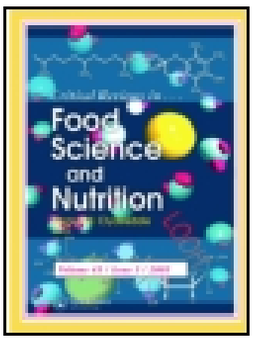

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REVIEW

Role of arachidonic acid-derived eicosanoids in intestinal innate immunity

Ningning Huang, Miaomiao Wang, Jian Peng, and Hongkui Wei

Department of Animal Nutrition and Feed Science, College of Animal Science and Technology, Huazhong Agricultural University, Wuhan, PR China

ABSTRACT

Arachidonic acid (ARA), an n-6 essential fatty acid, plays an important role in human and animal growth and development. The ARA presents in the membrane phospholipids can be released by phospholipase A2. These free arachidonic acid molecules are then used to produce eicosanoids through three different pathways. Previous studies have demonstrated that eicosanoids have a wide range of physiological functions. Although they are generally considered to be pro-inflammatory molecules, recent advances have elucidated they have an effect on innate immunity via regulating the development, and differentiation of innate immune cells and the function of the intestinal epithelial barrier. Here, we review eicosanoids generation in intestine and their role in intestinal innate immunity, focusing on intestinal epithelial barrier, innate immune cell in lamina propria (LP) and their crosstalk.

KEYWORDS

Arachidonic acid; prostaglandins; leukotrienes; cell proliferation/differentiation; innate immunity; intestinal epithelial barrier

Introduction

The complex immune system of the intestine contains innate and adaptive immunity. Innate immunity is a widely distributed form of immunity, which acts as the first line of defense against pathogen invasion (de Veer, Kemp, and Meeusen 2007). The type immunity is crucial to regulate and activate the adaptive immune response and maintain homeostasis (Iwasaki and Medzhitov 2015). Intestinal innate immune system can be divided into three components: The intestinal epithelial layer, mucus layer and the underlying lamina propria (LP). The intestinal epithelial layer which is composed of differentiated cells (enterocytes, enteroendocrine, goblet cells and Paneth cells), forms a physical barrier between the intestinal lumen and external environment via anchored by junctional proteins, which results in a defense response (Peterson and Artis 2014). The mucus layer throughout the entire intestinal tract, which acts as a chemical barrier, provides protection and prevents pathogenic bacteria from contacting the intestinal epithelium.

Mucins and antimicrobial peptides (AMPs) that are produced by goblet cells and Paneth cells, respectively (Jakaitis and Denning 2014). Below the intestinal epithelium is the LP. It is elucidated that the LP contains many innate immune cells, including dendritic cells (DCs), macrophages, mast cells, natural killer (NK) cells and innate lymphoid cells (ILCs). When infection occurs, these cells rapidly differentiate into effector cells, which fight against infections independent of acquired immunity (Janeway and Medzhitov 2002).

Arachidonic acid (ARA), an n-6 polyunsaturated 20-carbon fatty acid obtains directly through food consumption or via biosynthesis from linoleic acid (LA, 18:2 (n-6)) (Hanna and Hafez 2018) (Figure. 1). Scientific and clinical studies reveal that ARA plays a vital role in infant growth, brain development, and health (Hadley et al. 2016). ARA significantly reduces some markers of intestinal epithelial permeability (3H-mannitol and 14C-inulin) and histological evaluation shows that ARA reduces the lesions of ischemic ilea (Jacobi et al. 2012). It has been demonstrated that many functions of ARA depend on its metabolites, the eicosanoids. Generally, ARA is present in an esterified form in structural phospholipids in the cell membrane throughout the body (Calder 2007). ARA can be mobilized from cell phospholipids by phospholipase A2 (PLA2). Free ARA is oxidized through the pathway of cyclooxygenases (COXs), lipoxygenases (LOXs), or cytochrome P450 (CYP450) to generate prostaglandins (PGs), thromboxanes (TXs), lipoxins (LXs), hepoxilins, hydroxyeicosatetraenoic acids (HETEs), leukotriene (LT), cysteinyl LTs and epoxyeicosatrienoic acids (EETs) (Figure 2) (Panigrahy et al. 2010).

Emerging studies have revealed eicosanoids as mediators involved in the regulation of intestinal innate immunity and epithelial barrier. In this review, we summarize the production of eicosanoids in the intestinal tract. Then, we discuss the roles of eicosanoids in regulating the intestinal innate immune response, cell proliferation/differentiation and the paracellular permeability of the intestinal epithelium.

Eicosanoids production in the intestine

The production of eicosanoids is regulated in a cell-type-specific manner based on the content of ARA varies in the

CONTACT Hongkui Wei weihongkui@mail.hzau.edu.cn Department of Animal Nutrition and Feed Science, College of Animal Science and Technology, Huazhong Agricultural University, 430070 Wuhan, PR China.

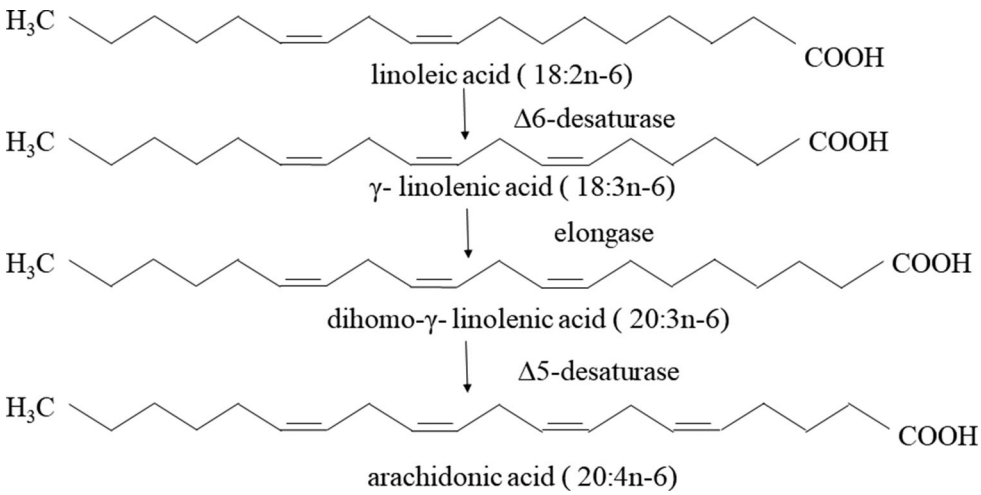

Figure 1. Pathway of arachidonic acid biosynthesis from linoleic acid.

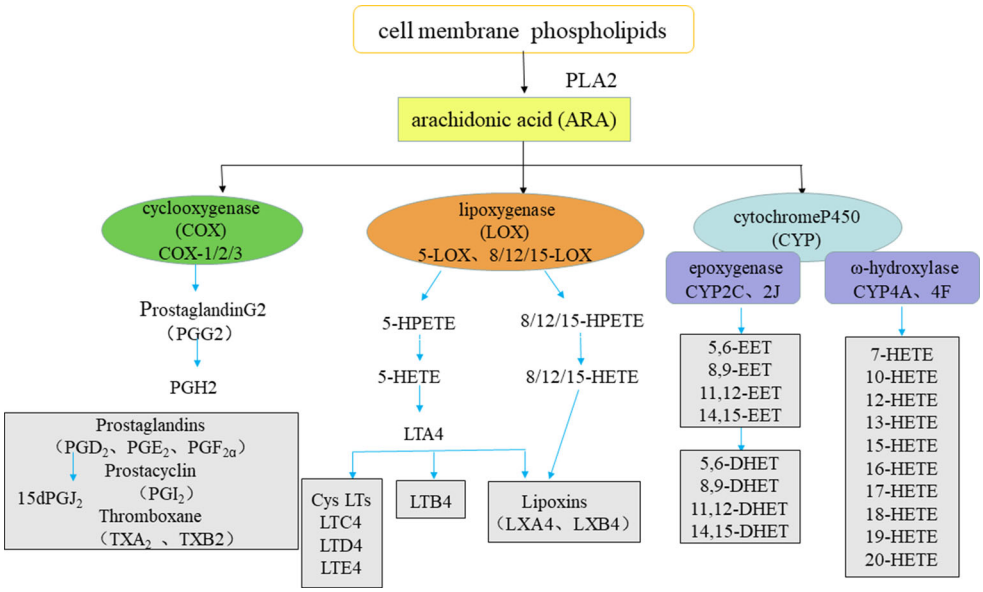

Figure 2. Different enzymatic pathways for the production of eicosanoids. PLA2, phospholipase A2; PG, prostaglandin; TX, thromboxane; LT, leukotriene; HPETE, hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acid; LX, lipoxins; EET, epoxyeicosatrienoic acid; DHET, dihydroxyeicosatrienoic acid.

type of cells and differential expression of these enzymes within cells. Intestinal epithelial cells (IECs) and immune cells in the LP are responsible for eicosanoids production in intestine (Smith, Warhurst, and Turnberg 1982). In addition, emerging evidence suggests that intestinal bacteria may also metabolize ARA to produce eicosanoids (Bezirtzoglou 2012).

Eicosanoids production in intestinal epithelial cells

A significant amount of research elucidates that IECs have a capable of eicosanoids production. COX-1, COX-2 and 5-LOX are expressed in human IECs lines Caco-2 and HT29 (Cortese et al. 1995). Many CYP enzymes have been described in the gut, except that CYP450 activity is nearly undetectable in IECs (Melillo de Magalhães et al. 2012). PGE_2 and 5-HETE are detected by LC-MS in the supernatant of IECs (Caco-2 cells lines) (Cabral, Martin-Venegas, et al. 2013; Martin-Venegas, Jáuregui, and Moreno 2014; Le Faouder et al. 2013). Previous research has also revealed that isolated rat colonic epithelial cells are shown to produce 15-HETE and LTB_4 (Craven and DeRubertis 1986). Additionally, IECs isolated from the jejunum and ileum of human embryo produce 15-HETE and LTB_4 via the 15-LOX pathway (Sjolander, Schippert, and Hammarstrom 1993).

Production of PGs and HETEs in IECs is regulated by physical conditions. In the healthy small intestine and colon, COX-1 expresses in crypt epithelial cells, and its expression is unchanged in inflammatory diseases. In contrast, COX-2 is undetectable in normal ileum or colon, but is induced in Crohn's disease and ulcerative colitis epithelial cells (Singer et al. 1998). Thus, in response to inflammation, more PGs are produced than non-inflammatory condition (Ricciotti and FitzGerald 2011). Moreover, human intestinal epithelial cell lines (Caco2 and HT29) infected with enteroinvasive *Escherichia coli* and *Salmonella dublin* increase the expression of COX-2 and production of PGE_2 (Resta-Lenert and Barrett 2002). In addition, increased release of $PGF_{2\alpha}$ is also observed in IECs after infection with *Salmonella* (Eckmann et al. 1997). After lipopolysaccharide (LPS) exposure (10 g/mL),

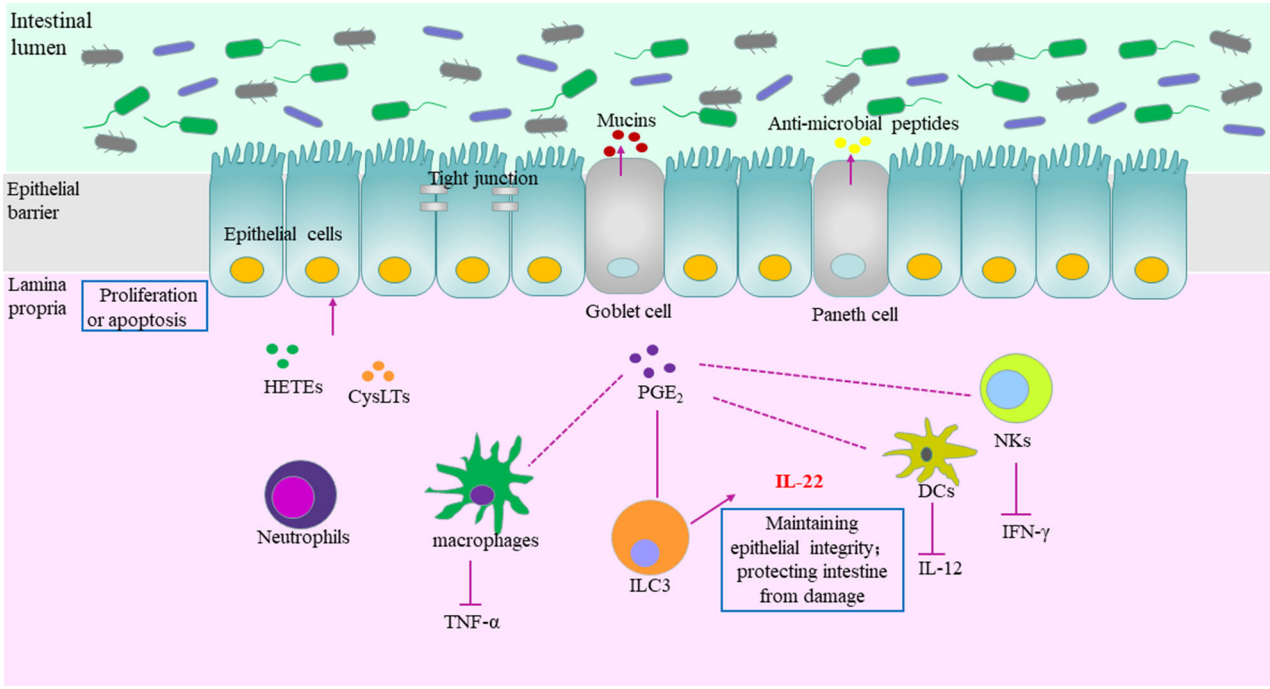

Figure 3. Prostaglandin E_2 (PGE_2) modulated intestinal epithelial barrier function by regulating cytokine production. PGE_2 inhibits the production of tumor necrosis factor-alpha (TNF-α) in macrophages (Scales et al. 1989) and interferon-gamma (IFN-γ) in natural killer cells (NKs) (Van Elssen et al. 2011), as well as the release of interleukin-12 (IL-12) from maturing dendritic cells (DCs) (Kaliński et al. 1997).However, PGE_2 can promote the production of IL-22 from ILC3 (Duffin et al. 2016). These pro-inflammatory cytokines can cause disruption of the intestinal barrier.

the synthesis of PGE_2, 5-HETE, 8-HETE, 12-HETE and 15-HETE is increased in human epithelial Caco2 cells (Le Faouder et al. 2013).

Eicosanoids production in innate immune cells

In the intestine, PGs are produced mainly by immune cells in the LP (Eberhart and Dubois 1995). It examines basal COX-2 expression and COX-2-dependent PGE_2 production in small intestine LP cells (Newberry, Stenson, and Lorenz 1999). Furthermore, COX-2 expression by small intestine LP stromal cells is not dependent upon exogenous stimuli, including LPS signaling via Toll-like receptor 4 or the proinflammatory cytokines TNF-α, IFN-γ, and IL-1β (Newberry et al. 2001). In line with COX-2 expression, $PGF_{2\alpha}$, 6-keto $PGF_{1\alpha}$, and PGD_2 are found in the LP mononuclear cells supernatants (Newberry et al. 2001).

Through the retrieval of the articles, importantly, the innate immune cells of the intestine are the main contributors to the production of eicosanoids. It has been demonstrated eicosanoids expressions are detected in the culture of intestinal innate immune cells in vitro. Gut macrophages have the potential for producing PGs, and there are no different amounts of PGE_2 production after stimulation with or without LPS (Ogle et al. 1994). Rat intestinal mast cells are chief contributors to PGD_2, LTC_4, and LTB_4 after stimulating by antigen or IgE (Heavey et al. 1988).

The intestinal microbiota and the ARA metabolism

In vitro, microorganisms have the ability to convert ARA to eicosanoids. One study reported that ARA could be metabolized to $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGE_1, and PGE_2 in cultures of the *genera Pseudomonas*, *Mycobacterium* and *Micrococcus* (Lamacka and Sajbidor 1995). In addition, PGs could be detected by adding ARA to the culture medium of some fungi. For example, *Gaeumannomyces graminis* converted exogenous ARA into 18-HETE and 19-HETE. On the contrary, other hydroxyl metabolites could not be detected in the medium (Sih et al. 1969).

LOXs derived from *Proteobacteria* can generate 15(S)-HETE from ARA (Vance et al. 2004). A new bacterial source of LOXs could convert ARA to 12(S)-HETE, providing an evidence for the microbial production of eicosanoids (An, Hong, and Oh 2018). Above results indicate that some eicosanoids can be synthesized through the exogenous addition of ARA to some bacterial and fungal cultures.

The gut microbiota can metabolize conjugated linoleic acid and conjugated linolenic acid, and that bacterial polyunsaturated fatty acid (PUFA) metabolites differ in different intestinal segments. Bacterial PUFA-derived metabolites (CLA (conjugated linoleic acids) and CLnA (conjugated linolenic acids)) are present in higher proportions in the content of the distal parts of the gut than in that of the proximal parts (Druart et al. 2014).

Microbiota modulate ARA enzyme expression via the production of metabolites. Such as short-chain fatty acids (SCFAs) are fermented by fiber in the large intestine. It has shown that 15-LOX is the major enzyme responsible after sodium butyrate (NaBT) induction of apoptosis and cell differentiation. With the challenge of NaBT, Caco-2 cells express 15-LOX mRNA which modulates NaBT-induced apoptosis and cell differentiation in Caco-2 cells (Kamitani, Geller, and Eling 1998). Recently, ARA is found in human

feces (Wan et al. 2019). It is shown that many intestinal bacterial strains possess CYP450 enzyme. *Eubacterium aerofaciens*, a major intestinal flora found in the human colon is detected CYP450-like protein (John et al. 2001). Moreover, It speculates that microbiota may converse ARA to produce 19-HETE and 20-HETE in a reaction network model of gut microbiota metabolism (Sridharan et al. 2014). A study further confirms this view, the plasma concentration of 12-Hydroxy-5*Z*,8*Z*,10*E*,14*Z*,17*Z* eicosapentaenoic acid (12-HEPE) is significantly higher in conventional mice than that in the germ-free mice (Wikoff et al. 2009). Nevertheless, whether the intestinal microbes that play an important role in health can metabolize ARA to produce more eicosanoids in humans or animals remains to be further studied.

Eicosanoids regulation of intestinal epithelial barrier function

Intestinal epithelial cell proliferation/ differentiation/apoptosis

The gastrointestinal tract is lined by a continuous monolayer of epithelial cells. It is known that IECs act as physical barrier by protecting the body from pathogens invasion and reducing the occurrence of diseases. Thus, the integrity of the intestinal epithelium is necessary to maintain intestinal homeostasis. Previous studies indicate iPLA2 regulates ARA release and the signaling pathways involved in the control of intestinal epithelial proliferation (Sanchez and Moreno 2002) (Figure. 3). PGs are major metabolites of the ARA-COX pathway and are regulators of the cell kinetics of the gastrointestinal epithelium. The effect of PGs on the regulation of epithelial cell proliferation has been presented (Ferrer and Moreno 2010). Studies have confirmed that molecular mechanisms are involved in PGs regulation of IECs proliferation. Dextran sulfate sodium (DSS)-induced colitis is a commonly used model of colonic injury. It has shown that DSS decreases the number of proliferating epithelial cells. However, administration of dimethyl PGE_2 with DSS reverses the effect of DSS on intestinal epithelial proliferation (Tessner et al. 1998). In support of the action of PGs, the administration of PGE_2 to mouse results in the maintenance of colonic epithelial proliferation through a cellular niche-modified mechanism (Brown et al. 2007). Furthermore, the activation of peroxisome proliferator-activated receptor-γ (PPARγ) is involved in the IECs. 15d PGJ_2 works as a novel glial-derived mediator in controlling proliferation and differentiation of IECs through the activation of PPARγ (Bach-Ngohou et al. 2010). Thus, these lines of evidences have shown that PGs possess the capability of promoting IECs proliferation and maintaining epithelial integrity.

Besides, PGE_2 regulates Caco-2 cell differentiation. Decreasing in both iPLA2 activity and COX-2 expression, consequently, a decrease in PGE_2 production could be necessary to complete Caco-2 differentiation (Martin-Venegas et al. 2006). In this way, it observes that PGE_2 inhibits the expression of differentiation-related genes and regulated chondrocyte maturation (Li et al. 2004).

Evidence supports that PGs regulates the survival of IECs. PGE_2 reduces radiation-induced apoptosis through enhancing transactivation of the epidermal growth factor receptor (EGFR) and activation of AKT (Tessner et al. 2004). PGE_2 protects IECs in the radiation injury model by decreasing radiation-induced apoptosis and increasing crypt survival (Stenson 2007).

Other eicosanoids have also been implicated in the control of IECs proliferation and survival. LTD_4 and LTB_4 induce IECs survival via expressing antiapoptotic protein Bcl-2 (Ohd, Wikstrom, and Sjolander 2000). LTB_4 (10 nM), 5-HETE, 12-HETE, and 15-HETE (100 nM) could induce the proliferation of non-differentiated Caco-2 cells after 48 h of incubation (Cabral, Martin-Venegas, et al. 2013). There is shown that LTD_4 involves in regulating proliferation and survival in IECs. The effects of CysLTs and HETEs on epithelial cell proliferation can be dependent, at least in part, on PGE_2 synthesis. LTD_4 is able to induce intestinal epithelial Caco-2 cell proliferation through CysLTR binding and this event is PGE_2-dependent (Cabral, Martin-Venegas, and Moreno 2015).

Tight junctions and intestinal epithelial permeability

There are three components between IECs: tight junctions (TJs), adherens junctions (AJs), and desmosomes (Farquhar and Palade 1963). TJs seal the intercellular space and control the permeability of the paracellular pathways, and the localization of TJs are major components of the intestinal barrier. Moreover, TJs have four transmembrane proteins: occludins, claudins, junctional adhesion molecules, and tricellulins (Groschwitz and Hogan 2009). There is increasing evidence has indicated that the ARA-derived eicosanoids have abilities to regulate the intestinal epithelial barrier.

Eicosanoids affect the intestinal epithelial barrier which is usually regulated directly through alteration of the TJ proteins or indirectly through effect on the cytoskeleton. According to clinical studies, intestinal epithelial barrier function is mainly reflected by permeability markers which are a class of substances that are hydrophilic, passively absorbed, inert (non-toxic), produced non-metabolically or endogenously, and excreted rapidly in urine (Chadwick, Phillips, and Hofmann 1977). COX-2 has been considered as one of the important molecules that regulates intestinal epithelial barrier function by reducing of ZO-1 and E-cadherin (Short et al. 2013). These findings are further confirmed in Caco-2 cells line in vitro, which the mRNA and protein levels of ZO-1 and E-cadherin are significantly increased after treating with celecoxib, a selective COX-2 inhibitor (Gao et al. 2016). This modulation of the epithelial barrier function is mediated by the interaction with PGE_2 receptors EP_1 and EP_4. PGE_2 from ARA induces the activation of PLC-IP 3^-Ca^{2+} and cAMP-PKA pathways that lead to an intracellular calcium concentration and the redistribution of TJ proteins (Rodríguez-Lagunas et al. 2010).

The addition of PGE_2 to differentiated intestinal Caco-2 cells increases paracellular permeability (PP), leading to disrupt epithelial barrier function (Martin-Venegas et al. 2006;

Table1. Eicosanoids regulated the proliferation and function of innate immune cells.

Eicosanoids	Cells	Function	Ref.
PGE_2	DCs	Differentiation and MHCII expression produce IL-10	Kalinski et al. 1997; Harizi, Grosset, and Gualde 2003; Hedi and Norbert 2004
	Macrophages	Promoting proliferation and IL-10/IL-12 release	Nieves and Moreno 2006; Huang et al. 1998
	ILC2s	Proliferation and function	Maric et al. 2018
	ILC3s	IL-22 production	Duffin et al. 2016
	Neutrophils	TNF-α production and IL-6 production	Yamane et al. 2000
	NKs	IFN-γ production	Walker and Rotondo 2004
PGD_2	ILC2s	producing type 2 cytokines	Xue et al. 2014
PGI_2	ILC2s	IL-5 and IL-13 release	Zhou et al. 2016
LTB_4	DCs	generation ; enhanced IL-10 production	Harizi and Gualde 2002; Jozefowski et al. 2005
LTB_4	Macrophages	Increasing generation	Harizi and Gualde 2002
LTB_4	ILC2s	Induction migration; Reducing apoptosis	Lund et al. 2017; Salimi et al. 2017

Rodríguez-Lagunas et al. 2010). It is indicated that PGE_2 acts as a host inflammatory mediator that causes diarrhea by disrupting intestinal epithelial permeability (Lejeune, Moreau, and Chadee 2011). During colitis, there is marked elevated synthesis of colonic PGD_2, which contributes to barrier dysfunction (Zamuner et al. 2003). Furthermore, authors proposed that the 3-series prostanoids from eicosapentaenoic acid (EPA) affects on epithelial barrier function. Similar to PGE_2 action, it indicates that PGE_3 increases PP through the interaction with EP_1 and EP_4 receptors (Rodriguez-Lagunas, Ferrer, and Moreno 2013).

A previous research study has reported that 5-HETE and LTD_4 participate in the regulation of intestinal barrier function. It is found that 5-HETE induces epithelial barrier disruption. Similarly, LTD_4 increases the intestinal permeability by its interaction with cysteinyl leukotriene receptor 1 (CysLT1R), which promotes the activation of the phospholipase C/Ca^{2+}/protein kinase C pathway, leading to disrupt intestinal barrier (Rodríguez-Lagunas et al. 2013). Enteric glial cells express 15-lipoxygenase-2 and produce 15-HETE, which increases intestinal epithelial barrier resistance and reduces intestinal permeability despite enteric glial cells from patients with Crohn's disease are unable to reduce intestinal permeability (Pochard et al. 2016). Thus, regulating production of ARA metabolites is important for the intestinal barrier function.

Antimicrobial peptides

AMPs are effector molecules of the innate immune defense and mainly express in intestinal Paneth cells which are only found in the base of the crypts of the small intestine. It provides the first line of defense to infection as direct antimicrobials and maintains the intestinal epithelial integrity. AMPs contain the highly cationic, microbicidal defensins, and the C-type lectin. Thus, the production of AMPs is vital for intestinal epithelial barrier. 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 (Cederlund et al. 2014). It is a new role for PGs in enhancing AMPs production and the innate immune response. TLRs signaling activates COX-2 expression, subsequent, leading to enhance AMPs production. In vitro, cells treated with the inhibitors of COX-2 may attenuate the production of PGs and inhibit antimicrobial activity (Bernard and Gallo 2010). Additionally, LTB_4 can activate the innate immune responses. In this regard, LTB_4 has been found to mediate the release of AMPs during viral infection (Gaudreault and Gosselin 2007). In the meantime, administration of LTB4 to HIV-uninfected subjects causes a dose-dependent plasmatic increase in α-defensins (Flamand et al. 2004).

Eicosanoids regulated the proliferation and function of innate immune cells

There are several lines of evidence supporting the role of eicosanoids in immune response. Eicosanoids affect immune regulation by modulating the activation, maturation, migration, and cytokine secretion of several immune cells, especially the innate immune cells, which depends on the binding to G-protein-coupled receptors on the cells surface (Table 1). Nevertheless, research poorly performs on the regulation of eicosanoids in the intestinal innate immune cells.

Dendritic cells

In the innate immune system, DCs are both a source and target of ARA-derived eicosanoids. Mouse bone marrow-derived DC (BM-DC) can express COX and produce PGE_2 (Fogel-Petrovic et al. 2004). PGE_2 appears to play a key role in modulating DC development and functions (Morelli and Thomson 2003). Previous studies have confirmed PGE_2 disrupts DC differentiation at the early stages of development (Kaliński et al. 1997). However, in the presence of pro-inflammatory factors, low concentrations of PGE_2 could induce DC maturation (Kaliński et al. 1998) and inhibit major histocompatibility complex class II (MHCII) protein expression through an EP_2- or EP_4-dependent mechanism in cultures of mouse BM-DCs (Harizi, Grosset, and Gualde 2003). The release of cytokines from DCs which play a vital role in resisting to infection is also found to be modulated by PGs. In response to PGE_2, BM-DCs produce IL-10, which in turn down-regulate their own production of IL-6, TNF-α, and COX-2-derived PGs, contributing to immune homeostasis (Hedi and Norbert 2004). Additionally, exposure of DCs to PGE_2 leads to promoting type 2 responses, which can dampen innate antifungal defenses during *Candida albicans* infection, indicating a role for eicosanoids in non-protective against fungal infections (Kundu and Noverr 2011). Most studies have demonstrated that eicosanoids have potent biological activities in the pathogenesis of many inflammatory diseases or in experimental models of inflammatory diseases (Moreno

2017; Ricciotti and FitzGerald 2011). In inflammatory conditions, high levels of PGE_2 exacerbates clinical colitis by promoting the release of IL-23 from DCs (Sheibanie et al. 2007).

PGD_2 represents another major cyclooxygenase metabolite supporting the migration of DC precursors and strongly modulating the maturation process of differentiated DC (Gosset et al. 2003). Upon stimulation with LPS or TNF-α/IL-1β, PGD_2 treatment of monocyte-derived DCs induces maturation with a markedly increased expression of HLA-DR, CD83, CCR7, but impacts efficient Th1 response by suppressing levels of IL-12 and enhancing IL-10 production (Gosset et al. 2005). As mentioned, PGD_2 and 15d-PGJ_2 affect the differentiation and maturation of DC by activating PPARγ (Nencioni et al. 2002; Gosset et al. 2001).

Maturation and cytokines production of DCs can be regulated also by LTs. Under the absence of PGE_2, the addition of exogenous LTB_4 to a bone marrow culture promotes BM-DCs proliferation (Harizi and Gualde 2002). Mouse BM-DCs exposed to exogenous CysLTs pulsing with dust mite antigen enhance IL-10 and IL-5 release but inhibit IL-12, leading to allergic airway inflammation in vivo. Conversely, treatment of BM-DCs with CysLT1 receptor-selective antagonists during antigen pulsing attenuates IL-10 generation and augments IL-12 production (Machida et al. 2004). Moreover, migration of DCs is regulated by utilizing LTC_4. Indeed, LTC_4 promotes chemotaxis to CCL19 and mobilization of DCs to lymph nodes (Robbiani et al. 2000). Recent studies have illuminated LXs as a unique class of lipoxygenase interaction metabolites with a strong ability to regulate the function of DC via suppressing the production of IL-12 in response to *Toxoplasma gondii* infection (Aliberti et al. 2002).

Macrophages

Macrophages are important cells in the innate immune response and are involved in immunomodulation through phagocytosis. Macrophages produce rapidly eicosanoids in response to bacterial and fungal pathogens. It is first reported the capacity of exogenous LTB_4 and LTC_4 to enhance macrophage phagocytosis of *Trypanosoma cruzi* in 1985 (Wirth and Kierszenbaum 1985a; Wirth and Kierszenbaum 1985b). *Hpb* larval extract (*HpbE*) treates human monocyte-derived macrophages (MDMs) or bone marrow–derived macrophages (BMDMs) resulting in modulating type-2 airway inflammation. It elucidates that *HpbE* triggers the shift pro-inflammatory 5-LOX metabolites (LTB_4, LTC_4, and 5-HETE) to PGE_2, TXB_2, and 12- hydroxyheptadecatrenoic acid (12-HHT) via inducing the expression of COX-2 and mPGES-1 (de Los Reyes Jiménez et al. 2020).

PGE_2 (1–10 nM) is found to stimulate macrophage proliferation (Nieves and Moreno 2006). In a study performed on a bone marrow cell culture in vitro, EP_2-deficient ($EP2^{-/-}$) macrophages enhance maturation compared with wild-type cells. It reveals that endogenously generated PGE_2 signaling suppresses macrophage maturation (Zaslona et al. 2012). PGE_2 could also regulate the production of macrophage cytokines. The notable feature is that PGE_2 up-regulates the production of immunoregulatory cytokines (IL-10 and IL-12) (Huang et al. 1998). Macrophages are treated with indomethacin, a COX inhibitor and stimulated with LPS, which markedly increase IL-12 and TNF productions. Similarly, EP_4 antagonist significantly augments IL-12 and TNF production in macrophages. It is shown that PGE_2 suppresses Th1 responses (Kuroda and Yamashita 2003). Besides, 15d-PGJ_2, a PGD_2 metabolite implicates in the biological activities of mouse macrophage cell line cells RAW264.7 and J774A.1 cells. It has demonstrated that 15d-PGJ_2 at micromolar concentrations significantly inhibits the phagocytic activity, cell proliferation and expression of pro-inflammatory cytokines in mouse monocyte/macrophage cell line RAW264.7 and J774A.1 cells upon LPS challenge (Liu et al. 2012).

Innate lymphoid cells

Eicosanoids directly influence the function of innate lymphoid cells (ILCs). ILCs are an emerging population of innate immune cells that closely resemble the $CD4^+$T cells. A body of evidence from mouse and human has demonstrated that ILCs play a critical role in maintaining and protecting the tissue barrier against invading pathogens (Eberl et al. 2015). ILCs can be grouped into three distinct groups based on their selective dependence on specific transcription factors for their development and function: group 1 ILCs (ILC1s), group 2 ILCs (ILC2s) and group 3 ILCs (ILC3s) including LTi cells (Spits et al. 2013).

An increasing number of evidence suggests that ILC2 plays an important role in allergic diseases through cytokines. PGE_2 suppresses ILC2 isolated from human tonsillar and blood function by inhibiting IL-5 and IL-13 production in response to stimulation with a combination of IL-25, IL-33, TSLP and IL-2. In line with that observation, PGE_2 decreases ILC2 proliferation. It provides a therapeutic approach in treating allergic diseases by suppressing ILC2 function (Maric et al. 2018). Human ILC2 could produce type 2 cytokines (IL-4, IL-5, and IL-13) through PGD_2 binding to CRTH2 (Xue et al. 2014). Type 2 cytokines in turn affect antibody class-switching and recruitment of inflammatory cell, contributing to the immune responses to parasite infection, allergen challenge, and tissue damage (Koyasu and Moro 2013; Neill and McKenzie 2011; Spits and Di Santo 2011). In models of LPS induced systemic inflammation in mice, PGE_2/EP_4 signaling could act directly on ILC3, which promotes the production of IL-22 and rescues mice from LPS-induced septic shock (Duffin et al. 2016).

Previously reported CysLTs that produced by 5-LOX of ARA mediate a direct effect on ILCs function. LTD_4 induces ILC2 to rapidly generate high levels of IL-5 and IL-13 within 6 h of stimulation in vitro. Additionally, LTD_4 potentiates ILC2 accumulation and proliferation and *Alternaria* species–induced eosinophilia (Doherty et al. 2013). The direct function is supported that both LTC_4 and LTE_4. ILC2 expresses $CysLT_1R$ and $CysLT_2R$ lead to enhance their responses. LTC_4 signaling through both $CysLT_1R$ and $CysLT_2R$ significantly increases the proliferation and cytokine expression of IL-33-activated ILC2, which induces type 2 immunopathology (Lund et al. 2017; Liu et al. 2018). Beyond the induction of cytokines, other studies show that LTE_4 induces migration of ILC2 and reduces the induction of apoptosis (Lund et al. 2017; Salimi et al. 2017). However, the effect of the eicosanoids on ILC1 is not understood.

Other innate immune cells

Evidences have shown that PGE_2 is produced in human neutrophils (St-Onge et al. 2007), subsequently, regulates the function of neutrophils. PGE_2 receptors in LPS-treated neutrophils regulates the processes of acute inflammatory and immune responses through suppressing the TNF-α production and enhancing the IL-6 production (Yamane et al. 2000). In addition, PGE_2 inhibits IL-12 and interferon-gamma (IFN-γ) production in a murine model of rheumatoid arthritis, which mediates IL-23/IL-17-induced neutrophil migration (Lemos et al. 2009). Moreover, the inhibitors of 5-LOX enhance neutrophil extracellular traps (NETs) formation which has an ability to trap bacteria, limiting microbial dissemination (Clark et al. 2007). It is clear that LTB_4 enhances neutrophil phagocytosis and kills of *Klebsiella pneumoniae* mediated by either the Fc or complement receptor (Mancuso, Nana-Sinkam, and Peters-Golden 2001).

Studies concern the modulation of NK activity induced by eicosanoids. NKs play a vital role in in the innate immune response against infectious (Andoniou et al. 2005). NKs described as powerful PGE_2-responding cells suppress cytokine-proudcing capacity and function of NKs. In vivo, natural cytolytic activities are directly inhibited by PGE_2 (Meron et al. 2013; Yakar et al. 2003). In addition, it supports playing a vital role in limiting innate inflammatory processes through the physiologically concentration of PGE_2 directly suppresses NK-cell IFN-γ synthesis (Walker and Rotondo 2004).

Eicosanoids have been identified as important regulators of mast cell maturation and function. PGE_2 and LTB_4 are chemotactic signals responsible for migration of mast cells in vivo (Weller et al. 2007). Promotion of mast cell maturation by PGD_2-DP1 signaling provides a mechanistic explanation for the protective effect of systemic DP1 ablation on asthma (Matsuoka et al. 2000). Recently, it describes a PLA2G3-L-PGDS-DP1 loop that drives mast cell maturation. PLA2G3, a major mast cell sPLA2 contributes to anaphylaxis via facilitating the maturation of mast cells by providing PGD_2 (Taketomi et al. 2013).

Eicosanoids modulate the intestinal epithelial barrier-innate immunity crosstalk

Eicosanoids from intestinal epithelial cells induce the innate immune response

IECs are capable of producing eicosanoids which contribute to host defense. When challenging the pathogen infection, enteric pathogens are shown to cause IECs to produce and release PGE_2 by up-regulating the expression of COX-2. This process is associated with diminished barrier function (Resta-Lenert and Barrett 2002). Interestingly, eicosanoids have been implicated in the recruitment of neutrophils which cross the epithelial barrier during active intestinal inflammatory disease (Podolsky 2002; McCormick et al. 1995). Migration of neutrophils across IECs requires the eicosanoid hepoxilin A3 (hepA3) produced by 12-LOX pathway. hepA3 is secreted by epithelial cells in response to *Salmonella typhimurium* infection, and can target neutrophils to the gut at sites of inflammation. Disruption of the 12-LOX pathway inhibits both neutrophils transmigration and the release of hepA3 (Mrsny et al. 2004). IECs have been reported to express the receptor for lipoxin A_4 (LXA_4). LXA_4 generated via neutrophil-epithelial interactions can rapidly act on epithelial LXA_4R to suppress intestinal epithelial inflammation (Kucharzik et al. 2003). In conclusion, eicosanoids make a significant contribution to intestinal epithelial defense.

The cytokines in innate immune cells induced by eicosanoid regulate intestinal barrier function

The production of cytokines from innate immune cells under the stimulation of eicosanoids may indirectly affect the intestinal epithelial barrier function. Previous studies illustrate that PGE_2 inhibits the production of TNF-α by macrophages (Scales et al. 1989) and the release of IL-12 from maturing DCs (Kaliński et al. 1997). It exerts anti-inflammatory effects (Figure 3). Moreover, PGE_2 can act directly on NK cells by inhibiting the production of cytokines, particularly, IFN-γ which increases epithelial barrier dysfunction by reducing the gene expression of occludin (Mankertz et al. 2000; Van Elssen et al. 2011). However, under LPS induced systemic inflammation, PGE_2 regulates the development of ILC3 and the production of IL-22 (Parks et al. 2015). In particular, IL-22 is important for protecting the intestine from damage during colitis in experimental models (Pickert et al. 2009; Zenewicz et al. 2008). Moreover, it is indicated that IL-22 protects the integrity of the intestinal epithelium during *Salmonella* infection (Lo et al. 2019). Whereas, eicosanoids mediated the release of cells cytokines from innate immune cells whether to directly regulate intestinal barrier function needs further study under the same test condition or the equivalent model.

Conclusions

ARA, the predominant long-chain polyunsaturated fatty acid (LCPUFA) in human milk plays a vital role in infant development. In case breastfeeding is not possible and infant formula is being fed, experts recommend that ARA is added at levels present in human milk (Salem and Van Dael 2020). This review provides a better understanding of how eicosanoids regulate the development and function of innate immune cells to prevent pathogens invasion and how they affect intestinal barrier function. The emerging evidences show that eicosanoids influence innate immune response to prevent pathogens invasion through regulating intestinal innate immunity. However, responding to inflammatory stimuli, IECs express a high level of ARA related metabolic enzymes, subsequently, promote ARA release and enhance PGE_2 production which increases the permeability of the intestinal epithelium and disrupts the intestinal barrier function.

Only a few studies have reported the metabolism of ARA by intestinal microbiota to produce eicosanoids, although

various ARA metabolic enzymes have been detected in the gut. The effect of the intestinal microbiota on eicosanoids remains to be further explored. It is not clear that the regulation of eicosanoids in intestinal innate immune cells. In future work, it will be important to completely understand how eicosanoids affect intestinal innate immunity to treat diseases or prevent against infection.

Disclosure statement

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