss of one of these lipids is complemented by the other. Future studies likely will further investigate the mechanism behind PIT-mediated clearance by neutrophils and roles for eicosanoids in this process.

CONCLUSION AND FUTURE DIRECTIONS

Bacteria-modulated changes in eicosanoid biosynthesis play a vital role during pyroptosis or inflammatory cell death (Fig. 2). Evidence is mounting to support a conserved mechanism used by Gram-negative pathogens. *S.* Typhimurium, EPEC, and *S. flexneri* use

T3SSs to inject virulence factors into host cells that alter COX-2 transcription. By increasing COX-2 levels, PGE_2, one of the most predominant COX-2-derived PGs, is released in large quantities during infection. PGE_2 enhances inflammasome activation, secretion of IL-1β and IL-18, and formation of PITs, which are associated with pyroptosis. Upon cell death, live bacteria are trapped in the cell matrix (called PITs), preventing escape from the dying cell. For complete clearance, neutrophils must migrate to PITs and subject them to efferocytosis to degrade the dying cell and immobilized bacteria. COX-2 induction by Gram-negative pathogens may seem counterintuitive considering how PGE_2 enhances inflammasome activation, but the secretion of IL-1β, IL-18, and PIT formation alone is not sufficient for the clearance of *Salmonella* infection *in vivo*. PGE_2 may inhibit normal leukocyte function by lowering the killing abilities of neutrophils and macrophages, such as inhibiting phagocytosis and reactive oxygen species (ROS) generation. Studies with COX-2-deficient mice or animals treated with COX-2 inhibitors display enhanced survival rates during later stages of *S*. Typhimurium infection. Future studies should focus on the role eicosanoids play in modulating the phagocytic and killing ability of neutrophils toward PITs formed during infection with Gram-negative pathogens and discovering new pathogens that alter eicosanoid production.

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