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Eicosanoid Storm in Infection and Inflammation

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Abstract

Controlled immune responses to infection and injury involve complex molecular signaling networks with coordinated and often opposing actions. Eicosanoids and related bioactive lipid mediators derived from polyunsaturated fatty acids constitute a major bioactive lipid network, which is among the most complex and challenging pathways to map in a physiological context. Eicosanoid signaling, similar to cytokine signaling and inflammasome formation, has been viewed as primarily a pro-inflammatory component of the innate immune response; however, recent advances in lipidomics have helped to elucidate unique eicosanoids and related docosanoids with anti-inflammatory and pro-resolution functions. This has advanced our overall understanding of the inflammatory response and its therapeutic implications. The induction of a pro- and anti-inflammatory eicosanoid storm through the activation of inflammatory receptors by infectious agents is reviewed.

Eicosanoids are locally acting bioactive signaling lipids derived from arachidonic acid and related polyunsaturated fatty acids (PUFAs) that regulate a diverse set of homeostatic and inflammatory processes^{1,2} linked to numerous diseases. Inhibiting the formation or receptor-mediated actions of classical eicosanoids (that is prostaglandins and leukotrienes) by aspirin and other **non-steroidal anti-inflammatory drugs (NSAIDs)**, by the leukotriene inhibitor zileuton, and by leukotriene receptor antagonists during inflammation remains a prevailing strategy to alleviate pain, swelling, fever and asthmatic conditions. However, pleiotropic effects are becoming increasingly appreciated for most eicosanoids and their related **docosanoids**.

Hundreds of structurally and stereochemically distinct eicosanoid species can be made from arachidonic acid and other ω 6-derived PUFAs such as dihomo- γ -linolenic acid (DGLA) whose origin is the 18-carbon essential fatty acid linoleic acid as well as ω 3-derived PUFAs from α -linolenic acid (ALA) including eicosapentaenoic acid (EPA) which can be further elongated to docosapentaenoic acid (DPA) and further desaturated to docosahexaenoic acid (DHA). Although the physiological roles of only a few of the eicosanoid and related docosanoid species are well understood, some of the agonists and receptors that activate **inflammasome** formation and the cytokine storm that accompanies infection^{3,4} appear to

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also initiate the release of arachidonic acid and related PUFAs, resulting in an eicosanoid storm⁵.

Mass spectrometric-based lipidomic profiling⁶ is now being used to identify, monitor and quantify hundreds of distinct eicosanoid and related PUFA species⁷ that appear to be involved in infection and inflammation, as well as in its resolution⁸. These lipidomics approaches, sometimes referred to as “eicosadomics”, facilitate the identification of the ‘eicosadome’ and can be used to accurately determine global changes in cellular lipids during specific physiological processes. Lipidomics is currently being used to more effectively screen for potential disease biomarkers⁹, and to provide scientists with a mechanistic understanding of eicosanoid biosynthesis and signaling at the cellular and multicellular tissue level. Integrating the latest genomics (transcriptomics), proteomics and lipidomics of pro-inflammatory and pro-resolution eicosanoid and related PUFA production should lead to new insights on infection and inflammation.

In this review, we will provide and discuss our current understanding of cellular eicosanoid metabolism^{2,10–12} and signaling, as well as their physiological consequences, including homeostatic, pro-inflammatory and resolving functions. We will also consider the importance of subcellular enzyme compartmentalization and stimulatory contexts involved in the regulation of eicosanoid metabolism^{5,13–16}. Although the production of cytokines is considered a hallmark of infectious disease, we will highlight the importance of the accompanying temporal production of both pro-inflammatory and anti-inflammatory (pro-resolution) eicosanoids and related docosanoids during the initiation and resolution of infection. The recent progress in lipidomic monitoring of arachidonic acid and related PUFA metabolism provides us with the comprehensive perspective needed to tackle the challenges of therapeutic targeting of eicosanoid pathways, which range from traditional enzyme inhibition^{17,18} with NSAIDs and prostanoid mimetics, to “natural” fish oil ω 3 fatty acid supplementation^{19,20}.

Eicosanoid biosynthesis and function

Eicosanoids arise from the oxidation of arachidonic acid and related PUFAs by cyclooxygenase²¹ (COX), lipoxygenase²² (LOX), and cytochrome P450 (CYP) enzymes, or via non-enzymatic free radical mechanisms (Figure 1; Supplementary information (Figures 1, 2, 3)). Although eicosanoids are most frequently associated with inflammation, they also have homeostatic functions (Box 1).

The vast collection of lipids produced by these eicosanoid and related biosynthetic pathways is the starting point for *in vivo* eicosanoid signaling networks in cells through their cognate receptors (Figure 1; Table 1). Cells are highly selective as to the specific eicosanoids they make but the amounts are altered by the activation state and the physiological conditions of the specific tissues in which they reside. For example, macrophages produce an array of arachidonic acid-derived prostaglandins in response to **Toll-like receptor** (TLR) stimuli but the specific prostaglandins and their quantities produced after stimulation differ dramatically between macrophages of different tissue origin and isolation method — for example, thioglycollate-elicited peritoneal macrophages and bone marrow-derived macrophages, as

well as between primary macrophages and a transformed macrophage cell line²³. Furthermore, the expression of receptors for specific eicosanoids is also cell and tissue specific.

Studies of eicosanoids in inflammation have mainly focused on the signaling pathways activated by lipids produced by the COX enzymes, since they collectively elicit the cardinal signs of inflammation, including heat, swelling, redness, pain, and loss of function²⁴. Understanding the physiological roles of these lipids is complicated by the differing roles they play in different tissues; for example, the binding of prostaglandin E₂ (PGE₂) to its cognate GPCR receptors, the EP receptor family, in neurons causes pain associated with inflammation, whereas autocrine EP signaling by PGE₂ in macrophages (and possibly other leukocytes) can downregulate TNF and up-regulate IL-10 production²⁵, leading to a net reduction in inflammatory signals.

While eicosanoids of the COX pathway control a wide spectrum of processes, the 5-LOX pathway (Figure 1) is more specifically operative during inflammation to promote bronchoconstriction²⁶ and leukocyte recruitment to sites of tissue damage²⁷. While the functions of 5-LOX-initiated leukotrienes in asthma and allergy are well understood, definitive biological functions for the intermediate metabolites 8-hydroperoxyeicosatetraenoic acid (8-HPETE), 12-HPETE and 15-HPETE, as well as their hydroxyeicosatetraenoic acid (HETE) products have not been identified, but some may be ligands for **peroxisome proliferator-activating receptor- α** (PPAR α)²⁸ and PPAR γ ²⁹, which induce anti-inflammatory effects and modulate liver \times receptor (LXR; which regulates cholesterol homeostasis). Thus, metabolites of specific LOXs may be anti-inflammatory, but the interconnections between LOXs and COXs during inflammation confound simple strategies to inhibit individual pathways for therapeutic gain. Despite a direct role for many of the LOX-derived mono-hydroxylated fatty acids produced by a single enzyme, in combination, numerous families of more complex di- and tri-hydroxylated fatty acids (**specialized pro-resolving mediators; SPMS**) are produced by LOX and COX enzymes that possess remarkably potent and specific binding to GPCRs that accelerate bacterial clearance, neutrophil clearance, and turn on anti-inflammatory cytokine programs.

The CYP pathway (Figure 1) comprises a large number of enzymes that contain a heme iron, and many CYPs are expressed in the liver, but also in other tissues where they inactivate and eliminate toxins and metabolites. The most upstream CYPs in the eicosanoid pathway convert arachidonic acid to epoxyeicosatrienoic acids (EETs) or ω -HETEs², which are thought to be anti-inflammatory, whereas the downstream diHETEs (which can be formed by soluble epoxide hydrolase (sEH)) are thought to be pro-inflammatory or inactive. Bioactive functions for the ω -HETEs are not well understood, as no cognate receptor or second messenger has been identified to date^{2,30}. It is also important to clarify that epoxidation is essential for the formation of all **SPMs** and thus, in addition to LOX enzymes, some CYPs and sEH may be partially responsible for the synthesis of SPMs. Clearly, additional work is needed to identify the physiological roles of all the eicosanoids and related PUFAs as well their receptors, and in particular their pro-inflammatory and anti-inflammatory functions. Systematic characterization of prostaglandin and leukotriene structures, biosynthetic pathways, natural receptors and biological functions have resulted in

the production of new drug classes in the form of analogs, as well as receptor and enzyme inhibitors. These therapies that target eicosanoids have afforded substantial improvements for treating inflammatory symptoms including swelling and pain, although more chronic diseases, like arthritis and atherosclerosis, and more life-threatening pathogenic diseases are largely unaffected by the inhibition of eicosanoids. As many additional mediators derived from PUFAs during infection and inflammation have continued to be identified and characterized, there is now a greater focus on determining which of these lipid mediators enhance specific aspects of host protection and which mediate a return to homeostasis. Along with regulation of anti-inflammatory responses, specific eicosanoid mediators have been associated with enhancing pathogen clearance, neutrophil clearance, and antibody-mediated immune responses.

Prostaglandins and leukotrienes are produced rapidly after inflammatory initiation and promote the early induction of oedema from postcapillary venules. While this occurs naturally to mediate complement and leukocyte recruitment to an acute site of injury, the eicosanoid-mediated response can be overwhelming and life threatening to the host during septic or toxic shock. For example, prostaglandins produced via COX1 during inflammasome activation have recently been shown to contribute to excessive vascular leakage and lethality in mice and constitute part of a major pro-inflammatory eicosanoid response to infection³¹. Also, dual inhibition of COX2 and 5-LOX with flavocoxid has been shown to improve survival in mice after **caecal ligation and puncture**³², with a reduction in the levels of circulating PGE₂ and LTB₄, an increase in LXA₄ expression, and a reduction in lung and liver **myeloperoxidase** (MPO) levels.

Cellular control of eicosanoid biosynthesis

Phospholipase A₂

The majority of eicosanoid metabolism requires free arachidonic acid, but it is primarily stored in an esterified form. Phospholipase A₂ (PLA₂) enzymes are critical for increasing the levels of free arachidonic acid for metabolism and eicosanoid biosynthesis under most physiological conditions but particularly following inflammatory cell activation. Three members of the PLA₂ superfamily have been most implicated in cellular eicosanoid production: cytosolic calcium-dependent PLA₂ (cPLA₂), cytosolic calcium-independent PLA₂ (iPLA₂), and secreted PLA₂ (sPLA₂). iPLA₂ is thought to be the primary PLA₂ involved in most daily cellular functions, particularly membrane homeostasis and remodeling^{16,33} and constitutively generating a low level of free fatty acids with relatively minimal specificity for the particular esterified fatty acid, but may include release of arachidonic acid. cPLA₂ is largely inactive during homeostatic conditions; but when activated by TLR, **purinergic** (a Ca²⁺ mobilizing agonist), and other receptors initiated during an infection or inflammatory response, it translocates to the perinuclear and ER membranes, where it hydrolyses arachidonic acid-containing phospholipids, leading to pro-inflammatory eicosanoids as well as the related ω3 PUFAs EPA, DPA and DHA that are precursors for anti-inflammatory **resolvins**²⁰. sPLA₂ is an inducible enzyme that augments cPLA₂ function to control the magnitude and duration of elevated free fatty acid levels including arachidonic acid³⁴.

As the most upstream regulators of eicosanoid biosynthesis, PLA₂s regulate the eicosanoid response during different phases of an inflammatory response, and likely do so through various receptor-mediated cues (see below). Indeed, the activation of cPLA₂ was shown to be responsible for the storm of pro-inflammatory eicosanoids that accompanies inflammasome formation induced by systemic flagellin or anthrax lethal toxin³¹. This study highlights the fact that a specific branch of the eicosanoid pathway, namely prostaglandins through COX-1, is life threatening when produced systemically rather than acutely. The specialized delivery of autocoids to an infectious site can therefore breakdown during severe infections and supports the use of COX-1 NSAIDs during severe traumas and infections, while chronic diseases require more refined therapies.

Functional enzyme coupling

Since free fatty acids and oxygenated eicosanoids and related PUFAs can rapidly diffuse out of the cell^{1,35} or become reincorporated within membrane lipids, and since activated PLA₂s are concentrated at specific organelle interfaces, free arachidonic acid and other fatty acid concentrations exist as gradients that restrict most downstream eicosanoid metabolism only to sites in very close proximity to PLA₂ activity. For this reason, the co-localization of downstream enzymes in relation to the immediate substrate pool is critical for effective bioactivity and resultant signaling by eicosanoids. Similarly, the close proximity of different cell types to one another is required to create intercellular communication pathways for distinct **metabolons** and eicosanoid profiles at the site of inflammatory episodes.

The COX pathway has received the most attention regarding the tight co-localization of PLA₂ enzymes with downstream enzymes within a cell, defined as functional coupling¹⁴ (Figure 2). Since cPLA₂ predominantly translocates to the perinuclear membrane and ER, downstream enzymes that are also expressed at, or that can migrate to, these sites can preferentially participate in the metabolism of arachidonic acid. Functional coupling of thromboxane A synthase (TXAS) and PGD synthase (PGDS) with COX1, which all partially co-localize to the ER, has been shown to preferentially produce the eicosanoids thromboxane A₂ (TxA₂) and PGD₂ during short-term stimulation of rat peritoneal macrophages³⁶. Furthermore, microsomal PGE synthase 1 (mPGES1) and PGIS are coupled with COX2 at the perinuclear membrane, and preferentially produce PGE₂ and PGI₂ during the later phase of the LPS-induced response (3–24 hours of stimulation)^{36,37}.

Another example is the 5-LOX pathway, where 5-lipoxygenase-activating protein (FLAP; which appears to be constitutively present and facilitates transfer of arachidonic acid substrate to the 5-LOX active site) is responsible for coupling of cPLA₂ to 5-LOX at the perinuclear membrane. Note, both cPLA₂ and 5-LOX are Ca²⁺-dependent. Furthermore, the activation-dependent formation of leukotriene C₄ (LTC₄) and LTB₄ is dependent on distinct complexes of LTC₄ synthase (LTCS) with 5-LOX at the outer nuclear membrane and LTA₄ hydrolase (LTAH) with 5-LOX at the inner nuclear membrane, respectively³⁸, giving rise to two potent but distinct inflammatory mediators.

Understanding these coupling issues underlie the challenge of modulating eicosanoid biosynthesis and function during inflammation because of the dynamic changes in eicosanoid enzyme expression and their subcellular trafficking. A number of these dynamic

changes have been recently documented by combining experimental and computational approaches³⁹: in this study essentially complete lipidomics monitoring of eicosanoids was used with kinetic modeling to accurately predict the fluxes and temporal changes in the quantities and composition of cyclooxygenase and lipoxygenase metabolites (based on enzyme transcript expression and functional coupling) in macrophages during stimulation of the TLR-4 and/or the P2×7 purinergic receptor, as well as in the presence of COX1- and COX2-specific inhibitors³⁹. This study demonstrated differential coupling of COX1 and COX2 with downstream synthases and proves that **fluxomics** modeling can predict inflammatory mediator levels in macrophages as a function of time, even with synergistic activation by TLR-4 (priming) followed by a P2×7 agonist at a later time. Thus, the systems view of eicosanoids provided by lipidomics is improving our ability to predict outcomes of specific enzyme inhibition at the cellular level, and potentially at the physiological level as a computational tool to predict outcomes of drug candidates.

Transcellular eicosanoid metabolism

The biosynthesis of eicosanoids and related lipid species is dramatically increased when cells are exposed to inflammatory stimuli that activate PLA₂ and certain downstream enzymes. Often pathway enzymes are robustly upregulated to enhance fatty acid metabolism and eicosanoid biosynthesis; the clearest examples are COX2 and mPGES1. Most cell types produce negligible amounts of eicosanoids in the steady state, and when activated produce only a small number of distinct eicosanoids, which is dictated by the specific enzymes that are expressed in that cell type²³. This physiological compartmentalization of the expression of specific eicosanoid biosynthetic enzymes to specific cell types (e.g., macrophages) greatly limits the production of eicosanoids and related lipids. During an immune response, this compartmentalization of specific enzymes can be overcome by the convergence of different cell types at an inflammatory site. Such conditions allow for the synthesis of more complex molecules by cell–cell transfer of intermediate eicosanoid metabolites and/or the metabolism of intermediate substrates, a process known as transcellular biosynthesis⁴⁰. Transcellular biosynthesis has a role in the synthesis of several COX and 5-LOX metabolites and is particularly important in the formation of ‘complex’ eicosanoids formed by multiple LOX activities.

In isolation, a number of cells express primarily one or two eicosanoid-producing enzymes (e.g. 12-LOX in platelets, 5-LOX in neutrophils, and 15-LOX/COX-2 in epithelial/endothelial cells); however combinations of these cells cooperatively produce lipoxins that are relevant in inflammatory contexts⁴¹, while other SPMS are produced through the same or similar mechanisms. The production of epimers of lipoxin A₄ (LXA₄) and LXB₄ (aspirin-triggered lipoxins) that are less prone to degradation by prostaglandin dehydrogenase (PGDH) was first demonstrated using co-cultures of neutrophils with endothelial cells, in which the upstream metabolite 5(S)-HpETE produced by 5-LOX in neutrophils was converted to lipoxins by acetylated COX2 that upregulated 15(R)-HpETE, 15-epi-LXA₄ and 15(R)-LXB₄ production in the endothelial cells by treating them with aspirin⁴². The conversion occurs because acetylation of the active site of COX-2 fills its pocket to inhibit the normal COX activity producing prostaglandins thereby promoting 15(R)-HpETE synthesis rather than 15(S)-HpETE; thus aspirin provides a novel activity not possible with

other NSAIDs (which bind but do not acetylate COX). Lipoxins promote the resolution of inflammation in humans, which is increased by low-dose aspirin⁴³, and in mouse models of arthritis through the upregulation of 15-LOX activity, as well as by PGE₂, both of which are derived from COX2^{44,45}.

Recently, it was found that activation of two or more receptors, such as TLR and purinergic receptors, which are known to induce inflammasome formation, also triggers lipoxin synthesis in an immune cell⁵. In addition, cPLA2 regulates **eicosanoid class switching** — that is, switch the class of eicosanoids produced by a cell from pro-inflammatory prostaglandins to anti-inflammatory lipoxins — in a parallel process to inflammasome formation and caspase activation⁵ (Figure 3). These data suggest that the same receptor-mediated events that lead to inflammasome formation might also trigger an eicosanoid storm that in addition to pro-inflammatory mediators can include mediators that trigger the initiation of resolution.

This receptor-mediated single cell formation of lipoxins likely provides a means for cells including macrophages to efficiently enhance production without the need for multiple cell types via transcellular routes, largely through co-localization of numerous enzymes, including COX2, on particular membranes such as the endoplasmic reticulum and nuclear envelope⁵. Thus, aspirin not only enhances formation of the lipoxin precursor (15(R)-HETE), but also enables concentrated positioning of 15(R)-HETE in close proximity to activated 5-LOX for maximal conversion in a receptor-activated cell.

Further exploration of the specific association of these enzymes will likely provide answers to other related and important questions, for instance, how precursors of SPMs are efficiently transferred via microparticles to other cells for processing. Microparticles shed from neutrophils have been shown to inhibit pro-inflammatory actions of macrophages activated by zymosan or LPS⁴⁶. More recently, these microparticles were found to contain the DHA derived SPM precursors 14-hydroxydocosahexaenoic acid (14-HDHA) and 17-HDHA and could enhance **efferocytosis** of apoptotic neutrophils⁴⁷. If SPM production involves PLA₂-mediated mechanisms, for example a role for cPLA₂ in releasing arachidonic acid for lipoxin synthesis during inflammasome activation or releasing DHA for SPM synthesis, the effectiveness of nanomedicines that mimic microparticles could be enhanced. Of note, a “resolving sPLA₂” has been identified as having a role in the production of SPMs and the resolution of skin inflammation⁴⁸ and provides a potential candidate for action on microparticles for efficient delivery of SPM precursors to final lipoxygenation pathways.

Lipidomic perspective on the inflammatory process

The cell-specific compartmentalization of eicosanoid pathway enzymes in macrophages, neutrophils and other immune cells can be exploited using lipidomic strategies to assess the homeostatic and inflammatory environment. An elegant example of this approach comes from a study that demonstrates how 12/15-LOX in resident peritoneal macrophages regulates the phenotype of leukocytes entering and exiting the peritoneal cavity during sterile inflammation. Here, the disappearance and reappearance of resident macrophages, as well as the appearance and clearance of infiltrating macrophages, corresponded to the steady fall and eventual rise in the levels of 12-HETE and other LOX products⁴⁹. Thus, by using

temporal lipidomics or fluxomics³⁹ monitoring of specific eicosanoids, one can follow the progression of leukocyte trafficking as the infection progresses.

While the presence of specific leukocytes is commonly used as an indicator of disease severity, lipidomic profiles can potentially be used in addition to cell-specific protein markers as a more complete readout of phenotype and disease severity, but with the added benefit of assessing dietary, metabolic and biosynthetic factors (the quantities of eicosanoids and related molecules derived from EPA, DHA, and other fatty acids). A recent study using a macrophage-specific knockout of NCoR, which is a co-repressor associated with NF- κ B-specific genes, showed decreased inflammatory markers and insulin sensitization in obese mice compared with control mice⁵⁰. Using quantitative profiling, this study showed that the expression of omega-3 fatty acids, which are the precursors of many anti-inflammatory and pro-resolution mediators, were increased, a phenotype that protects against high fat diets. This illustrates the use of quantitative lipidomics to monitor disease phenotypes and severity.

The complexity of eicosanoid biosynthesis is layered in the dynamic expression and intracellular compartmentalization of the biosynthetic machinery that is time-, condition-, and cell type-dependent. Generally, the upregulation of COX2 and mPGES1 begins early during inflammatory programs in cells such as macrophages, endothelial cells and dendritic cells to form PGE₂, whereas IL-4- and PGE₂-mediated increases in 12/15-LOX begin at later stages in the activation of macrophages, neutrophils and several other cell types that result in increased formation of SPMs that stimulate resolution. The “inactivation” of prostaglandins by downstream enzymes may also function to produce anti-inflammatory PPAR agonists⁵¹, and similar downstream mechanisms may also exist for other lipid mediators that are less well understood. This model of progression is tightly regulated and will require further dissection in specific disease states to identify specific intervention strategies.

Eicosanoids in infection and inflammation

A recurring theme in the case of *Mycobacterium tuberculosis* infections is that PGE₂ inhibits **necrotic cell death** in macrophages resulting in the promotion of pathogen resistance and host protection, while a specific level of TNF α dictated by a delicate balance between LTB₄ and LXA₄ is critical for maximal control of infection^{52,53}. Although the protective effect of PGE₂ in *M. tuberculosis* infection has been linked to the inhibition of the type I IFN response⁵⁴, PGE₂ has been shown to compromise immunity to influenza A virus by inhibiting macrophage antigen presentation and T cell immunity⁵⁵. While the roles of different eicosanoid species are emerging as enhancers of various aspects of inflammation and innate immunity in general, skewing the profile of these mediators to effectively treat specific pathogens is likely and will require multiple strategies in line with personalized medicine.

Genetic variability also plays a role in how the host is affected by pathogenic exposure. For example, DBA mice are resistant to developing arthritis associated with **Lyme disease** following *Borrelia burgdorferi* infection while C3H mice exhibit prolonged inflammation

and delayed resolution despite a similar control of bacterial loads; these differences have been profiled with lipidomics⁵⁶. Resistant DBA mice expressed high levels of protectin 1 (PD1), resolvin D1 (RvD1), hepxilin A3 (HXA₃), PGE₂, and 15-keto PGE₂ levels in ankle joints while C3H mice expressed high LTE₄ levels. This eicosanoid expression pattern was largely sustained for the duration of the disease course, suggesting a defect in eicosanoid class-switching and in anti-inflammatory and pro-resolving mediator synthesis in Lyme disease-susceptible C3H mice. These results are in line with previous studies demonstrating that inflammation resulting from *B. burgdorferi* fails to resolve with 5-LOX⁵⁷ or COX2⁵⁸ ablation; loss of 5-LOX in particular led to decreased macrophage-mediated efferocytosis and phagocytosis of spirochetes by macrophages and neutrophils.

An example of the importance of eicosanoids and their metabolism in the sequelae of disease-associated inflammation comes from transcriptomic analysis of a cystic fibrosis disease phenotype, where subsequent lipidomic analysis of eicosanoids helped to identify the PGE₂ metabolite 15-keto-PGE₂ as an endogenous PPAR γ agonist and a potential pharmacological therapeutic⁵¹ that suggests an important anti-inflammatory action of prostaglandin inactivation. Interestingly, another reported PPAR γ agonist, 15-deoxy-PGJ₂, has recently been shown to inhibit peritoneal NLRP3-induced IL-1 β secretion and leukocyte recruitment⁵⁹, although the direct mechanism has yet to be identified. The resolvins RvD1 and RvD5 have recently been shown to reduce antibiotic requirements for microbial clearance in mice⁶⁰ through their ability to synergize with protectins and increase bacterial phagocytosis in human macrophages (Box 2); these data suggest that therapies derived from natural pro-resolving responses can be applied to counteract antibiotic resistance, suggesting that eicosanoid related signaling has bactericidal implications for infection. Eicosanoids like lipoxins, along with these DHA-derived SPMs, appear to be enhancers of microbial clearance that arise after microbicidal components including complement and neutrophils have been deployed partly through the actions of prostaglandins and leukotrienes.

Recent studies of influenza virus infections in mice have integrated transcriptomics, proteomics of cytokine formation, and lipidomics with disease progression to isolate promising therapeutics⁶¹ and biomarkers⁶² such as protectin D1, one of the many pro-resolution mediators derived from omega-3 fatty acids in fish oil (Box 2). Samples from human patients with high clinical scores and increased levels of cytokines and chemokines also contained significantly higher percentages of eicosanoid metabolites from the LOX and CYP pathways, including those derived from EPA and DHA, compared with healthy individuals. The amounts of individual lipid mediators, including PGE₂, LTE₄, and 17-hydroxy-DHA (17-HDHA; a 15-LOX derived product of DHA which is a stable form of 17-HpDHA, the precursor to all D-series resolvins and to PD1), were increased in nasopharyngeal lavages from those patients with high cytokine levels and severe symptoms of influenza infection compared to patients with low and medium cytokine production and symptom levels⁶². More recently, 17-HDHA has been shown to increase the levels of antigen-specific antibody levels when administered to mice in combination with H1N1 influenza virus-derived hemagglutinin, or with ovalbumin, which resulted in increased resistance to live H1N1 infection⁶³. These findings suggest that specific lipid-derived components of potential or existing adjuvants, such as in the oil of Freund's adjuvant, could

be further refined for therapeutics. While some eicosanoids and related species are established mediators that progressively promote the neutralization and clearance of pathogens and trafficking/clearance of leukocytes, understanding which of these molecules and how they are biosynthesized and signal to link innate and adaptive immunity remains unclear, but the studies just mentioned highlight some potential pathways that may be utilized for signaling during a deluge of lipid mediators.

Therapeutic Interventions

Drugs that target eicosanoid pathways (Figure 4) have been used for over a century; aspirin is the oldest of the numerous effective NSAIDs that have been marketed. The discovery that NSAIDs inhibited prostaglandin synthesis through the inhibition of COX¹⁷ have led to the development of COX1- and COX2-specific NSAIDs and these molecules have helped to determine the homeostatic importance of this enzyme family (Box 1). In addition, the 5-LOX pathway is a major drug target for treatment of allergic and asthmatic conditions (Figure 4) and the 5-LOX inhibitor zileuton can inhibit all downstream metabolism. Furthermore, leukotriene receptor antagonists (LTRAs), such as montelukast, inhibit the actions of cysteinyl leukotriene receptor 1 (cysLT₁), including bronchoconstriction during inflammatory pulmonary events⁶⁴. The inhibition of COX enzymes by NSAIDs results in a switch to arachidonic acid oxidation by 5-LOX and increased signaling by cysLTs, and therefore combining 5-LOX inhibitors and/or LTRAs with NSAIDs may be more effective. Other LOX pathways as well as CYP pathways, including soluble epoxide hydrolase (sEH) (Figure 4), are also being pursued as drug targets for various inflammatory diseases.

The most upstream target for eicosanoid mediators would be PLA₂, but clinical trials for cardiovascular indications using a sPLA₂ inhibitor [clinicaltrials.gov/, identifier: NCT00743925 and NCT01130246] or a lipoprotein-associated PLA₂ inhibitor [clinicaltrials.gov/, identifier: NCT00799903 and NCT01000727] were unsuccessful, and a clinical trial for a cPLA₂ inhibitor [clinicaltrials.gov/, identifier: NCT00396955] was stopped because it exhibited the same side effect profile as non-selective NSAIDs¹⁶. Future studies with plasma lipidomics monitoring should be able to identify “problematic” side products at an earlier stage in the drug discovery process, especially given the challenges of drug discovery when there is a complex network of enzymes involved. The use of mass spectrometry to help define the global outcomes of lipid profiles in relation to different inflammatory responses is likely to refine the specific eicosanoid targets and reveal which to avoid. For example, while inflammatory bowel disease is an inflammatory condition and standard treatments include the long-term use of salicylate derivatives, aspirin and other traditional NSAIDs are contraindicated.

Though drugs that target COX and 5-LOX pathways comprise arguably the most widely consumed drug class, they are not actually able to stop or resolve innate immune responses alone. This is understandable because cytokines, chemokines, and other bioactive mediators are also critical players in immune signaling. Furthermore, while this review has focused on eicosanoids produced from arachidonic acid, many of the enzymes discussed are also capable of acting on the essential fatty acids containing 18 carbons (linoleic and linolenic acid) as well as on more unsaturated and longer fatty acids (docosanoids) including fish oil-

derived ω 3 fatty acids (EPA, DPA, and DHA). Recent **UPLC/MS-MS technology**⁶⁵ can accurately quantify over 150 eicosanoid and related metabolites (if present) in a 5 minute metabolomics analysis from less than 50 microliters of human plasma and this number is increasing as new standards become available. These new methodologies have replaced older methodologies, such as ELISA and traditional mass spectrometry, where specificity and quantitation can be compromised and these new methodologies are generally carried out on urine or blood plasma.

Novel bioactive oxygenated lipids can also be produced by the traditional “pro-inflammatory” enzymes including COX, LOX, and CYP, and some of these can promote resolution⁸. Also, several fatty acids, nitrated fatty acids, eicosanoids and related DPA- or DHA-derived oxygenated lipids appear to be agonists of the anti-inflammatory nuclear receptors PPAR α , PPAR δ , and PPAR γ ^{28,29,66–69}. None of these PPAR-activating eicosanoids and related species display the same very low nanomolar potencies possessed by prostaglandins, leukotrienes and lipoxins for their natural receptors, questioning the biological relevance of their proposed anti-inflammatory actions¹. These criticisms have been voiced again more recently⁷⁰ and also in reference to the reported *in vivo* levels of transcellularly formed lipoxins and other SPMs⁸; more work is clearly needed to resolve these issues.

However, the number of identified PPAR agonists and SPMs continue to mount, multiplying the potential for their *in vivo* relevance. Thus, the ability to measure nearly all eicosanoids and related species should become increasingly focused on their collective bioactivity rather than as distinct species working in isolation. However, current analytical strategies cannot determine the precise concentration of specific eicosanoids at the receptor level or at confined inflammatory sites in real time, where eicosanoids are rapidly formed and inactivated. Hopefully, future developments in lipidomics such as secondary ion mass spectrometry (SIMS-C₆₀), which allows for profiling of lipids at the single-cell level⁷¹, may provide a useful platform to eventually solve the current debate over the presence of and biological relevancies of specific eicosanoids in specific cells during infection and inflammation. Recent studies on the spatial organization of lipids in the human retina and optic nerve by matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry⁷² identified individual phospholipids, some containing DHA, in different layers of the human retina, suggesting that with future technological advances local pools of released fatty acids and eicosanoid products may be detectable in relevant human tissues under inflammatory conditions.

Conclusion

The overall impacts of the eicosanoid and cytokine storms on host survival are likely context dependent and will require greater focus on age, diet, and genetic variation in addition to the specific pathogenic assault and severity of trauma. Refined application of lipidomics methodologies and similar approaches will be critical to advance the understanding of eicosanoids in health and disease. With the ability that lipidomics brings to now assess changes in the majority of eicosanoid species simultaneously, determining both the pro-

inflammatory and anti-inflammatory contributions of eicosanoids in specific diseases will likely accelerate.

The expanded view of eicosanoid signaling since the introduction of lipidomics is remarkably more complex, but the potential for improving therapeutic design is promising. Advancing treatment beyond NSAIDs may need to be more focused on isolating and correcting deficiencies in bioactive eicosanoids, rather than blunting entire pathways. The ability to now analyze hundreds of eicosanoids and related lipid species, alongside the handful of well-characterized prostaglandins and leukotrienes, provides a wealth of possibilities to understand and develop novel treatments for inflammatory and metabolic conditions. A better understanding of the cytokine storm and its integration with the eicosanoid storm that accompanies classic inflammation and its resolution should provide new insights leading to novel strategies for the understanding and treatment of infection and inflammation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY

Eicosanoids	Bioactive oxygenated polyunsaturated fatty acids containing twenty carbons.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Non-steroidal anti-inflammatory drugs, such as aspirin and naproxen, are used to ablate the inflammatory response. They work by inhibiting cyclooxygenase-1 and -2 (COX1 and COX2) blocking the biosynthesis of prostaglandins including thromboxane.
Docosanoids	Bioactive oxygenated polyunsaturated fatty acids containing twenty-two carbons.
Inflammasome	A molecular complex of several proteins that upon assembly cleaves pro-IL-1 and pro-IL-18, thereby producing active forms for these pro-inflammatory cytokines.
Toll-like receptor (TLR)	A family of pattern-recognition receptors that recognize conserved molecules from pathogens, such as lipopolysaccharide, that initiate innate immune responses.
Peroxisome proliferator-	Nuclear receptors that participate in the regulation of cellular metabolism and differentiation. PPARs have anti-inflammatory

activated receptors (PPARs)	properties by limiting the availability of limited cofactors or blocking promoters of pro-inflammatory genes.
Specialized pro-resolving mediators (SPMs)	Eicosanoids and docosanoids that promote efferocytosis, the process by which dying cells are engulfed and removed by macrophages in an immunologically inert manner, and also inhibit neutrophil diapedesis and pro-inflammatory cytokine expression. SPMs include lipoxins, resolvins, protectins, maresins, and the newly discovered MCTR sulfido-conjugate series.
Purinergic receptors	Family of plasma-membrane molecules that are involved in several known cellular functions, such as vascular reactivity, apoptosis and cytokine secretion.
Resolvins	Lipid mediators that are induced in the resolution phase following acute inflammation. They are synthesized from the essential omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
Metabolons	Complex of multiple enzymes (bound or in close proximity) that coordinately synthesize eicosanoids and docosanoids which is often dependent on receptor activation and cell-cell transfer of intermediates.
Eicosanoid class switching	A process by which pro-inflammatory eicosanoid synthesis changes to anti-inflammatory or pro-resolution eicosanoid and docosanoid synthesis.
Fluxomics	The study of the flux or the change in the concentration of products/metabolites in a biosynthetic pathway as a function of time in a cell.
Lipoxins	A class of eicosanoids, composed of LXA ₄ and LXB ₄ , that are produced by lipoxygenase-mediated metabolism of arachidonic acid. They are trihydroxytetraene-containing structures with potent biological activities in the resolution of inflammation.
Caecal ligation and puncture	An experimental model of peritonitis in rodents, in which the caecum is ligated and then punctured, thereby forming a small hole. This leads to leakage of intestinal bacteria into the peritoneal cavity and subsequent peritoneal infection.
Myeloperoxidase	A peroxidase enzyme that is most highly expressed by neutrophils. It is a lysosomal protein that is stored in azurophilic granules of neutrophils. Myeloperoxidase produces hypochlorous acid from hydrogen peroxide and chloride ions during the respiratory burst in neutrophils.

Necrotic cell death	A form of cell death that frequently results from toxic injury, hypoxia or stress. Necrosis involves the loss of cell integrity and release of cell contents into the interstitium. This form of cell death usually occurs together with inflammation. Depending on the context, the self antigens that are released by necrosis could become immunogenic.
Lyme disease	A disease caused by the bacterium <i>Borrelia burgdorferi</i> or other <i>Borrelia</i> spp. that is transmitted to humans via the bites of infected blacklegged ticks. Symptoms can include skin rash, fever, fatigue, headache, muscle pain, stiff neck and swelling of the knee and other large joints. Most cases can be successfully treated with antibiotics.
Efferocytosis	The phagocytic clearance of apoptotic cells (from the Latin 'effero', meaning to take to the grave or bury) before they undergo secondary necrosis. The process usually triggers an anti-inflammatory response.
UPLC/MS-MS technology	Ultra-high performance liquid chromatography combined with tandem mass spectrometry for chemical separation and quantitative analysis

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Box 1. Homeostatic Function of Eicosanoids

Classic eicosanoids play important homeostatic roles ranging from regulating vascular leakage and barrier formation, to protecting mucosal integrity in the stomach and regulating platelet aggregation. For example, the COX1-derived metabolite TxA₂ is produced by platelets and some other cell types and plays a homeostatic role in platelet aggregation, as well as a role in the platelet response to injury. By contrast, COX2-derived PGI₂ produced by endothelial cells inhibits platelet aggregation and promotes vasodilation.

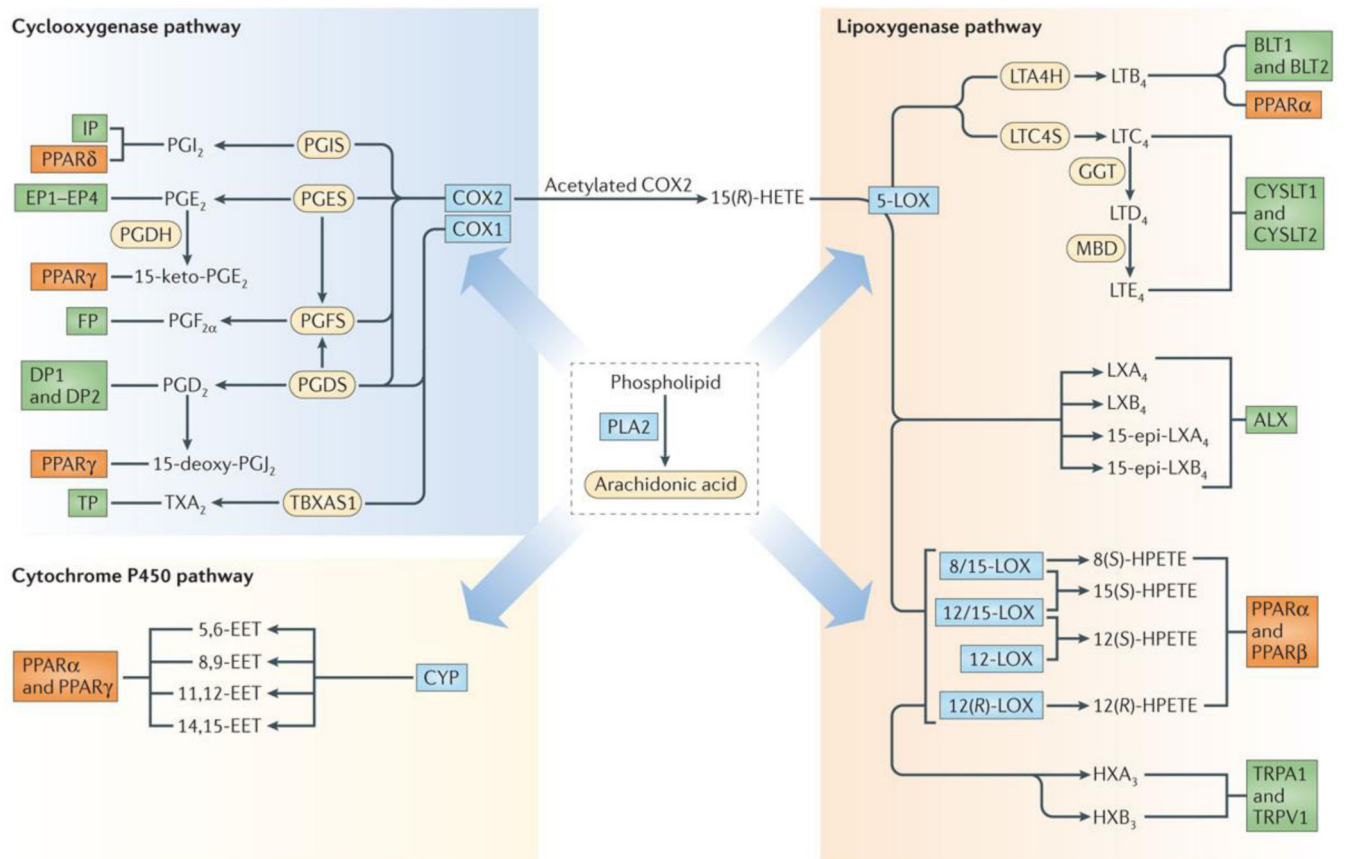
Unique therapeutic side effects have been attributed to blocking COX1 or COX2 isoforms: COX1-specific inhibitors can cause stomach toxicity and delays in blood clotting, while COX2-specific inhibitors (coxibs) largely avoid stomach toxicity and promote platelet aggregation. Although coxibs potently inhibit COX2, which is upregulated during inflammation, the resulting vascular imbalance of PGI₂ and TxA₂ has been associated with an increase in myocardial infarction and stroke events in coxib-treated patients. The most potent and specific COX-2 inhibitor, rofecoxib, was removed from world markets a decade ago because of cardiovascular risk.

The significance and complexity of eicosanoid signaling in critical physiological processes has recently been evaluated in detail^{73,74}. As a result, low doses of aspirin are now commonly prescribed as cardioprotection agents, and limit thromboxane formation by COX1 in platelets without inhibiting COX2-mediated PGI₂ formation by endothelial cells. One approach that could potentially circumvent this is to inhibit the major inflammatory PGE₂ synthase (mPGES1), which is coupled to (and upregulated with) COX2 in many tissues during inflammation. However, this approach is questionable in light of the several anti-inflammatory effects that have now been attributed to PGE₂.

Fish oil-derived ω3 fatty acid supplementation is also commonly prescribed for the treatment of various inflammatory ailments and for cardioprotection. The clearest evidence for this reasoning is the ability of ω3 EPA and DHA to inhibit arachidonic acid metabolism by COX-1 (but less so by COX2)²⁰, similar to low dose aspirin. However, the cardioprotective effects of ω3 fatty acids may be obscured by the widespread use of statins, which appear to have anti-inflammatory properties.

Box 2. Resolution Functions of Eicosanoids (SPMs)

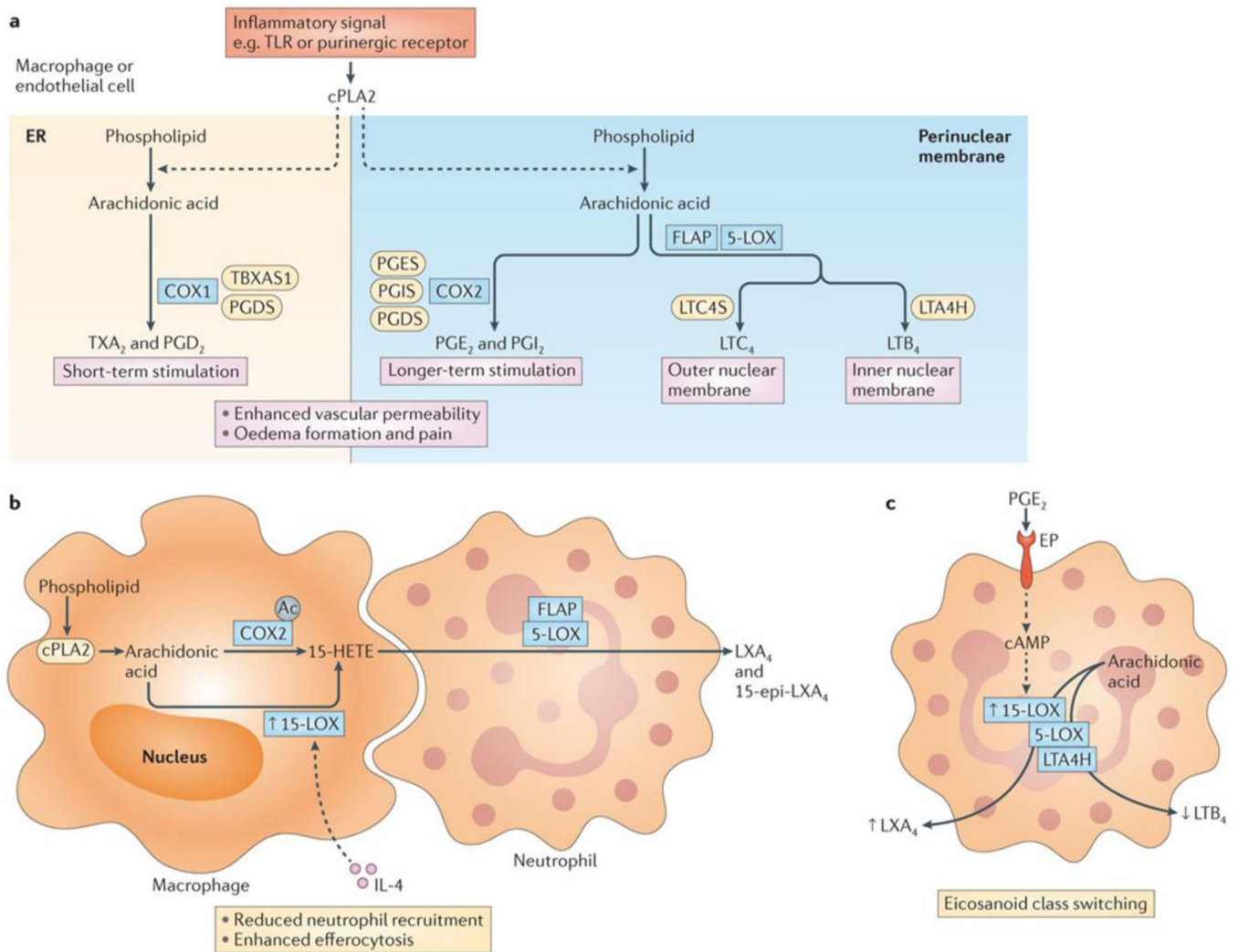
Inflammatory exudates initially serve to neutralize pathogens and local injury; however, this results in an increased presence of leukocytes and pro-inflammatory mediators that can potentially propagate tissue damage and inflammation if not resolved in a timely manner. Lipoxins comprise a family of tri-hydroxy eicosanoids that include LXA₄ and LXB₄ (as well as aspirin-triggered 15-epi-LXA₄ and 15-epi-LXB₄)^{42,75}, which inhibit neutrophil recruitment via activation of the LXA₄ receptor (ALX-FPR2). Subsequently, this family of specialized pro-resolving mediators (SPMs)⁸ has grown to include di- and tri-hydroxylated fatty acids derived from the omega-3 fish oils EPA and DHA that have been isolated from inflammatory exudates and leukocytes. SPMs now include the EPA-derived resolvins (RvE1, RvE2, and RvE3) and DHA-derived resolvins (RvD1, RvD2, RvD3, RvD4, RvD5, and RvD6) as well as protectin D1 (PD1) and macrophage mediators in resolving inflammation (maresins) (MaR1 and MaR2), also derived from DHA. PD1 has also been termed neuroprotectin D1 (NPD1) since it was isolated from and protects retinal pigment epithelial cells from oxidative stress-induced apoptosis⁷⁶ and displays neuroprotective properties in brain ischemia-reperfusion⁷⁷. In addition to ALX-FPR2, these mediators activate BLT1, ChemR23 and G protein-coupled receptor 32 (GPR32), which appear to recognize both the stereochemically specific triene/tetraene and di-/tri-hydroxy motifs within the fatty acid backbone. Collectively, SPMs have been shown to enhance bacterial clearance⁶⁰, down-regulate pro-inflammatory cytokines, and enhance clearance of apoptotic neutrophils (a process termed efferocytosis). Most recently, a sulfido-conjugate family of mediators derived from DHA was identified in mouse inflammatory exudates (maresin conjugates in tissue regeneration; MCTR that promote tissue regeneration in planaria and possess the classic actions of SPMs⁷⁸).



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Figure 1. Eicosanoid biosynthesis and receptor signaling

Lipidomic view of phospholipase A₂ (PLA₂), cyclooxygenase-1 and -2 (COX1/2), 5-lipoxygenase (5-LOX), 8-, 12-, and 15-lipoxygenases (8/12/15-LOX) and cytochrome P450 epoxyhydrolase (CYP) pathways of eicosanoid biosynthesis derived from arachidonic acid. Downstream enzymes are shown as yellow ovals followed by eicosanoid species and their receptors as green boxes. The peroxisome-proliferator activating receptors (PPARs), indicated as orange boxes, that are potentially activated by the eicosanoids are also shown. The CYP ω-hydroxylase pathway and lipid species derived from other fatty acids are not shown. Abbreviations: COX, cyclooxygenase; CYP, cytochrome P450; EET, epoxyeicosatrienoic acid; GGT, gamma-glutamyl transferase; HETE, hydroxyeicosatetraenoic acid; HX, hepoxilin; LOX, lipoxygenase; LT, leukotriene; LTAH, LTA₄ hydrolase; LTCS, LTC₄ synthase; LX, lipoxin; MBD, membrane bound dipeptidase; PLA₂, phospholipase A₂; PPAR, peroxisome proliferator-activated receptor; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; and TX, thromboxane.



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Figure 2. Enzyme functional coupling, transcellular biosynthesis, and eicosanoid class switching (a) Functional coupling of cPLA₂ with metabolons comprised of COX-1 or COX-2 and different prostaglandin or thromboxane synthases; 5-LOX coupled to LTAH or LTCS; PGES represents microsomal PGES-1 and PGDS represents hematopoietic PGDS, while other isoforms are not shown; coupling schemes are not completely insulated thus products may derive from alternate routes depending on cell type and degree of cell activation. Functions of these products collectively describe the cardinal signs of inflammation. (b) Transcellular biosynthesis of lipoxins from arachidonic acid (AA) involving a cell expressing COX-2 acetylated by aspirin and/or 15-LOX that is upregulated by IL-4, both of which produce the same intermediate 15-HETE, which diffuses or is transported to an adjacent cell where it becomes incorporated in and subsequently released from membrane phospholipids by cPLA₂ (not shown). This 15-HETE is converted by 5-LOX (with its functionally coupled FLAP) to LXA₄/15-epi-LXA₄, thereby initiating eicosanoid class switching. Coordinate macrophage-neutrophil lipoxin biosynthesis and related SPM production (as depicted) provides putative mechanisms to enhance efferocytosis and

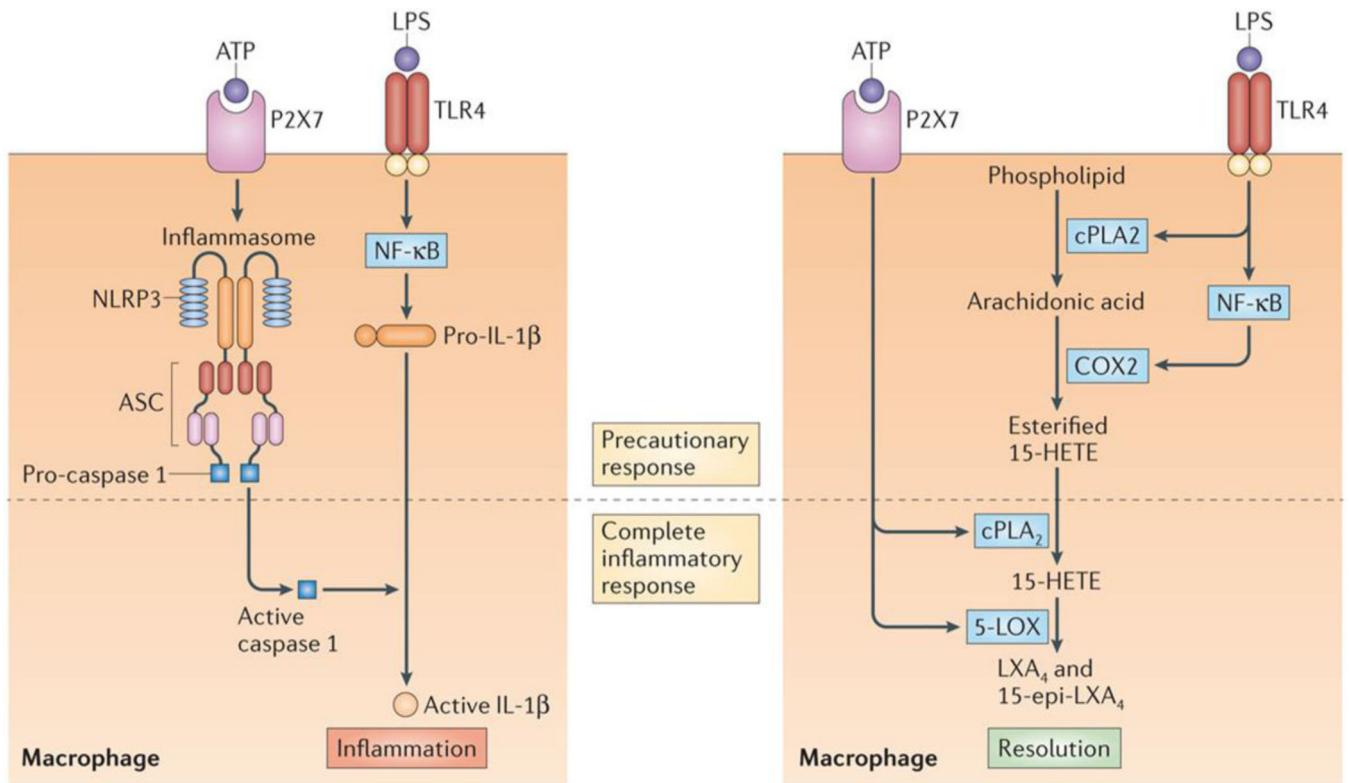
redirection of neutrophils to the vasculature. (c) Eicosanoid class-switching involves receptor mediated reprogramming of biosynthetic enzyme expression or activation. A neutrophil is depicted being activated by PGE₂ binding of a cyclic adenosine monophosphate (cAMP) increasing EP receptor that increases 15-LOX expression, which shunts arachidonic acid (AA) synthesis from LTB₄ production by 5-LOX/LTAH to LXA₄ by 15-LOX/5-LOX.

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Figure 3. Inflammasome formation and caspase activation parallels lipoxin formation for a complete inflammatory response

TLR4-mediated priming of macrophages by LPS induces pro-IL-1 β production via activation of NF- κ B. Subsequent purinergic P2X₇ receptor engagement by ATP initiates the process of caspase-1 activation through inflammasome initiation, which converts pro-IL-1 β to IL-1 β , but a parallel pathway in macrophages exists to initiate the resolution of inflammation. TLR4-mediated priming also activates cPLA₂ and induces COX2 production via NF- κ B; this results in the release of arachidonic acid and conversion to 15-HETE, which becomes esterified into phospholipids. Subsequent purinergic P2X₇ receptor engagement activates cPLA₂ and 5-LOX in Ca²⁺-dependent processes, leading to the release of 15-HETE from membrane phospholipids and conversion of the 15-HETE to lipoxin. The first step in this process is enhanced by aspirin which causes complete eicosanoid class switching from pro-inflammatory prostaglandins to anti-inflammatory lipoxins.

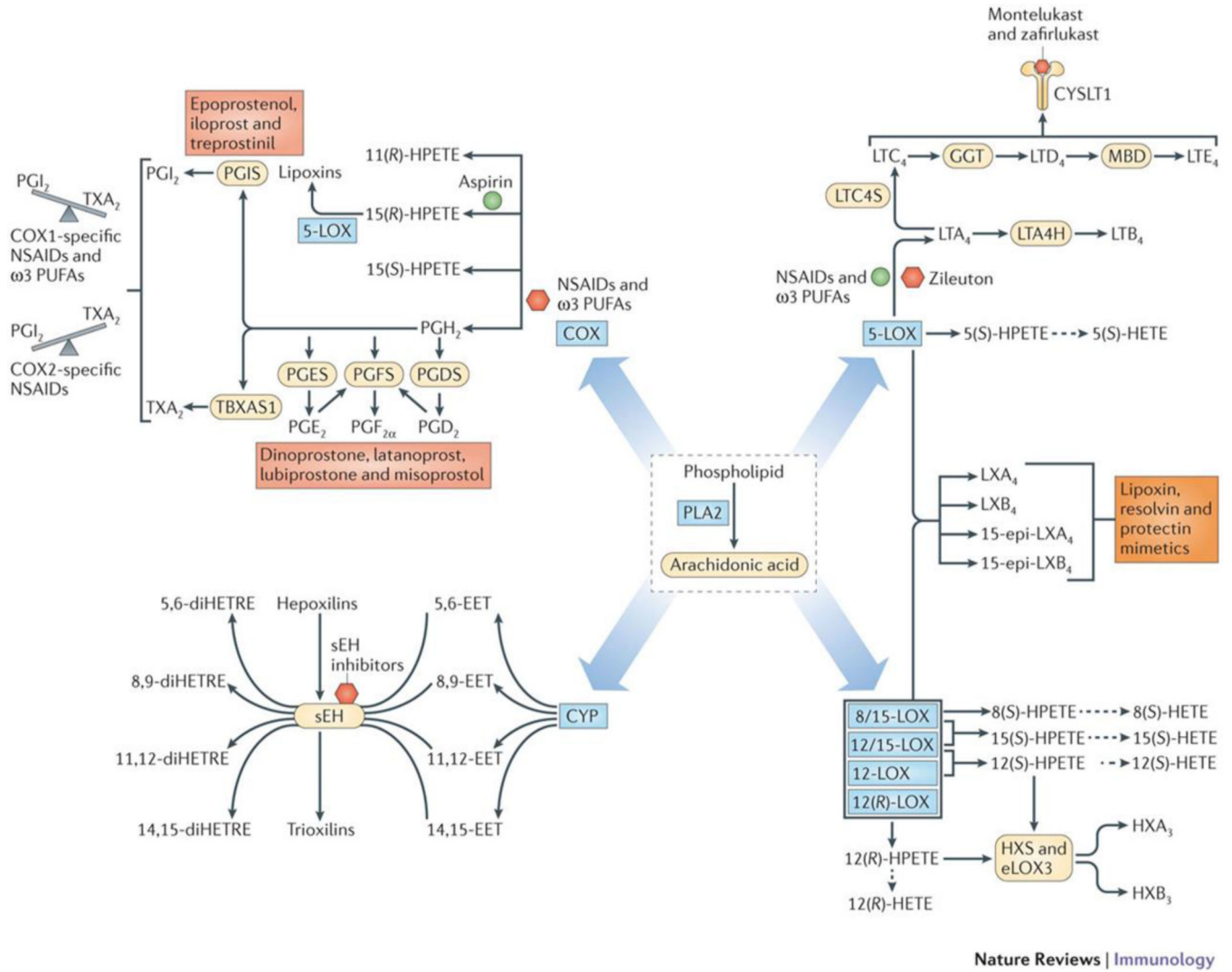


Figure 4. Therapeutics targeting eicosanoid pathways

Enzymes in the cyclooxygenase pathway generate prostaglandins, thromboxanes, and lipoxins; lipoxygenase pathway enzymes generate leukotrienes, HETEs, and hepxilins; and cytochrome P450 epoxyhydrolase pathway enzymes generate epoxides and dihydroxy polyunsaturated fatty acids (PUFA). All of the pathways have pharmacological intervention points including enzyme inhibitors and receptor antagonists (red hexagon), product enhancers (green circle) and mimetics (red box). NSAIDs and ω3 PUFAs inhibit COX formation of each product derived from AA (red hexagon), with the exception of one NSAID, aspirin, which enhances COX-2 formation of 15(R)-HETE (green circle) that can be converted to lipoxins by 5-LOX. COX-1-specific NSAIDs and ω3 PUFAs shift the vascular balance to higher PGI₂, whereas COX-2 specific NSAIDs shift the vascular balance to higher TxA₂ (gray), which are in opposite directions due to coupling of platelet COX-1 with TXAS and endothelial COX-2 with PGIS; analogs of prostaglandins are used clinically to mimic endogenous bioactivity (red box). Montelukast and zafirlukast specifically inhibit activation of cysLT1 (red hexagon). Zileuton inhibits 5-LOX conversion of arachidonic acid (red hexagon), but NSAIDs and ω3 PUFAs can increase conversion (green circle) via

shunting of AA from inhibited COX-1 and COX-2. Inhibitors of sEH reduce inactivation of EETs as well as hepxilins (red hexagon). Lipoxin, resolvin, and protectin mimetics (orange box) are being developed for treatment of ocular, periodontal, and cardiovascular diseases.

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Table 1

Eicosanoid pathways, mediators, receptors, and their physiological roles.

Major Pathway	Mediator	Receptor	Physiological responses and biochemical effects	Reference
COX	PGE ₂	EP1, EP2, EP3 and EP4	Vasodilation and vascular leakage; hyperalgesia; fever; IL-10 ↑ TNF-α ↓; PMN eicosanoid class switching	25,44,79–86
	15-keto-PGE ₂	PPAR _γ	Adipogenesis ↑; mucus retention ↓; bicarbonate secretion ↑	51,67
	PGD ₂	DP1	Mast cell maturation, vasodilation, neuroprotection	87–89
		DP2	Eosinophil recruitment and allergic response ↑	90,91
	15d PGJ ₂	PPAR-γ	Adipogenesis ↑	92,93
	PGF _{2α}	FP	Uterine, vascular and respiratory smooth muscle contraction	94
			Intraocular pressure ↓	95
	PGI ₂	IP	Platelet aggregation ↓; hyperalgesia; vasodilation; IL-10 ↑ TNF-α ↓	25,83,96–98
PPAR-δ		Embryo implantation	99,100	
TxA ₂	TP	Platelet aggregation ↑; vasoconstriction; T-cell activation ↓	101,102,103,104	
5-LOX	LTB ₄	BLT1	Neutrophil recruitment and vascular leakage	26,27,80
		BLT2	Enhanced epithelial barrier function	105
		PPAR-α	Negative feedback of LTB ₄ biosynthesis	106,107
	LTC ₄ , LTD ₄ , LTE ₄	CysLT1, CysLT2	Bronchoconstriction; vascular leakage; neutrophil extravasation	26,108
8-,12-,15-LOX	HpETEs, HETEs and diHETEs	TRPV1	Hyperalgesia	109
		PPAR-α,γ	Fatty acid translocase/CD36 ↑	28,29
CYP	EETs	PPAR-α,γ	Vasodilation; antihyperalgesia; COX-2 expression ↓	110–112
(LOX-LOX; COX-LOX)	HXA ₃ HXB ₃	TRPA1	Hyperalgesia	113
		TRPV1		
		?	Mucosal epithelial-directed neutrophil recruitment	114–116
	LXA ₄ , 15-epi-LXA ₄ , LXB ₄ , 15-epi-LXB ₄	ALX	Neutrophil recruitment ↓; Efferocytosis ↑	8
Membrane-esterified eicosanoids	PL-HETE	?	Modulation of signal transduction; lipoxin precursor storage	117,118
	PL-PG	?	TLR response ↓	119
Non-enzymatic	IsoP	?	Function not established	
	AA-NO ₂		COX-1 inhibition	120