Review

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Immune-regulation and -functions of eicosanoid lipid mediators

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Abstract: Bioactive lipids regulate most physiological processes, from digestion to blood flow and from hemostasis to labor. Lipid mediators are also involved in multiple pathologies including cancer, autoimmunity or asthma. The pathological roles of lipid mediators are based on their intricate involvement in the immune system, which comprises source and target cells of these mediators. Based on their biosynthetic origin, bioactive lipids can be grouped into different classes [e.g. sphingolipids, formed from sphingosine or eicosanoids, formed from arachidonic acid (AA)]. Owing to the complexity of different mediator classes and the prominent immunological roles of eicosanoids, this review will focus solely on the immune-regulation of eicosanoids. Eicosanoids do not only control key immune responses (e.g. chemotaxis, antigen presentation, phagocytosis), but they are also subject to reciprocal control by the immune system. Particularly, key immunoregulatory cytokines such as IL-4 and IFN-γ shape the cellular eicosanoid profile, thus providing efficient feedback regulation between cytokine and eicosanoid networks. For the purpose of this review, I will first provide a short overview of the most important immunological functions of eicosanoids with a focus on prostaglandins (PGs) and leukotrienes (LTs). Second, I will summarize the current knowledge on immunological factors that regulate eicosanoid production during infection and inflammation.

Keywords: cytokines; eicosanoids; immunity; inflammation; leukotrienes; prostaglandins.

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Introduction

Eicosanoids are potent mediators of inflammation with central roles in infectious disease, allergy, cardiovascular disease and cancer. The name eicosanoids originates from the greek word εἴκοσι, meaning twenty, and describes lipid mediators derived from the 20 carbon polyunsaturated fatty acid (PUFA) arachidonic acid (AA). AA is metabolized either via the cyclooxygenase (COX) pathway to form prostanoids or via the 5-lipoxygenase (5-LOX) pathway, giving rise to leukotrienes (LTs) (Ferreira and Vane, 1967; Samuelsson et al., 1975; Samuelsson, 1983) (Figure 1). Prostanoids include prostaglandins (PGs), thromboxanes and prostacyclins, which can be produced by most cells in the body. The PG PGE_2 and prostacyclin PGI_2 are particularly important for the immune system as they regulate the migration and activation of key immune cells (Ham et al., 1983; Scandella et al., 2002; Zhou et al., 2007). LTs, which are mainly produced by myeloid cells, include LTB_4, a powerful chemotactic agent and the cysteinyl LTs (LTC_4, LTD_4 and LTE_4), which regulate vascular permeability, smooth muscle contraction and immune cell activation; for a comprehensive review see (Peters-Golden and Henderson, 2007). In addition to 5-LOX, human cells express 12- and 15-LOX enzymes, which participate in the biosynthesis of immunoregulatory eicosanoids such as hydroxyeicosatetraenoic acids (12-/15-HETE), lipoxins or hepoxillins (Serhan and Reardon, 1989; Huang et al., 1999; Aliberti et al., 2002a; Mrsny et al., 2004;) (Figure 1). Finally, cytochrome P450 enzymes (e.g. CYP1A1 and CYP1B1) represent another pathway that metabolizes AA or AA-derived mediators, thus further enhancing the immunoregulatory repertoire of eicosanoids (Nebert and Karp, 2008; Divanovic et al., 2013; Lefèvre et al., 2015). Indeed, there is a large body of literature describing the regulation and immunological functions of eicosanoids and not all studies could be covered in this review. Thus, this article focuses on key references and on recent advancements regarding the immune-regulation of eicosanoids.

The potent immunological effects of eicosanoids indeed necessitate a tight regulation of their biosynthesis. Thus, the expression or activation of COX or LOX pathways

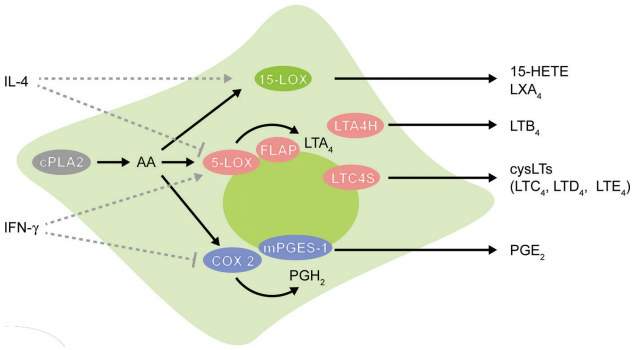

Figure 1: Production of major immunoregulatory eicosanoids by a myeloid immune cell (macrophage as example) and modulation by IL-4 and IFN-γ.
Upon cellular activation, arachidonic acid (AA) is liberated from membrane phospholipids by cytosolic phospholipase A2 (cPLA2), AA is metabolized by 5-lipoxygenase (5-LOX) with the help of 5-LOX activating protein (FLAP), by 15-lipoxygenase (15-LOX) or by cyclooxygenase (COX). 5-LOX metabolism generates leukotriene A_4 (LTA_4), which is hydrolyzed by leukotriene A4 hydrolase (LTA4H) into LTB_4 or conjugated to glutathione by leukotriene C4 synthase (LTC4S) to form LTC_4. LTA_4 can also be metabolized into lipoxin A_4 (LXA_4) by 15-LOX. 15-LOX converts AA into 15-hydroxyeicosatetraenoic acid (15-HETE). COX metabolism of AA generates prostaglandin H_2 (PGH_2), which is converted by microsomal prostaglandin E synthase (mPGES-1) into PGE_2; dashed lines indicate cytokine-mediated regulation; solid lines indicate enzymatic reactions.

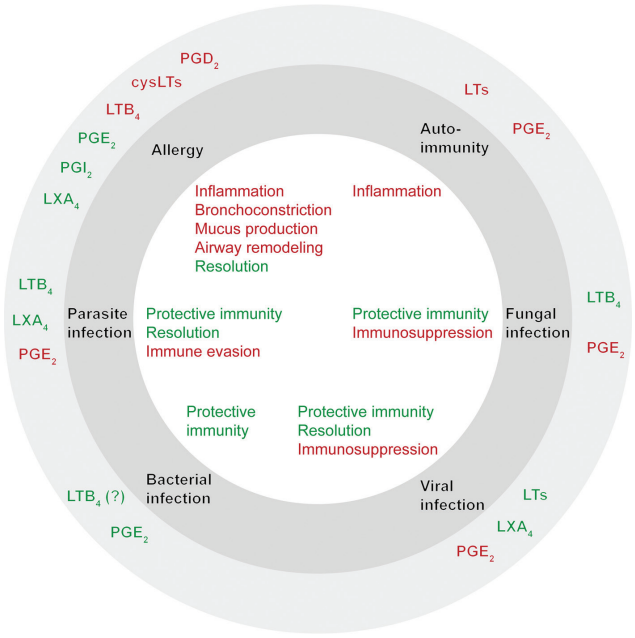

Figure 2: Roles of eicosanoids in immunity and inflammation. Eicosanoids (outer gray circle) with an involvement in particular immunological contexts (shown in inner white circle), are displayed next to the respective disease (inner gray circle). Green or red text indicates beneficial or detrimental effects in the corresponding disease context, respectively.

is regulated by the cellular milieu and by the nature of the ensuing immune response. In general, upregulation or activation of COX and or LOX pathways can be either adaptive (e.g. in protective immunity against pathogens) or maladaptive (e.g. in chronic inflammation) (Figure 2).

In the case of infection, the immune system is faced with highly diverse challenges depending on the type of pathogen encountered (e.g. intracellular vs. extracellular pathogens or tissue damage by macroparasites). This requires different cellular and molecular effector mechanisms targeted at pathogen killing and subsequent return to tissue homeostasis. Similarly, chronic inflammatory diseases such as autoimmunity and allergy are driven by exaggerated immune responses of different flavors. For the purpose of this review, I will follow the classification into type 1, type 2 and type 17 immune responses.

Lipid mediators in the regulation of type 1 immune responses

Although often ignored in infectious disease research, eicosanoids play central roles in a multitude of infections with both intra- and extracellular pathogens (Figure 2). In type 1 immune responses to intracellular pathogens, eicosanoids can be both immunostimmulatory or immunosuppressive.

Viral infection

Most studies supporting a role of eicosanoids in viral infection have been performed in animals. However, evidence from human studies supports the involvement of LOX and COX metabolites during viral infection in human patients. As an example, myeloid cells from the blood of HIV patients showed impaired production of LTs, but increased production of PGE_2 (Thorsen et al., 1989; Longo et al., 1993). These shifts in the eicosanoid profile correlated with reduced numbers of $CD4^+$ T-cells in patients with low LT levels but high PGE_2 levels, respectively (Thorsen et al., 1989; Longo et al., 1993). A protective role for LTs during viral infection was confirmed in several experimental models, making use of pharmacological inhibitors (e.g. the 5-LOX inhibitor zileuton) or of mice genetically deficient in 5-LOX. During experimental infection with cytomegalovirus (CMV), 5-LOX deficient mice showed increased mortality and reconstitution with exogenous LTB_4 could partially restore host defence against

CMV (Gosselin et al., 2005). LTs also contributed to host defence during the early phase of vesicular stomatitis (VSV)-driven encephalitis by preventing viral replication in the CNS (Chen et al., 2001). More recently, a role for LOX metabolites (LXA_4 and resolvin E1) in the resolution phase following respiratory syncytial (RSV) infection has become apparent. 5-LOX deficient mice showed increased lung pathology after RSV infection, which was linked to an impaired activation of regulatory M2 macrophages (Shirey et al., 2014). The same study also suggested that increased COX-2 expression in 5-LOX and 15-LOX deficient macrophages was responsible for the defect in M2 polarization. Indeed, several recent studies have implicated COX-2 derived PGs in detrimental immune responses during viral infection, including virus-induced immunosuppression (Chen et al., 2015; Gandhi et al., 2015; Alfajaro et al., 2017).

Bacterial infection

In addition to their protective effects against viral infection, a contribution of LTs to host defence against intracellular bacteria has been supported by studies on tuberculosis. Pharmacological inhibition of 5-LOX during experimental infection with *Mycobacterium tuberculosis* (*Mtb*) resulted in increased bacterial burdens and increased mortality (Peres et al., 2007). A key role for the 5-LOX pathway during *Mtb* infection was further supported by a study identifying the gene of LT A_4 hydrolase (LTA_4H), which is involved in LTB_4 biosynthesis, as a major susceptibility locus in mycobacterial infection (Tobin et al., 2010). However, a later study found no association between LTA_4H polymorphisms and susceptibility to tuberculosis (Curtis et al., 2011). In addition to 5-LOX metabolites, PGE_2 was reported as a key antimicrobial mediator in *Mtb* infection as mice deficient in prostaglandin E synthase ($PTGES^{-/-}$) showed impaired protective immunity (Chen et al., 2008). Furthermore, one of the four prostaglandin E_2 receptors (EP2) has recently been highlighted as being associated with susceptibility to tuberculosis (Liang et al., 2016). Taken together, eicosanoids play essential roles during the type 1 immune response to mycobacterial infection, although their exact roles and relative contributions are only partially understood (Chen et al., 2008; Divangahi et al., 2010; Peres-Buzalaf et al., 2011; Kaul et al., 2012). Finally, important roles for eicosanoids have also been reported for infections with several other bacterial species including *Klebsiella pneumonia*, *Streptococcus pyogenes* and *Pseudomonas aeruginosa* (Bailie et al., 1996; Sadikot et al., 2007; Goldmann et al., 2010; Guillemot et al., 2014).

Parasite infection

Lipid mediators also play a crucial role during infection with intracellular parasites such as *Toxoplasma gondii*. Whilst LTB_4 was reported to contribute to *T. gondii* killing by macrophages, PGE_2 promoted the immune evasion of this parasite (Yong et al., 1994; Delemarre et al., 1995a,b). In addition, the anti-inflammatory LOX product lipoxin A4 (LXA_4) suppressed the activation of dendritic cells (DC), including IL-12 production by these cells in response to *T. gondii* (Aliberti et al., 2002a). As exaggerated IL-12 production by DCs may contribute to pathological inflammation, LXA_4 production provides an anti-inflammatory mechanism to control aberrant inflammation and mortality during infection with intracellular parasites (Aliberti et al., 2002b).

Thus, eicosanoids play diverse roles in the modulation of type 1 responses to intracellular pathogens with LTs generally being immunostimulatory and antimicrobial and PGE_2 mostly playing immunosuppressive roles.

Auto-inflammatory diseases

In contrast to its immunosuppressive roles in infection, a pro-inflammatory role of PGE_2 was reported for experimental models of autoimmune disease. In experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis, or in contact hypersensitivity, PGE_2 promoted the differentiation of T helper 1 (T_H1) cells, which play a pathogenic role in type 1 inflammation. This effect of PGE_2 depended on the activation of the EP4 receptor, which is one of the four PGE_2 receptors (EP1–EP4). EP4 was expressed on naïve T-cells and mediated their PGE_2-driven differentiation into IFN-γ producing T_H1 cells (Yao et al., 2009). In parallel to its effect on T_H1 cells, PGE_2 also supported the activation of T_H17 cells, potentially by enhancing IL-23 production by DCs (Yao et al., 2009; Esaki et al., 2010). However, in addition to its role in the early induction of T_H1 and T_H17 differentiation during EAE, PGE_2 was found to be anti-inflammatory in the later phase by preventing T-cell recruitment to the brain (Esaki et al., 2010).

Lipid mediators in the regulation of type 2 immune responses

Analogous to their multifaceted roles in type 1 immunity, eicosanoids also modulate all major aspects of type 2 immune responses. Depending on the specific

immunological context, this may result in both beneficial and detrimental outcomes during infection or during chronic type 2 inflammation.

Helminth infection

Infection with multicellular worm parasites (helminths) represents a particular challenge for the immune system, requiring both strategies for worm killing and trapping (Esser-von Bieren et al., 2013, 2015a; Chen et al., 2014) as well as rapid tissue repair (Allen and Wynn, 2011; Chen et al., 2012; Esser-von Bieren et al., 2015b; Minutti et al., 2017). Although lipid mediators are produced during helminth infection (e.g. with the trematode *Schistosoma mansoni or* the nematode *Brugia malayi*) (Tripp et al., 1988; Thomas et al., 2012), their roles in host defence, parasite-mediated immunosuppression or tissue repair remain unclear. Making use of 5-LOX deficient mice, early studies suggested a contribution of 5-LOX metabolites to inflammation and granuloma formation during *S. mansoni* infection (Secor et al., 1998). Indeed, recent work confirmed the involvement of LTs in the control of *S. mansoni*-induced tissue remodeling (Toffoli da Silva et al., 2016). Whilst LTs contributed to the inflammatory response to liver and lung stages of the parasite, PGE_2 was found to act as an immunoregulatory factor during skin penetration of *S. mansoni* larval stages, thus suppressing early host immunity (Ramaswamy et al., 2000). Important roles for both LOX and COX metabolites were also identified in host defence against the helminth *Strongyloides venezuelensis* (*S. venezuelensis*) (Machado et al., 2005, 2010). These studies also reported altered type 2 cytokine levels in helminth-infected mice genetically deficient in 5-LO or treated with COX inhibitors, thus suggesting cross-regulation of cytokine and eicosanoid pathways during type 2 immunity.

Allergy

The central roles of eicosanoids in allergy have long been appreciated as these mediators are potent inducers of hallmark allergic responses such as vascular leakage (edema), mucus production, eosinophilia or airway smooth muscle constriction; for comprehensive reviews see (Honda and Kabashima, 2015; Liu and Yokomizo, 2015). In particular, cysLTs and PGD_2 have been highlighted as inducers of type 2 cytokine production by innate lymphoid 2 cells (ILC2s) and T helper 2 (T_H2) cells (Barrett et al., 2011; Xue et al., 2015; Salimi et al., 2017). As ILC2s and T_H2 cells are the critical cellular sources of type 2 cytokines (IL-4, IL-5, IL-13) in allergy (Robinson et al., 1992; Gold et al., 2014), their activation by cysLTs and PGD_2 contributes to pathological type 2 inflammation (Barrett et al., 2011; Xue et al., 2015; Salimi et al., 2017). In contrast, the prostanoids prostacyclin (PGI_2) and PGE_2 can counter-regulate type 2 immune responses, e.g. by reducing the activation of ILC2s or eosinophils (Sturm et al., 2008; Zhou et al., 2016). In addition, PGE_2 can condition macrophages into an anti-inflammatory phenotype, which suppressed allergic lung inflammation in a murine model of house dust mite allergy (Draijer et al., 2016). Taken together, eicosanoids regulate chronic type 2 inflammation on multiple levels, thus making their regulation by the immune system particularly relevant in allergic diseases.

Lipid mediators in the regulation of type 17 immune responses

Fungal infection

Whilst type 1 responses or type 2 responses target bacteria and viruses or helminths, respectively, type 17 responses are implicated in host defence against pathogenic fungi (Conti et al., 2009; Wüthrich et al., 2011). Several eicosanoids (including LTB_4 and PGE_2) are induced by fungal products and play important roles in the immune response during fungal infection (Fernández et al., 2005; Olynych et al., 2006; Esser et al., 2011). Of note, LTB_4 and PGE_2 have opposing effects on antimicrobial type 17 responses against fungi: whilst LTB_4 promoted host defence against fungi, PGE_2 suppressed anti-fungal immunity by inhibiting IL-17 production by T-cells (Secatto et al., 2012; Serezani et al., 2012; Valdez et al., 2012). However, in a non-infectious setting, PGE_2 was shown to promote T_H17 differentiation, thus suggesting that regulatory roles of eicosanoids in type 17 responses are context specific (Napolitani et al., 2009).

Auto-inflammatory diseases

In addition to their roles in chronic type 1 and type 2 inflammation, eicosanoids have been implicated in type 17 inflammation e.g. in rheumatoid arthritis. Thus, in experimental models of arthritis PGE_2 enhanced the production of IL-17, thereby promoting joint inflammation (Sheibanie et al., 2007; Lemos et al., 2009). Similarly, LTs were shown to promote T_H17 differentiation and to contribute to arthritis in mice (Griffiths et al., 1997; Chen et al., 2009; Mathis et al., 2010).

However, the immunomodulatory roles of lipid mediators are not limited to settings of infection, tissue damage or inflammation. Prostanoids in particular also exert essential homeostatic immunoregulation. As an example, PGE_2 released from airway epithelial cells controls the production of pro-inflammatory cytokines (TNF-α, IL-12) by DCs, whilst inducing regulatory factors such as IL-10 and Arginase-1 under homeostatic conditions (Schmidt et al., 2011).

Regulators of lipid mediator synthesis

The potent immuno-stimulatory or -suppressive functions of lipid mediators in these various immunological settings require a tight control of their biosynthesis. Research in recent decades has identified a large number of immunological factors and mechanisms that control lipid mediator pathways to regulate immune responses during infection and inflammation (Figure 3).

Cytokines

Cytokines are immunoregulatory proteins that control all key processes of host defence and inflammation. As the central regulators of immune responses, cytokines also determine the eicosanoid profiles of immune and non-immune cells. This is mostly due to cytokine-induced transcriptional changes, i.e. up- or down-regulation of eicosanoid biosynthetic enzymes. In addition, cytokines can prime eicosanoid-producing cells (e.g. granulocytes) to respond with increased lipid mediator production upon stimulation with a secondary stimulus.

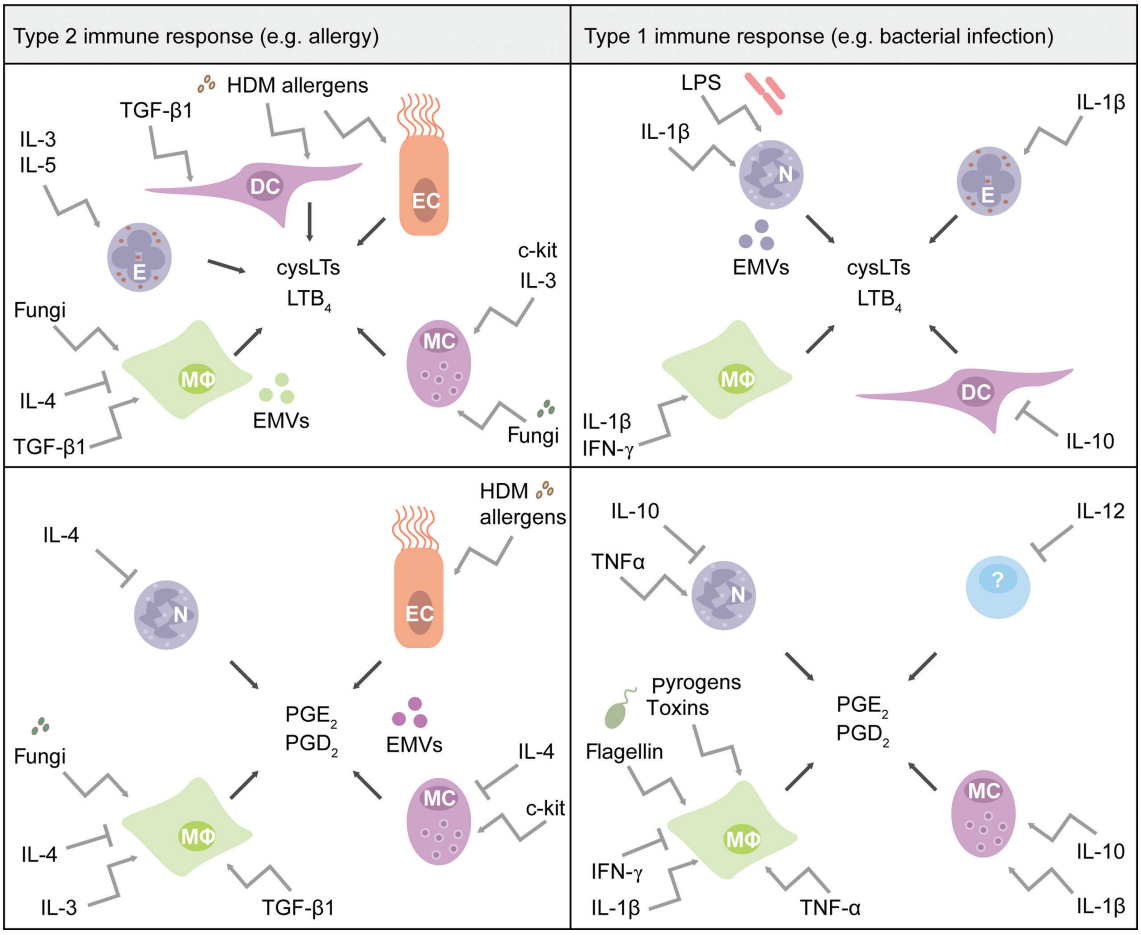

Figure 3: Immune-regulation of eicosanoids in immunity and inflammation.
Gray arrows indicate modulation of eicosanoid production by the respective immunological factors. Black arrows indicate eicosanoid production by certain (immune) cell types; dendritic cell (DC), eosinophil (E), epithelial cell (EC), exosomes and microvesicles (EMVs), house dust mite (HDM), macrophage (MΦ), mast cell (MC), neutrophil (N).

Interleukin-1 beta (IL-1β)

The IL-1β-triggered generation of PGE_2 represents one of the best-studied mechanisms of cytokine-regulated eicosanoid generation. Indeed, IL-1β-PGE_2 crosstalk represents the central mechanism of the fever response (Dinarello and Wolff, 1982; Baracos et al., 1983). These early studies also showed that the IL-1β-induced production of PGE_2 can occur in various cell types including both hematopoietic cells (e.g. monocytes) and non-hematopoietic cells (e.g. skeletal muscle cells). Furthermore, IL-1β can induce the expression of COX-2 in mast cells, thus promoting PGD_2 generation (Ashraf et al., 1996). In addition to increasing PGD_2, an activator of eosinophils, ILC2s and T_H2 cells, IL-1β also increases LTB_4 release by macrophages, thus inducing neutrophil chemotaxis (Oliveira et al., 2008). More recently, IL-1β was found to regulate cysLT synthesis by eosinophils by activating secretory phospholipase A2 group 10 (sPLA2-10) in these cells (Hallstrand et al., 2015). Thus, IL-1β generally increases eicosanoid generation during inflammation without the counter-regulatory effects seen for most other cytokines, which differentially influence particular biosynthetic pathways.

Interleukin-3 (IL-3)

IL-3 is an important leukocyte survival and differentiation factor that increases the expression of the complete enzymatic cascade for cysLT generation [5-LOX, 5-LOX activating protein (FLAP), cytosolic phospholipase A2 (cPLA2) and leukotriene C_4 synthase (LTC_4S)] in murine mast cells, thus promoting IgE-triggered LTC_4 generation by these cells (Murakami et al., 1995a). However, the effect of IL-3 was not specific for the 5-LOX pathway as PGD_2 generation by mast cells was also increased during differentiation with IL-3. In addition, IL-3 increased the expression of mPGES-1 in bone marrow derived macrophages, resulting in increased PGE_2 synthesis and a type 2 immune bias during bacterial infection (Kuroda et al., 2007).

Interleukin-4 (IL-4)

IL-4, the signature cytokine of type 2 immunity, exerts differential effects on different eicosanoid pathways. Multiple studies have shown that IL-4 promotes 15-lipoxygenase (15-LOX) expression in human monocyte derived macrophages and DC (Huang et al., 1999; Spanbroek et al., 2001; Esser et al., 2010), while reducing 5-LOX and COX-2 expression in these cells (Spanbroek et al., 2001; Teloni et al., 2007; Cho et al., 2011; Esser et al., 2011). Consistent with its effects on monocytes, IL-4 also suppressed LPS-induced COX-2 expression in neutrophils (Niiro et al., 1997). Similarly, IL-4 attenuated IgE-triggered PGD_2 production in mast cells by reducing COX-2 expression (Murakami et al., 1995b). In mast cells, IL-4 also supressed c-kit ligand-induced expression of cPLA2, thus modifying overall eicosanoid release. However, during helminth infection *in vivo*, IL-4 signaling shifted the eicosanoid profile of resident macrophages without major effects on overall eicosanoid levels (Thomas et al., 2012). Taken together, the current literature suggests that the modulation of eicosanoid pathways may represent a central mechanism underlying the immunoregulatory potential of IL-4 during type 2 immunity. However, no clear-cut pattern regarding the overall (patho-) physiological outcome of IL-4-driven changes in eicosanoid production has hitherto emerged.

Interleukin-5 (IL-5)

IL-5 is a central survival factor of eosinophils that also acts as a priming agent for these cells. Thus, pre-incubation with IL-5 resulted in a strongly increased capacity to generate LTC_4 upon subsequent stimulation with complement component C5a, platelet-activating factor (PAF) or the bacterial peptide fMLP (Takafuji et al., 1991). IL-5 further promoted LT production by eosinophils by increasing the expression of FLAP and by triggering nuclear translocation of 5-LO (Cowburn et al., 1999). In addition, IL-5 increased the expression of the cysteinyl leukotriene receptor cysLT1 during eosinophil differentiation, resulting in an increased chemotactic response of eosinophils towards cysLTs (Thivierge et al., 2000). Thus, the type 2 cytokine IL-5 and cysLTs engage in positive feedback loops to increase eosinophilic inflammation, particularly in settings of allergy and asthma (Doherty et al., 2013; Salimi et al., 2017).

Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine that regulates the expression of pro-inflammatory cytokines (Schaljo et al., 2009) as well as the production of lipid mediators. Early studies showed that IL-10 suppressed the LPS-driven induction of COX-2 expression in neutrophils *in vitro* (Niiro et al., 1997). The *in vivo* relevance of this finding was demonstrated in IL-10 deficient mice, which showed exaggerated PG production and inflammation during LPS

exposure (Berg et al., 2001). In contrast to its suppressive effect in neutrophils or mixed splenocytes, IL-10 increased the expression of COX-2 in murine mast cells (Ashraf et al., 1996). With regards to the 5-LOX pathway, IL-10 was shown to inhibit LT biosynthesis in DCs by reducing FLAP expression (Harizi et al., 2003). Of note, PGE_2 can induce IL-10 production, thus providing an additional immune-modulatory mechanism, by which this mediator can suppress LT production. Finally, IL-10 also downregulated expression levels of LT receptors (cysLT1/cysLT2) in DCs, leading to reduced cysLT-stimulated chemotaxis (Woszczek et al., 2008). In summary, IL-10 reduces the production and signaling of pro-inflammatory eicosanoids. However, how this regulatory IL-10-eicosanoid axis contributes to resolution or immunosuppression *in vivo* is poorly understood.

As the counterpart to IL-4, interferon gamma (IFN-γ) has opposing effects on the production of LOX products by various immune cells. Whilst IL-4 or IL-13 suppressed LT generation by reducing 5-LOX expression, IFN-γ priming lead to an increased production of LTs (Meslier et al., 1992). In addition, IFN-γ downregulated 12/15-LOX expression in the lungs of allergen-sensitized mice, which was associated with reduced allergic airway inflammation (Lindley et al., 2010). However, in contrast to their opposing effects on lipoxygenases, IL-4 and IFN-γ were both found to exert suppressive effects on the COX pathway. IFN-γ treatment of human macrophages downregulated COX-2 expresssion and PGE_2 synthesis, thus providing a mechanism to prevent PGE_2-mediated immunosuppression during type 1 immune responses (Boraschi et al., 1984; Barrios-Rodiles and Chadee, 1998).

Transforming growth factor-beta 1 (TGF-β1)

TGF-β1 is involved in immunoregulation and tissue repair and has been identified as an important regulator of eicosanoid production in myeloid cells. In particular, TGF-β1 upregulated 5-LOX activity during myeloid cell maturation (Steinhilber et al., 1993). TGF-β1 also increased 5-LOX and LTA_4H expression in human macrophages and DCs, which resulted in increased LT generation by these cells (Esser et al., 2010). In contrast to this pro-inflammatory role of TGF-β1, which may contribute to its capacity to promote airway remodelling, TGF-β1 contributes to immunoregulation by modulating eicosanoid production upon efferocytosis. Thus, the uptake of apoptotic neutrophils by macrophages results in the upregulation of COX-2 and increased production of PGE_2 via a TGF-β1-dependent mechanism (Freire-de-Lima et al., 2006). Taken together, TGF-β1 generally increases the production of eicosanoids by promoting the expression of multiple biosynthetic enzymes.

Tumor necrosis factor-alpha (TNF-α)

TNF-α is a cytokine produced during the acute phase of inflammation that exerts some of its pro-inflammatory actions by increasing LT production by neutrophils (Steadman et al., 1990; Petersen et al., 1992). In addition, TNF-α was found to increase the expression of COX-2 after priming of human macrophages with IFN-γ (Arias-Negrete et al., 1995). However, the positive effect of TNF-α on COX-2 gene expression was restricted to short-term stimulation as longer exposure of macrophages to TNF-α resulted in decreased COX-2 mRNA stability (Huang et al., 2000). Thus, during acute inflammation, TNF-α promotes a rapid increase in both LOX and COX products, contributing to more sustained inflammation, fever and pathogen clearance.

Innate immune recognition pathways

Many of the above-described cytokine-driven eicosanoid alterations are downstream of innate immune recognition of microbial ligands. However, in addition to such indirect cytokine-mediated effects of microbes, they can also directly modify eicosanoid production [e.g. via activating pattern recognition receptors (PRR) and kinases].

Pattern recognition receptors

LPS, the ligand of toll like receptor 4 (TLR4), was identified as a regulator of eicosanoid biosynthesis in the early days of eicosanoid research (Schade, 1987; Doerfler et al., 1989). Later studies confirmed the *in vivo* relevance of this finding by demonstrating increased LT and PG biosynthetic capacity after LPS administration to mice as well as in leukocytes from sepsis patients (Pacheco et al., 2002). Whilst LPS-primed cells for increased eicosanoid generation upon secondary stimulation, ligands of TLR2 (e.g. yeast zymosan) could directly stimulate eicosanoid production by monocytes and mast cells (McCurdy et al., 2003; Lindner et al., 2009). Of note, short-term stimulation of myeloid cells with TLR2 ligands augments LT generation, whilst prolonged exposure results in an upregulation of COX-2 and subsequent PGE_2-mediated suppression of LT

production (Lindner et al., 2009; Esser et al., 2011). Such feedback mechanisms may contribute to immune homeostasis by preventing the persistent production of pro-inflammatory mediators after microbial challenge.

In addition to TLRs, C-type lectin receptors (CLRs) have been shown to mediate the regulation of eicosanoid synthesis, most notably during exposure to fungi. For example, activation of dectin-1, a receptor for fungal beta-glucans, triggered the rapid generation of cysLTs by mast cells and macrophages (Olynych et al., 2006; Suram et al., 2006). However, the *in vivo* relevance of dectin-1-triggered eicosanoid production in infection or allergy has not received further attention. In contrast, innate immune recognition leading to subsequent eicosanoid alterations has been identified as a key mechanism in the induction of allergic inflammation. In particular, *dectin-2* ligation by house dust mite (HDM) increased cysLT generation by DCs (Barrett et al., 2009, 2011; Clarke et al., 2014). In addition, HDM can also induce LT production in epithelial cells, which was however mediated by protease-activated receptor 2 (PAR2) (Trian et al., 2015; Dietz et al., 2016). However, HDM components could not only trigger LT production, but also promoted PGE_2 synthesis by airway epithelial cells (Knight et al., 2000). Thus, increased eicosanoid production in response to fungi or dust mites may determine the outcome of both antimicrobial responses against fungal pathogens as well as inflammatory responses triggered by allergenic species.

The inflammasome is a multiprotein signaling platform responsible for the production of IL-1β and IL-18 as well as for inducing pyroptotic cell death upon infection or cellular damage (Agostini et al., 2004; Mariathasan et al., 2004; Fink et al., 2008). In addition to these canonical roles, the inflammasome has been shown to trigger a so-called "eicosanoid storm" by activating cPLA2 and COX-1 during exposure to the pathogen molecules flagellin or anthrax lethal toxin (von Moltke et al., 2012). More recently, the eicosanoid balance (i.e. LTB_4/PGE_2) was shown to determine the outcome after scorpion venom-triggered inflammasome activation *in vivo* (Zoccal et al., 2016). Inflammasome mediated-control of eicosanoid production thus represents an early innate immune mechanism to regulate acute inflammation triggered by toxins or other microbial components.

Kinases

Kinase activation via a variety of immunoregulatory factors (e.g. cytokines or PRR ligands) represents an efficient and plastic mechanism of eicosanoid regulation in diverse immunological settings. As an example, microbe-induced PGE_2 can activate protein kinase A (PKA), which suppresses LT synthesis by inhibitory phosphorylation of 5-LOX (Luo et al., 2004). In contrast, the activation of mitogen-activated protein kinases (MAPK) and extracellular-signal regulated kinases (ERK), e.g. by TLR ligands, can stimulate the rapid generation of LTs by activating the phosphorylation of 5-LOX (Werz et al., 2000, 2002). Further immunologically relevant kinases that regulate LT synthesis include protein kinase C (PKC) (Peters-Golden et al., 1990; Sjölinder et al., 1995) and ribosomal protein S6 kinase (p70S6K), a downstream component of mTOR signaling (Esser et al., 2011; Ahmad et al., 2016). While PKC activation results in increased AA release by activating cPLA2 (Godson et al., 1993), PKC also mediates inhibitory phosphorylation of LTC_4 synthase (LTC_4S), thus inhibiting cysLT production (Sjölinder et al., 1995; Gupta et al., 1999). Thus, PKC activation results in increased PG and LTB_4, but decreased cysLT release. Similarly, p70S6K reduces cysLT production by catalyzing the inhibitory phosphorylation of LTC_4S (Esser et al., 2011; Ahmad et al., 2016). Depending on the presence of particular TLR ligands, cytokines and/or growth factors, a multitude of kinases can be activated to fine-tune the local eicosanoid profile and thus the ensuing inflammatory response.

Epigenetics

Only more recently, epigenetic regulation of eicosanoid biosynthetic enzymes and eicosanoid receptors has come into focus. This includes both DNA methylation and histone modifications of genes involved in eicosanoid synthesis and signaling. Indeed, a genome-wide analysis comparing DNA methylation profiles in primates and humans identified the LTB_4 receptor BLT1 (LTB4R) as the most divergent gene, thus highlighting the relevance of epigenetic regulation of eicosanoid genes (Wilson et al., 2014). Furthermore, a potential role of aberrant methylation of eicosanoid genes in the pathophysiology of chronic airway inflammation was suggested by a study showing differential methylation of the genes coding for the terminal synthases for PGE_2 or PGD_2 production [mPGES-1/prostaglandin D synthase (PGDS)] as well as the LT pathway proteins FLAP and LTB4R in chronic rhinosinusitis with nasal polyps (Cheong et al., 2011). However, how the differential methylation of eicosanoid genes may contribute to protective immune responses or chronic inflammation

remains to be elucidated. In addition to regulation via DNA methylation, the expression of several eicosanoid genes is controlled by histone modifications including histone methylation (e.g. H3K4me3) and histone acetylation (e.g. H3K27ac). The best-studied example is the 5-LOX (ALOX5) gene, which is regulated not only by DNA methylation at its promoter, but also by acetylation of histones H3 and H4 and by H3K4 trimethylation (Katryniok et al., 2010; Pufahl et al., 2012). Similar to the 5-LOX pathway, the COX pathway is also subject to epigenetic regulation. In LPS-activated microglia, HDAC inhibitors induced hyperacetylation of both mPGES-1 and COX-2 genes, thus increasing PG release (Singh et al., 2014). In addition to regulating genes coding for PG synthesizing enzymes, histone acetylation (H3K27ac) has also been suggested to control the expression of the PGE_2 receptor EP2 in human airway fibroblasts (Cahill et al., 2015). Taken together, epigenetic mechanisms are likely to determine eicosanoid production and subsequent immunological outcomes in various infectious and inflammatory settings. However, the contribution of such epigenetic regulation to host defence or chronic inflammatory diseases remains poorly understood.

Extracellular vesicles

Extracellular vesicles (exosomes and microvesicles, EMVs) have been identified as another means of eicosanoid regulation that may determine lipid mediator profiles in various immunological settings. The first cells that were found to produce EMVs with the capacity to synthesize and or carry bioactive lipids were human macrophages and DC as well as rat basophilic leukemia cells (Esser et al., 2010; Subra et al., 2010). More recently, also neutrophils were shown to release exosome-associated LTB_4, which was crucially involved in chemotactic responses (Majumdar et al., 2016). Thus, during infection or inflammation, EMVs released by cells of the innate immune system likely contribute to eicosanoid generation, which can either be direct or through transcellular metabolism with neighboring cells (Esser et al., 2010). Owing to their stability, EMVs may provide an efficient mechanism to generate a sustained eicosanoid environment. This may foster host defence on the one hand, but also drive chronic inflammation on the other. Indeed, the capacity of exosomes to metabolize AA or downstream metabolites has been suggested to contribute to immunopathology both in allergy (Esser et al., 2010; Torregrosa Paredes et al., 2012) and in lung cancer (Lukic et al., 2016). Taken together, EMVs provide an extracellular platform of eicosanoid production and signaling, which may even outlive the original cellular immune response.

Concluding remarks

Similar to cytokines, eicosanoids govern all types of immune responses and they engage in intricate regulatory networks with a multitude of other immunological factors (Figure 3). However, the regulation of eicosanoid production by the immune system is exceptionally complex as it occurs on multiple levels including transcriptional and post-translational mechanisms. While the mutual regulation of eicosanoids, growth factors and cytokines has been recognized for decades, these networks are often neglected in immunological studies. This results in an incomplete understanding of immunoregulatory mechanisms that control eicosanoid production and function *in vivo*. Translation of *in vitro* findings about the immunoregulation of lipid mediators to experimental disease models and clinical studies could provide valuable insights into its actual immunological functions. As new immunological concepts such as trained immunity and immunometabolism continue to emerge, the functional roles and regulation of lipid mediators in these contexts will likely be subject to future studies.

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