Cell
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Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology

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Arachidonic acid (AA)-derived eicosanoids belong to a complex family of lipid mediators that regulate a wide variety of physiological responses and pathological processes. They are produced by various cell types through distinct enzymatic pathways and act on target cells via specific G-protein-coupled receptors. Although originally recognized for their capacity to elicit biological responses such as vascular homeostasis, protection of the gastric mucosa and platelet aggregation, eicosanoids are now understood to regulate immunopathological processes ranging from inflammatory responses to chronic tissue remodelling, cancer, asthma, rheumatoid arthritis and autoimmune disorders. Here, we review the major properties of eicosanoids and their expanding roles in biology and medicine.

Introduction

Eicosanoids, including prostaglandins (PGs), leukotrienes (LTs) and lipoxins (LXs), are signalling molecules that are generated primarily through an oxidative pathway from arachidonic acid (AA) (Figure 1) but also from pathways originating from eicosapentaenoic and dihomo-γ-linolenic acids [1–3]. AA-derived eicosanoids exert complex control over a wide range of physiological processes (Table 1). Many important aspects of immunity, such as cytokine production, antibody formation, differentiation, cell proliferation, migration and antigen presentation, are regulated by eicosanoids. Cells of the innate immune system, including tissue macrophages, sentinel dendritic cells (DCs) and neutrophils, are major producers of eicosanoids, which act locally at nanomolar concentrations on target cells. They exert their effects in an autocrine and paracrine fashion and affect the function of neighbouring cells. It has become increasingly apparent that eicosanoids and their receptors cooperate with other signalling molecules, particularly cytokines and chemokines, and have a crucial role in modulating physiological processes in both homeostatic and inflammatory conditions (Box 1).

Eicosanoid production is considerably increased during inflammation, and their biosynthetic pathways are of particular clinical relevance because their products are involved in the pathogenesis of various pathologies related to immune functions [4–6]. A variety of therapeutic strategies based on eicosanoids and their receptors are currently being used, and others are on the horizon. However, pharmacological inhibition of eicosanoid biosynthesis might simultaneously be beneficial and deleterious. This review highlights recent developments in eicosanoid biology and immunopathology. We will discuss the major properties of AA-derived eicosanoids and their expanding roles in health and disease, focusing on the involvement of PGs, LTs and LXs in inflammation, cancer, autoimmunity and allergic diseases.

Eicosanoid biosynthesis from arachidonic acid

The biosynthesis of eicosanoids depends on the availability of free AA. When tissues are exposed to diverse physiological and pathological stimuli, such as growth factors, hormones or cytokines, AA is produced from membrane phospholipids by the action of phospholipase A2 (PLA2) enzymes and can then be converted into different eicosanoids. AA can be enzymatically metabolized by three main pathways: P-450 epoxygenase, cyclooxygenases (COXs) and lipoxygenases (LOXs) (Figure 1). The P-450 epoxygenase pathway produces hydroxyeicosatetraenoic acids (HETEs) and epoxides. The COX pathway produces PGG2 and PGH2, which are subsequently converted into PGs and thromboxanes (TXs). COX exists in two isoforms commonly referred to as COX-1 (encoded by a constitutively expressed gene) and COX-2 (encoded by an immediate early response gene) [7]. The LOXs are more numerous and convert AA into diverse hydroperoxyeicosatetraenoic

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Glossary

Antigen-presenting cells (APCs): a functionally defined group of cells that are able to take up antigens and present them to T lymphocytes to stimulate immune responses. APCs include macrophages, endothelial cells, dendritic cells (DCs), Langerhans cells and B cells. DCs are considered 'professional' APCs because they are able to stimulate naïve T cells.

Eicosanoids: (from the Greek *eikosi* for 'twenty') are members of a family of oxygenated metabolites mainly synthesized from the 20-carbon fatty acid arachidonic acid. They exert their effects mainly locally through interaction with G-protein-coupled receptors on the cell surface or with nuclear receptors.

Leukotrienes (LTs): the name *leukotriene*, introduced by Swedish biochemist Bengt Samuelsson in 1979, comes from the words leukocyte and *triene* (indicating the compound's three conjugated double bonds). LTs are naturally produced eicosanoid lipid mediators that are responsible for potent proinflammatory responses. Their production is part of a complex response that usually includes the production of histamine.

Lipoxins (LXs): are short-lived endogenously produced nonclassic eicosanoids whose appearance in inflammation signals the resolution of inflammation. At present, two LXs have been identified: LXA4 and LXB4.

Non-steroidal anti-inflammatory drugs (NSAIDs): drugs with analgesic, antipyretic and, in higher doses, anti-inflammatory effects. They reduce pain, fever and inflammation. The term 'non-steroidal' is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. The most prominent members of this group of drugs are aspirin, ibuprofen and naproxen.

Prostanoids: an important class of COX-derived eicosanoids including prostaglandins (PGs), thromboxanes (TXs) and prostacyclin.

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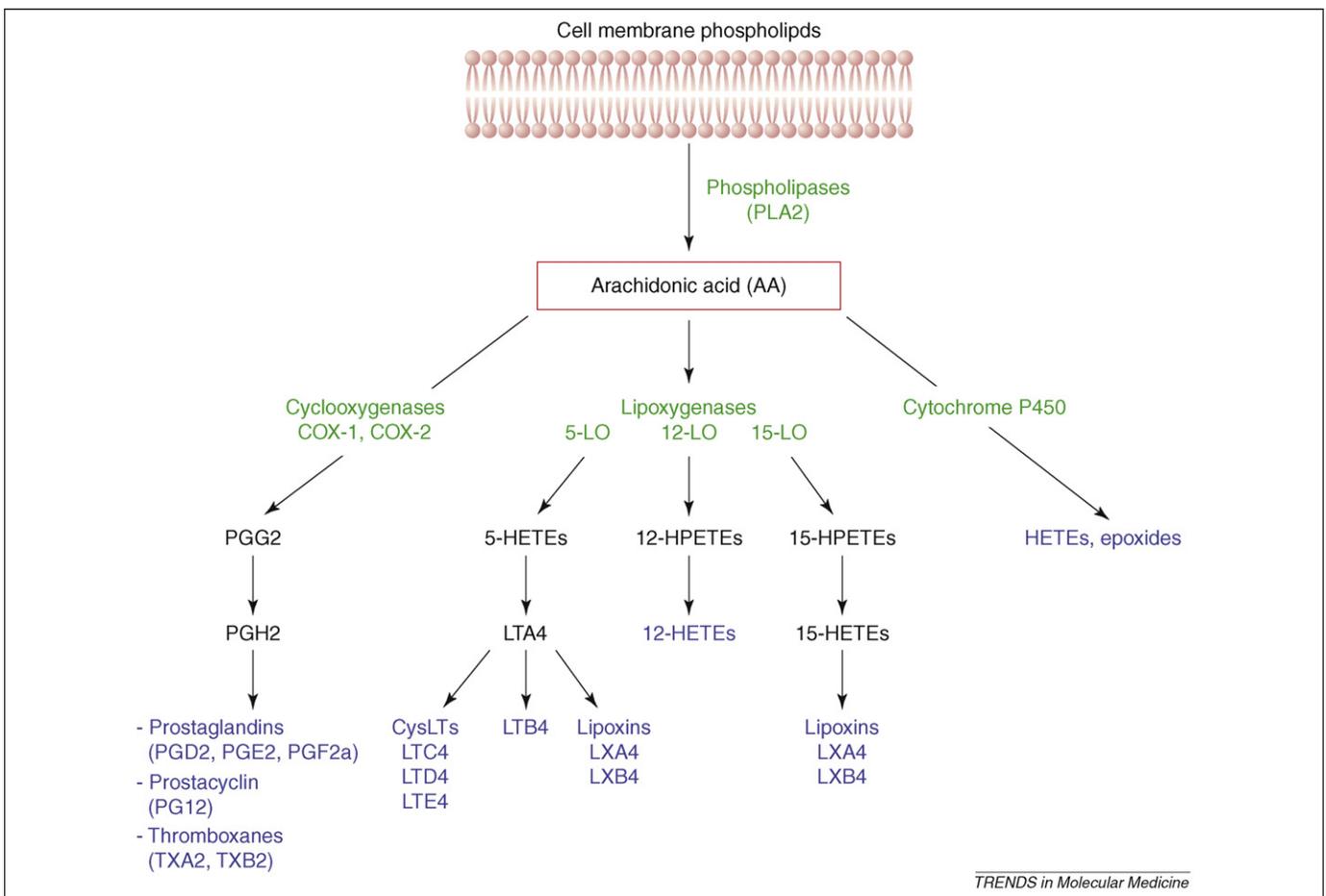
Figure 1. Eicosanoid biosynthesis from AA. In response to a variety of non-specific activating stimuli, including cytokines, hormones and stress, AA is released from membrane phopholipids by phospholipases, especially cytosolic phospholipase A2 (cPLA2). Free AA can be converted to bioactive eicosanoids through the cyclooxygenase (COX), lipoxygenase (LOX) or P-450 epoxygenase pathways. LOX enzymes (5-LO, 12-LO, 15-LO) catalyse the formation of LTs, 12(S)hydroperoxyeicosatetraenoic acids and lipoxins (LXs), respectively. COX isozymes (constitutive COX-1 and inducible COX-2) catalyse the formation of PGH2, which is converted by cell-specific PG synthases to biologically active products, including PGE2, PGF2α, PGI2 and TXA2, known collectively as prostanoids. The P-450 epoxygenase pathway catalyses the formation of hydroxyeicosatetraenoic acids (HETEs) and epoxides. Reproduced from Ref. [23].

acids (HPETEs) and HETEs. 5-HETE is converted into the leukotriene LTA4, which is the precursor of LTB4, cysteinyl-LTs (CysLTs) (including LTC4, LTD4 and LTE4) and LXs. Synthesis of LXs is dependent on the activity of the

requisite interacting LOXs and the proximity of cells that are necessary for the metabolism of AA to the LX end products. In some instances, the metabolite is transferred to another cell that in turn converts it into another compound. For example, PGI2 and LXA4 can be produced during cell–cell interactions, utilizing enzymes in adjacent cells. PGI2 is produced from PGH2 (of platelet origin) by the vascular epithelium or lymphocytes. Similarly, LTA4 produced by neutrophils can be converted into LTC4 by

Table 1. Physiological effects of major eicosanoids

Organs or cells	Effects	Eicosanoids
Vessels	Vasoconstriction	PGF2, TXA2, LTC4, LTD4
	Vasodilatation	PGI2 (most active), PGE2, PGD2
Platelets	Anti-aggregation	PGE1, PGI2
	Pro-aggregation	TXA2
Bronchi	Bronchoconstriction	PGF2α, TXA2, LTC4, LTD4
	Bronchodilation	PGE2, PGI2
Intestines	Nausea, diarrhoea	PGE1, PGF2α
	Motility	PGE1, PGF2α
Stomach	Inhibition of gastric acid secretion	PGE2, PGI2
	Motility	PGE2, PGF2α
Uterus	Contraction, parturition	PGE2, PGF2, TXA2
Kidney	Filtration and renal blood flow	PGH2, PGE1, PGI2
Hypothalamic and pituitary axis	Increase in hypothalamic and pituitary hormone secretion	PGE1, PGE2

Box 1. Eicosanoids

- Eicosanoids are lipid signalling molecules synthesized from arachidonic acids (AAs), eicosapentaenoic or dihomo-γ-linolenic acids.
- They exert their effects mainly locally through interaction with receptors on the cell surface or nuclear membrane.
- NSAIDs block cyclooxygenase-dependent downstream effects of eicosanoids.
- Prostaglandins and leukotrienes, eicosanoid-derived molecules, are important effectors in immunity and inflammation.
- Eicosanoids participate in critical physiological functions, such as the regulation of smooth muscle tone, vascular permeability and platelet aggregation.
- Eicosanoids are involved in inflammation, autoimmunity, allergic diseases and cancer.

vascular epithelium or platelets or into LTB4 by erythrocytes. Thus, biosynthesis of different eicosanoids is dependent on local production and distribution of specific precursors and enzymes in specific cells.

Eicosanoid receptors and signalling

Eicosanoids exert their effects by binding to membrane receptors. This can trigger an increase or decrease in the rate of cytosolic second messenger generation (cAMP or Ca^{2+}), activation of a specific protein kinase or a change in membrane potential. We will focus here on PG and LT signalling because of their importance in the pathogenesis of several immunological and inflammatory diseases.

Endogenously produced PGs can undergo facilitated transport from the cell through known prostanoid transporters or other carriers to exert autocrine or paracrine actions on a family of prostanoid membrane receptors. There are at least nine known prostanoid receptor forms in mouse and man, as well as several additional splice variants with divergent carboxy terminal regions [8]. Four of the receptor subtypes bind PGE2 (EP1–EP4), two bind PGD2 (DP1 and DP2) [9,10] and specific receptors bind PGF2α, PGI2 or TXA2 (FP, IP and TP, respectively). On the basis of homology and signalling attributes, there are three clusters of prostanoid receptors within a distinct subfamily of the G-protein-coupled receptor (GPCR) superfamily of seven transmembrane proteins. The lone exception is DP2, which is a member of the chemoattractant receptor subgrouping. IP, DP1, EP2 and EP4 act as 'relaxant' receptors and form one cluster signalling through G_s-mediated increases in intracellular cAMP. The 'contractile' receptors EP1, FP, and TP form a second group that signals through G_q-mediated increases in intracellular calcium. The EP3 receptor modulates adenyl cyclase activity through the activation of G_i and G_s proteins. However, EP3 also signals through G-protein–Rho interactions [11]. It can also stimulate the PLC-dependent Ca^{2+} response and might be involved in activation of other biological processes, such as tumour-associated angiogenesis. Although most of the prostanoid receptors are localized at the plasma membrane, some are present at the nuclear envelope, but the function of nuclear membrane prostanoid receptors is yet to be understood [12,13].

The proinflammatory LTs act on target cells through four GPCRs [14–16]. The high-affinity leukocyte BLT1 receptor binds LTB4 and activates a guanylyl cyclase to generate cGMP. It also signals through G_q and G_i. High concentrations of LTB4 activate the BLT2 receptor, which signals through G_q coupling and stimulates cell activation. Two subtypes of cysteinyl-leukotriene receptors, CysLT1 and CysLT2, mediate the actions of LTC4 and LTD4.

Eicosanoids and immune cells: production and immunomodulation

Eicosanoid synthetic profiles differ from one cell type to another. Among the cells involved in the immune response, macrophages are important producers of eicosanoids [17]. They are able to synthesize PGs as well as LTs. Resting macrophages exhibit COX and LOX activities, and cell stimulation activates both pathways. *In vitro*, many stimuli, including calcium ionophore, zymosan and

immune complex, increase eicosanoid production. Mast cells are also able to produce eicosanoids, such as PGD2, LTB4 and LTC4 [18]. These diverse lipid mediators can initiate, amplify or dampen inflammatory responses and influence the magnitude, duration and nature of subsequent immune responses.

The production of PGs and LTs has been reported for lymphocytes and leukaemia cell lines such as Jurkatt cells [19]. Activated human T lymphocytes strongly express COX-2 and produce PGD2, which is then converted to the short-lived 15-deoxy-PGJ2 [20]. Recent studies indicate that activated B cells express COX-2 and produce significant amounts of downstream PGE2 [21]. These properties might be central to several functions of B lymphocytes [22].

Recently, much interest has focused on the interaction between eicosanoids and DCs, the most potent antigen-presenting cells (APCs) of the immune system [23,24]. Although DCs are a heterogeneous group of cells with differences in origin, anatomic location, phenotype and function, they all have potent antigen-presenting capacity for stimulating naïve, memory and effector T cells [25]. A fundamental aspect of DC function is their ability to produce various endogenous mediators, such as cytokines and eicosanoids. Indeed, DCs are both a source and target of AA-derived eicosanoids. We and others and have reported that mouse bone-marrow-derived DCs (BM-DCs) express both isoforms of COX (COX-1 and COX-2) and are able to produce PGE2 but not PGD2 [26,27]. Similar data have been obtained for human monocyte-derived DCs [28].

In contrast to PGs, which are produced by practically all cells of the body, LTs are synthesized predominantly by inflammatory cells such as polymorphonuclear leukocytes, macrophages, mast cells and DCs. Upon cellular activation of mast cells or macrophages by immunoglobulin E (IgE)–antigen complexes, ionophore or other stimuli, a cascade of cell activation events leading to the biosynthesis of LTs occurs. Mouse BM-DCs have been shown to be an important source of proinflammatory LTs [29].

Thus, eicosanoids seem to be potent modulators of key aspects of immunity through their effects on DCs, macrophages and lymphocytes.

Dendritic cells

In the immune system, eicosanoids are produced predominately by APCs and have particular effects on DCs [30,31].

Box 2. Eicosanoids and dendritic cells

- Dendritic cells (DCs) produce PGs as well as LTs and express their receptors, and many aspects of DC biology are regulated by eicosanoids.
- In immune regulation, PGE2 is the best studied COX metabolite.
- The major effects of PGE2 on DCs are mediated through EP2 and EP4 receptor subtypes.
- PGE2 affects DC biology through pro- and anti-inflammatory actions.
- PGE2 inhibits DC IL-12 production via an IL-10-dependent mechanism and suppresses the antigen-presenting function of DCs.
- PGE2 and LTC4 regulate DC trafficking.
- Proinflammatory LTB4 stimulates IL-6 production by DCs.

Studies concerning the modulation of DC biology by eicosanoids show that PGs and LTs have the potential to affect the maturation, cytokine-producing capacity, Th-cell-polarizing ability and migration of DCs (Box 2). Understanding the actions of eicosanoids and their receptors on APC functions is crucial for the generation of efficient DCs for therapeutic purposes.

One of the most studied PGs is PGE2. This lipid mediator is produced by many cell types, including macrophages, DCs, fibroblasts, endothelial cells and some types of malignant cells. PGE2 can have an inhibitory or stimulatory action depending on the anatomical and tissue localization of DCs [1]. In peripheral tissues, PGE2 seems to have a positive role in activating DCs. However, once the cells have migrated to the secondary lymphoid organ, PGE2 has an inhibitory role, reducing the maturation of DCs, their expression of MHC class II molecules and their ability to activate T cells [32,33]. The reduction in MHC class-II expression by PGE2-treated DCs corroborates the well-known suppressive influence of the PGs on the immune response. Of the four PGE2 receptors, EP2 and EP4 have generally been associated with immunological modulation. EP2 and EP4 receptors mediate most, if not all, of the PGE2 effects on DCs [34–36].

Migration of DCs to secondary lymphoid organs can be regulated not only by PGE2 [37] but also by LTC4 [38]. Indeed, these lipid mediators stimulate surface expression of C-C chemokine receptor type 7 (CCR7), a chemokine that promotes DC migration [39]. COX-2-derived PGs affect the maturation and the function of human monocyte-derived DCs [40]. Cytokine release from DCs was also found to be modulated by PGs and LTs in an autocrine and paracrine manner [27,41]. PGE2 modulates interleukin (IL)-12 secretion by selectively inhibiting the production of IL-12p70 and stimulating that of IL-12p40 [42,43]. COX-2-derived PGE2 can inhibit the production of IL-12p70 via an IL-10-dependent mechanism [44]. LXs, which were the first eicosanoids to be identified and recognized as potential anti-inflammatory mediators, are able to inhibit the production of IL-12 by DCs and modulate immunity against microorganisms [45].

The effects of PGE2 on murine and human DCs are sometimes the subject of controversy. Kalinski *et al.* [42] demonstrated that addition of PGE2 to a cocktail of proinflammatory cytokines, such as IL-1β + tumour necrosis factor-α (TNF-α) ± IL-6 promotes human monocyte-derived DC maturation and alloantigen naïve CD4$^+$ T-cell stimulation. In the absence of PGE2, cytokines have no effect, suggesting that PGE2 acts as a cofactor in DC differentiation in the presence of proinflammatory cytokines. It should be noted that studies showing a proinflammatory role of PGE2 have been carried out on human DCs. PGD2, another COX-2-derived prostanoid, has an important role in modulating DC function by inhibiting DC production of IL-12, leading to Th2-polarized immune responses *in vivo* [46].

Macrophages

The major function of macrophages is the generation of cytokines that coordinate the immune response to infection. A key proinflammatory cytokine produced by macrophages is TNF-α. Several lines of evidence have shown that eicosanoids regulate macrophage inflammatory function. For example, macrophage-derived PGs act in an autocrine fashion to limit TNF-α production [47]. The effects of PGE2 on macrophages are suppressive for Th1 immune responses. Indeed, a study of zymosan-treated mouse peritoneal macrophages showed that PGE2 downregulates TNF-α production and upregulates IL-10 production through EP2 and EP4 receptor signalling [48].

Lymphocytes

Eicosanoids have various effects on T lymphocytes. It was recently reported that PGE2 inhibits mature T-cell proliferation and protects T cells from activation-induced cell death (AICD) [49]. The reduction of intracellular calcium release [50] and the inhibition of p59 protein tyrosine kinase activity [51] were proposed as mechanisms responsible for the observed decrease in T-cell proliferation. PGE2-mediated suppression of T-cell proliferation could also result from reduction in polyamine synthesis [52]. Furthermore, PGE2 might inhibit T-cell function by the induction of suppressive cells. Recently, Bryn *et al.* [53] showed that COX-2-derived PGE2 suppresses T-cell immune responses by inducing Foxp3$^+$ T regulatory cells. Indeed, PGE2 converts resting CD4$^+$CD25$^-$ T cells into Foxp3$^+$ T cells with a suppressive phenotype. Collectively, the effects of PGs on T cells appear to be suppressive, and this is well-established for PGE2.

LTs elicit variable responses depending on the lymphocyte population. The actions of LOX metabolites, HETEs and LTs on T lymphocytes are not well understood. It has been reported that LTB4 activates T cells that inhibit B-cell proliferation in Epstein-Barr virus (EBV)-infected-cord-blood-derived mononuclear cell cultures [54]. *In vivo*, LTB4 cooperates with chemokines and directs T-cell migration, particularly in the pathogenesis of asthma [55]. LTs could have a major role in thymic cell differentiation because these proinflammatory mediators are produced in the thymus.

The effects of eicosanoids on B lymphocytes are also not well characterized. When PGE2 is added to purified B lymphocytes, immunoglobulin (Ig) synthesis is decreased. This inhibition is linked to an increase in cAMP (forskoline elicits similar results) [56]. Physiologically, it is likely that Ig synthesis is regulated through T lymphocyte action. In autoimmune disorders, it is possible that PGE2 could increase autoantibody production by limiting the activity of T-suppressor lymphocytes. B-lineage cells can modulate the immune response by both producing and responding to PGE2 [1]. However, this lipid mediator is thought to act predominantly to induce a Th2 immune response by enhancing Ig-class switching and inducing IgE production from B cells [57].

Other cytotoxic cells

PGs have been shown to suppress natural killer (NK) cell function in number of studies. NK cells play crucial parts in immune responses against tumours or virus infections by generating type 1 cytokines and cytotoxicity responses. *In vivo*, natural cytolytic activities are strongly inhibited by PGE2 [58]. Synthesis of interferon γ (IFN-γ) by NK cells is

an important proinflammatory event, and PGE2 was found to suppress NK-cell IFN-γ synthesis, limiting innate inflammatory processes *in vivo* [59]. During type 2 dominant immune responses, such as allergic diseases, the activities of NK cells are often impaired. Type 2 immune-mediated diseases have been reported to be closely associated with local production of PGD2, which suppresses human NK cell function via signalling through the DP receptor [60].

Eicosanoids and immunopathology

AA-derived eicosanoids seem to have important roles in immunopathology and have been implicated in inflammation, autoimmunity, allergic diseases and cancer. Examples of diseases in which pathogenesis involve eicosanoids are summarized in Table 2.

Inflammation

PGs and LTs are endogenous mediators with potent biological activities in the pathogenesis of many inflammatory diseases. In chronic inflammatory conditions, the levels of eicosanoids are increased. Granulocytes, macrophages, neutrophils, platelets, mast cells and endothelial cells might be involved in eicosanoid production during inflammation. LTs, which are known to be potent proinflammatory eicosanoids, have vasomotor properties and induce contraction of smooth muscle [61,62]. During inflammation, these properties are associated with cardiovascular, renal, pulmonary and cutaneous manifestations. Conversely, PGE2 induces vasodilation and smooth muscle relaxation (deceasing peripheral resistance and blood pressure). Thus, the effects of PGs appear opposed to those of LTs, although the cardiovascular system is considered to be more sensitive to PGs than to LTs.

In general, during inflammation eicosanoids will be present and will act as proinflammatory molecules (PGH2), chemoattractants (LTB4), platelet aggregating factors (TXA2), contractors of smooth muscle (CysLTs) and modifiers of vascular permeability (LTs). PGs might act as both proinflammatory and anti-inflammatory mediators depending on the context, which is due in part to the array of EP receptors with different signal transduction pathways. LXs also appear to play an active part in controlling the resolution of inflammation by stimulating endogenous anti-inflammatory pathways [63–65]. Given their clinically relevant anti-inflammatory properties, targeting LXs might be worth investigating as an approach for the treatment of inflammatory diseases.

Autoimmune diseases

Pharmacological and genetic evidence has shown that eicosanoids have crucial roles in autoimmune diseases, such as rheumatoid arthritis (RA). In arthritis models, mice null for cPLA2, COX-2, PGE synthase, EP4 or IP receptors display reduced inflammation. In joint inflammation, intra-articular PGE2 is generated by synoviocytes and macrophages and has a proinflammatory role in the progression of RA [4]. This overproduction of PGE2 could also have an immunosuppressant function and could explain the observed low production rate of IL-2 by lymphocytes, upon which PGs might act either directly or through activation of CD8$^+$ suppressor cells [66].

Table 2. Examples of diseases in which pathogenesis involves eicosanoids

Pathology	Eicosanoids	Drugs	Refs
Asthma	Leukotrienes	LXA4 analogues	[72]
	Leukotrienes	Montelukast, Zafirlukast, Pranlukast	[70,98]
Pancreatic cancer	LTB4	LY293111	[80]
Colon cancer	PGE2	Celecoxib	[99,100]
		Atorvastatin	[101]
Lung cancer	PGE2	Celecoxib	[87,102]
Rheumatoid arthritis	PGE2	Celecoxib	[4]
		Rofecoxib	[103]

LTs are important mediators of acute or chronic joint inflammation. Many recent studies in mouse models have suggested a crucial role for LTB4 and its receptors in the development of inflammatory arthritis [67,68]. Inhibitors of LTB4 biosynthesis and LTB4 receptor function are protective in mouse models of RA. Mice deficient in LTB4 biosynthetic enzymes or LTB4 receptors are resistant to disease development. Using BLT1 knockout animals, Kim *et al.* [69] also showed a crucial role for BLT1 in arthritis.

Allergic diseases

Eicosanoids are well-known mediators of allergic diseases. In allergic models, immune manifestations are reduced in knockout mice for genes encoding cPLA2, 5-LO, DP1, DP2, BLT1 or CysLT1 and are exacerbated in $EP3^{-/-}$ knockout mice. Eicosanoids do not appear to act as immunomodulators during allergic responses but are released from cells during hypersensitivity responses and are responsible for clinical manifestations incuding bronchial spasms, diarrhoea and blood pressure variations. The eicosanoids involved (PGD2, PGF2α, LTs) are not stored in the cells but are produced acutely during the allergic responses, in which fixation of the allergen on IgE triggers activation of PLA2, producing AA that is then metabolized by COX or LOX pathways. Amongst LOX metabolites, LTC4, LTD4 and LTE4 are the key mediators (hence their original name: slow reacting substance of anaphylaxis). This is explained by (i) the presence of allergen-specific IgE and (ii) the presence of mast cells in lung tissue (which is not limited to asthmatic subjects).

Asthma

Eicosanoids are also key mediators in the pathogenesis of asthma. LTs are potent proinflammatory mediators that stimulate fibroblast chemotaxis, proliferation and collagen synthesis. Anti-LT agents are beneficial in patients with aspirin-sensitive asthma. The efficacy of antagonists to CysLT1 in asthma validates the importance of CysLTs in this disease [70]. PGs normally have both bronchoconstrictive and bronchoprotective effects, but bronchoconstriction mediated by PGD2 and PGF2α occurs in asthmatic patients rather than in healthy subjects. As already mentioned, LXs were the first agents to be identified and recognized as potential anti-inflammatory endogenous lipid mediators [71]. LXs counter-regulate the proinflammatory actions of LTs and activate resolution of the inflammatory response [5,72]. At least two classes of

receptors, CysLT1 receptors and aspirin-triggered LXA4 (ALX) receptors, can interact with LXA4 and LXA4 analogues to mediate their biological actions. The pivotal role of LXs in the lung is airway homeostasis, and LXs have therefore been investigated as part of a novel, multi-pronged approach for treating human asthma [72,73].

Cancer
Clinical and pharmacological studies have documented the importance of eicosanoids in the development of many cancers [74,75]. In knockout mice for genes encoding cPLA2, COX-1, COX-2, PGE synthase and EP receptors, tumour development is reduced and, conversely, in PGD synthase gene knockout mice, tumour development is increased [76–79]. The two enzymes COX-2 and 5-LO, as well as the metabolites they generate, have been recognized as essential regulators of cancer development and progression in several different tumour types [80–83]. The aberrant expression and function of several prostanoid synthetic enzymes has been documented in cancer [6]. Overexpression of COX-2 and its major metabolite PGE2 has been noted in many cancers, including cancers of the breast, colon and prostate [82]. COX-2-derived PGE2 can stimulate cellular proliferation and angiogenesis, reduce apoptosis, enhance cellular invasiveness and inhibit immune surveillance. Each of these effects contributes to the pathogenesis and progression of tumours [84,85]. Although PGE2 and its receptors play a predominant part in promoting cancer progression, the other COX-2-derived mediator implicated in oncogenesis is TXA2, which was reported to promote angiogenesis [86]. Targeting these downstream prostanoids might provide a new avenue of investigation for the inhibition of tumour progression. Novel strategies for the treatment of cancer by targeting eicosanoids have been recently proposed [87]. Although the overall results of a randomized phase II trial were not particularly encouraging, targeting eicosanoids is considered to have potential as a therapeutic approach for cancer [87,88]. Further studies are warranted, particularly for the newly discovered PGD2 metabolite 15-deoxy-PGJ2, which has emerged as a potent anti-tumour agent [89].

Tumour-induced immunosuppression is a fundamental problem in cancer biology and immunotherapy. Increasing evidence suggests that tumours evade immunosurveillance by production of immunosuppressive factors that act on DC function. PGE2-induced inhibition of DC differentiation and function appears to be a key mechanism involved in cancer-associated immunosuppression [90,91]. Reduced T-cell and DC function is related to COX-2 overexpression and PGE2 production in patients with breast cancer [92]. Therefore, the relationship between PGE2 and tumour progression is potentially important. Further understanding of the mechanisms of COX-2 expression in tumourigenesis might reveal new diagnostic, prognostic or therapeutic markers and facilitate future development of targeted strategies for cancer prevention and/or treatment.

Targeting eicosanoids
Both COX and LOX pathways are of particular clinical relevance (Table 2). The COX pathway is the major target

for non-steroidal anti-inflammatory drugs (NSAIDs), the most popular medications used to treat pain, fever and inflammation. NSAIDs inhibit the production of primary prostanoids by blocking the active site of COXs. Although their anti-inflammatory effects are well known, their long-term use is associated with gastrointestinal (GI) complications, such as ulceration [93]. For this reason, COX-2 selective inhibitors (Coxibs) have been developed as anti-inflammatory agents to decrease the risk of GI toxicity.

As mentioned above, targeting downstream prostanoid synthetic enzymes might provide a new approach for inhibiting tumour progression. Various epidemiological and laboratory studies have indicated that NSAIDs might reduce the risk of cancer (colorectal cancer in particular) [94–97]. The therapeutic contribution of COX-2 specific inhibitors has yet to be fully evaluated, and these agents might delay the healing of duodenal ulcers and interfere with important physiological COX-2 functions.

The clinical pharmacology of targeting eicosanoid receptors in humans is still very limited because (i) eicosanoids are short-lived compounds, (ii) pharmacological characterization and clinical applications of eicosanoid receptors are still under development and (iii) given the extraordinary complexity of eicosanoid effects, it is difficult to investigate the specific effects of a particular agonist or antagonist through systemic and local administration. Nonetheless, more refined investigations into the targeting of eicosanoids and eicosanoid receptors might result in an increase of specificity and a decrease in the side effects associated with the pharmacological regulation of the eicosanoid pathways in human disorders and thus lead to promising therapies in the future.

Concluding remarks
The biological effects of eicosanoids are particularly important in immunity and inflammation. The roles of eicosanoids in biology and pathology are diverse and complex. This diversity is due to their variety in composition, targets and GPCR signalling. Further understanding of eicosanoid biology will be important for understanding the organ-specific effects of these unique compounds in health and disease. Several outstanding questions in this field are listed in Box 3.

Mice deficient in each of the eicosanoid receptors have been generated and have been investigated in various

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Box 3. Outstanding questions

- What is the biological significance of the coexpression of various eicosanoid receptors in the same cell or organ?
- What are the primary mechanisms by which eicosanoids modulate immune response and induce immunopathologies?
- How can eicosanoid receptors trigger intracellular signalling during inflammatory conditions, and what is the connection between chronic inflammatory diseases and neoplastic transformation?
- Can specific expression patterns of eicosanoids or eicosanoid receptors be used as biomarkers and diagnostics for inflammatory diseases and cancer?
- What are the most effective approaches for targeting eicosanoids: receptor signalling or eicosanoid biosynthetic enzymes?
- What are the effects and potential risks of NSAID-based therapies?

experimental models of diseases, such as arthritis, asthma and cancer. These studies have revealed roles for eicosanoid receptor signalling in various pathological conditions. The differences between humans and mice should obviously be taken into consideration, and any extrapolation from the mouse models to human pathologies should be performed with careful reservation. However, new and often unexpected insights into the biology and clinical importance of AA-derived metabolites are continuing to emerge, particularly concerning the role of eicosanoids in cancer, inflammatory diseases and immunity. We are exploring the immunoregulatory function of eicosanoids and especially their effects on DC-mediated immunity, considering that DC–T-cell interactions provide a target for pharmacological interventions. The potential relevance of eicosanoids in inflammation, cancer or disease susceptibility and individual variations in drug responses will also be an important area for investigation. Ultimately, it is hoped that further understanding of the mechanisms by which eicosanoids induce immunological disorders might provide a rationale for the development of new anti-inflammatory therapeutic approaches for cancer, asthma and arthritis.

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