Lipid Mediators in Inflammation

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ABSTRACT Lipids are potent signaling molecules that regulate a multitude of cellular responses, including cell growth and death and inflammation/infection, via receptor-mediated pathways. Derived from polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), each lipid displays unique properties, thus making their role in inflammation distinct from that of other lipids derived from the same PUFA. This diversity arises from their synthesis, which occurs via discrete enzymatic pathways and because they elicit responses via different receptors. This review will collate the bioactive lipid research to date and summarize the major pathways involved in their biosynthesis and role in inflammation. Specifically, lipids derived from AA (prostanoids, leukotrienes, 5-oxo-6,8,11,14-eicosatetraenoic acid, lipoxins, and epoxyeicosatrienoic acids), EPA (E-series resolvins), and DHA (D-series resolvins, protectins, and maresins) will be discussed herein.

INFLAMMATION AND ITS ONSET

Before we discuss lipids and their role in homeostasis and host defense, we will recount the essence of the inflammatory response. Inflammation is a reaction of the microcirculation; it’s a protective response initiated after infection or injury. While both local and systemic responses can be activated, inflammation is an essential biological process with the objective of eliminating the inciting stimulus, promoting tissue repair/wound healing, and, in the case of infection, establishing memory such that the host mounts a faster and more specific response upon a future encounter. The acute inflammatory response is a complex yet highly coordinated sequence of events involving a large number of molecular, cellular, and physiological changes. It begins with the production of soluble mediators (complement, chemokines, cytokines, eicosanoids—including prostaglandins [PGs], free radicals, vasoactive amines, etc.) by resident cells in the injured/infected tissue (i.e., tissue macrophages, dendritic cells, lymphocytes, endothelial cells, fibroblasts, and mast cells), concomitant with the upregulation of cell adhesion molecules on both leukocytes and endothelial cells that promote the exudation of proteins and influx of granulocytes from blood (1). Upon arrival, these leukocytes, typically polymorphonuclear leukocytes (PMNs) in the case of nonspecific inflammation or eosinophils in response to allergens, function primarily to phagocytose and eliminate foreign microorganisms via distinct intracellular (superoxide, myeloperoxidase, proteases, and lactoferrins) and/or extracellular (neutrophil extracellular traps) killing mechanisms (2). It is likely that the magnitude of the infectious load and its eventual neutralization signal the next phase of active anti-inflammation and proresolution (3).

RESOLUTION OF INFLAMMATION

It is important to distinguish between inflammatory resolution and inflammatory onset. At onset, local release/activation of soluble mediators (e.g., complement, vasoactive amines, cytokines, and lipids) from histiocytes and stromal cells and upregulation of cell adhesion molecules on the microvascular endothelium collectively facilitate extravascular leukocyte accumulation, manifesting in Celsius’ cardinal signs of inflammation: heat, redness, swelling, and pain (Rudolf Virchow added loss of function in the 19th century) (4).
well-characterized phase of the inflammatory response is routinely targeted using drugs including nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-tumor necrosis factor α (TNF-α) agents that inhibit or antagonize the action of these inflammatory drivers, forming the mainstay for treating chronic inflammatory disease. Resolution, however, switches inflammation off. Inasmuch as onset is orchestrated by a host of sequentially released mediators, resolution is an active process that is no longer considered a passive event in which the response was hitherto thought to simply fizzle out (5, 6). For instance, a critical requirement for the inflammatory response to switch off is the elimination of the injurious agents that initiated it in the first place. Failure to achieve this first step will lead to chronic inflammation, as exemplified by chronic granulomatous disease, which results from a failure of the phagocytic NADPH oxidase enzyme system to produce superoxide and kill invading infections, leading to a predisposition to recurrent bacterial and fungal infections and the development of inflammatory granulomas (7). Successfully dispensing with the inciting stimulus will signal a cessation of proinflammatory mediator synthesis and lead to their catabolism. This will halt further leukocyte recruitment and edema formation. These are probably the very earliest determinants for the resolution of acute inflammation, the outcome of which signals the next stage of cell clearance. The clearance phase of resolution, be it PMN or eosinophil driven or adaptive (lymphocyte mediated) in nature, also has a number of mutually dependent steps. The clearance routes available to inflammatory leukocytes include systemic recirculation or local death by apoptosis/necrosis of influxed PMNs, eosinophils, or lymphocytes, followed by their phagocytosis or efferocytosis by recruited monocyte-derived macrophages. Once phagocytosis is complete, macrophages can leave the inflamed site by lymphatic drainage, with evidence that a small population may die locally by apoptosis (8).

Eliminating the injurious agent leads to the next phase of proinflammatory mediator catabolism, in which levels of cytokines, chemokines, eicosanoids, cell adhesion molecules, etc., must revert back to that expressed during the preinflamed state. In terms of chemokines, the atypical chemokine receptors such as D6 are unable to initiate classical signaling pathways after ligand binding, thereby acting as a type of scavenging system for proinflammatory signals, such that in tetradecanoyl phorbol acetate-induced skin inflammation, D6-deficient mice exhibit an excess concentration of chemokines, resulting in a notable inflammatory pathology with similarities to human psoriasis (for review, see reference 9). In addition, the work of Ariel and colleagues showed that CCL3 and CCL5 were increased in peritoneal exudates of Ccr5−/− mice during the resolution of acute peritonitis. Transfer of apoptotic PMNs resulted in CCR5-dependent scavenging of CCL3, CCL4, and CCL5. It transpires that CCR5 surface expression on apoptotic PMNs was reduced by proinflammatory cytokines and was increased by proresolving lipid mediators including lipoxin A4 (LXA4) (10), which will be discussed in detail later. Thus, endogenous systems exist to facilitate proinflammatory mediator clearance and whose function, when it becomes dysregulated, may lead to chronic inflammation. If all of these pathways of stimulus removal, inhibition of granulocyte trafficking, proinflammatory mediator catabolism, appropriate cell death/efferocytosis (phagocytosis of apoptotic cells), etc., are followed, then acute inflammation will resolve without causing excessive tissue damage and give little opportunity for the development of chronic, nonresolving inflammation.

Each stage of the resolution cascade represents an opportunity to be harnessed to drive ongoing inflammatory diseases down a proresolving pathway. Yet we caution that this will not be a panacea for all diseases driven by ongoing inflammation. We suspect that resolution processes may vary from tissue to tissue and be dependent on the nature of the injurious stimulus. Thus, designing proresolving drugs will have to be organ and disease specific. With that comes the need for more-appropriate animal models of ongoing inflammation that best reflect the intended human condition. In addition, more studies must be focused on examining resolution pathways in healthy and diseased humans.

RESOLUTION: A DYNAMIC PROCESS WITH CHECKS AND BALANCES

At this stage, it must be emphasized that inflammation leading to resolution is not a sequence of separate events that occur in isolation, but is a dynamic continuum of overlapping events where pro- and anti-inflammation blend seamlessly into proresolving. For instance, proinflammatory signals are activated in an immediate and early manner concomitant with anti-inflammatory signals that serve to temper the magnitude of the early-onset phase of acute inflammation, with PMN influx being a good barometer of inflammation severity. Over the course of hours and only after tissues have sensed that the injurious agent has been neutralized, is it safe to catabolize proinflammatory soluble mediators and switch off proinflammatory signaling pathways. Along-
side this is the synthesis of factors that terminate further PMN trafficking and prepare the injured tissue for resolution.

In other words, while it is recognized that proinflammatory mediators generated in the inflamed tissue drive acute inflammation, there is also the systemic and local production of endogenous mediators that counterbalance these proinflammatory events. These internal checks and balances have evolved to avert development of pathologies such as those highlighted above. Lipid mediators derived from polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA) and the omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are synthesized during normal cell hemostasis or, more often, after cell activation and in conditions of stress, functioning as activators of counterregulatory, anti-inflammatory, and proresolution mechanisms. Interestingly, these immunomodulatory effects are also found with a family of lipids, called prostanoids, which help to drive some of the cardinal signs of inflammation (heat, redness, swelling, pain, and loss of function). As the role of lipids in inflammation is diverse, this review aims to provide an update of AA/DHA/EPA-derived signaling molecules that not only drive acute inflammation but also counterregulate its severity and bring about its timely resolution.

**AA METABOLISM AND THE INFLAMMATORY RESPONSE**

AA is a 20-carbon fatty acid and the main eicosanoid precursor and is a constituent of all cells. Although it is not freely available, stimulation by various cellular agonists, including receptor-mediated agonists (e.g., N-formyl-methionyl-leucyl-phenylalanine [fMLP], interleukin-8 [IL-8], and platelet-activating factor), microorganisms, phagocytic particles, and nonspecific stimuli such as damage or injury (1), activates several phospholipase enzymes (predominantly PLA2), which releases AA from membrane phospholipid stores. Once in the cytosol, AA can be metabolized via three principal pathways to form an important family of oxygenated products, collectively termed eicosanoids, that are released from the source cell and act at nanomolar concentrations in an autocrine/paracrine manner on target cells. PGs and thromboxane (collectively termed prostanoids), formed by cyclooxygenase (COX); leukotrienes (LTs) and lipoxins (LXs), by lipoxigenases (LOXs) (12, 13); and epoxyeicosatrienoic acids (EETs), by cytochrome P450 (CYP) enzymes (14), are members of the eicosanoid family.

**CYCLOOXYGENASE**

COX is a bifunctional enzyme that acts successively as a bis-dioxygenase and peroxidase to carry out a complex free radical reaction. It begins by catalyzing the bis-oxygenation and cyclization of AA to form the hydroperoxy arachidonate metabolite PGG2 (15), after which the peroxoxygen element of the enzyme reduces the carbon 15-position hydroperoxide to its corresponding alcohol to form PGH2 (16, 17). There are two main isoforms involved in the conversion of AA, COX-1 and COX-2. While COX-1 is constitutively expressed in most cells and tissues, COX-2 is rapidly induced when cells are challenged with inflammatory stimuli (18). Although not exclusive, it is generally accepted that COX-1 is involved in cellular housekeeping functions necessary for normal physiological activity, whereas COX-2 acts primarily at sites of inflammation. Formation of biologically active prostanoids from PGH2 occurs through the actions of a set of synthases that are expressed in a tissue- and cell type-selective fashion. These synthases include prostaglandin D synthase (PGDS) (19), prostaglandin E synthase (PGES) (20), prostaglandin F synthase (PGFS) (21), prostaglandin I synthase (PGIS) (22), and thromboxane A synthase (TXAS) (23), which form PGD2, PGE2, PGF2α, PGI2 (also known as prostacyclin), and TXA2, respectively. It is the differential expression of these enzymes within cells that determines the profile of prostanoid production. For example, mast cells predominantly produce PGD2 while macrophages produce PGE2 and TXA2. Moreover, alterations in the profile of prostanoid synthesis can occur upon cell activation such that resting macrophages produce TXA2 in excess of PGE2, but upon cell activation this ratio changes to favor PGE2 (24). Several biochemical mechanisms have been proposed to explain this altered synthetic profile. First, it has been suggested that physical compartmentalization of COX-1 and COX-2 with specific terminal synthases could link the activity of these enzymes with the synthesis of specific prostanoid end products (25). Second, some of the synthases are inducible, and their expression may be regulated by environmental signals. For example, expression of the glutathione-dependent isoform of PGES is enhanced by IL-1β (26). Finally, it has been proposed that differences in substrate affinity and kinetics of PGES and TXAS account for different production profiles of resting and activated monocytes (27). There is also evidence that the two COX isoforms may preferentially contribute to the synthesis of distinct prostanoids. For instance, in primary peritoneal macrophages, expressing all terminal synthases, COX-1 yields a balance of prostanoids (i.e.,
PGE₂, PGD₂, PGI₂, and TXA₂) while COX-2 preferentially generates only PGE₂ and PGI₂ (28).

The biological effect of prostanoids is initiated by binding to specific cell surface receptors. Currently there are nine known prostanoid receptors in mice and man: the PGD receptors, DP1 and DP2; the PGE₂ receptors, EP₁, EP₂, EP₃, and EP₄; the PGF receptor, FP; the PGI receptor, IP; and the TXA receptor, TP. In addition, there are splice variants of the EP₃, FP, and TP receptors differentiated only in their C-terminal tails. All belong to the G protein-coupled receptor (GPCR) superfamily of seven-transmembrane-spanning proteins, with the exception of DP2 (also known as CRTH2), which is a member of the chemotactrant receptor family (29–31). The IP, DP1, EP₂, and EP₄ receptors signal through Gₛ, resulting in increased intracellular cyclic AMP (cAMP), whereas the EP₃ receptor couples to Gₛ to reduce cAMP. EP₁, FP, and TP receptors signal through Gqid to induce calcium mobilization.

**PROSTANOIDS**

In the mid-1930s, potent bioactive compounds in human semen were identified as prostanoids (32). Today it is appreciated that prostanoids are generated in most tissues and cells, modulating a wide range of biological processes such as smooth muscle tone (33–35), vascular permeability (36, 37), hyperalgesia (38), fever (39–41), and platelet aggregation (42). Indeed, the clinical importance of prostanoids is emphasized by the fact that prostanoid biosynthesis is the target of NSAIDs, one of the most widely used classes of pharmacotherapeutic agents for the treatment of chronic inflammatory diseases.

The more widely studied prostanoids, PGE₂ and PGI₂, both enhance vasodilation (43), edema formation, and vascular permeability, particularly in the presence of histamine, bradykinin, and 5-HT (44–49). Genetic depletion of their respective receptors (IP, EP₂, and EP₃) in mice significantly reduced pleural exudation after insult with carrageenin or zymosan (50, 51). PGE₂ is also one of the most potent pyretic agents known, with elevated concentrations found in cerebrospinal fluid taken from patients with bacterial or viral infections (52). Indeed, a number of lines of evidence from EP-deficient mice have shown that the febrile response to PGE₂ occurs through the action of PGE₂ on the EP₃ receptor present on sensory neurons in the periphery and brain (53–56). This has been postulated to cause an increase in thermogenesis through activation of brown adipose tissue and reduced passive heat loss through the skin by tail artery vasoconstriction (57–61). Although none of the COX metabolites overtly cause pain, PGI₂ and PGE₂ cause peripheral and central hyperalgesia when bound to IP, EP₁, EP₃, and EP₄ receptors by reducing the threshold of nociceptor sensory neurons to stimulation (34, 38, 62–70).

In addition, prostanoids play an important role in protecting against oxidative injury in cardiac tissue (71) and in maintaining cardiovascular (CV) homeostasis. Indeed, the protective effect has been demonstrated in clinical studies undertaken with NSAIDs, which found that COX-2-specific inhibitors increase the risk of stroke, myocardial infarction (MI), thrombosis, systemic and pulmonary hypertension, congestive heart failure, and sudden cardiac death (72, 73). Furthermore, deleting specific prostanoid synthases and receptors results in an augmentation of ischemia/reperfusion injury (74) as well as exacerbating the decline in cardiac function after MI (75, 76). The maintenance of CV health is dependent on a very fine balance between vasodilatory PGI₂ and prothrombotic TXA₂ (77, 78), where PGI₂ functions to counterbalance the actions of TXA₂ (73). Indeed, PGI₂ released from endothelial cells and in synergy with nitric oxide prevents TXA₂-induced platelet aggregation and thrombosis (42, 79, 80). TXA₂ is derived from platelet COX-1, causing platelet aggregation and vascular smooth muscle contraction (81–83). Clinical CV diseases, such as unstable angina, MI, and stroke, can be a result of overproduction of TXA₂. Importantly, the cardioprotective properties of aspirin can be attributed to the covalent inhibition of COX-1 (84).

As well as having “proinflammatory” properties, many prostanoids also exert immunosuppressive effects through upregulation of intracellular cAMP (85–87). For example, PGE₂ and PGI₂ reduce the ability of inflammatory leukocytes to phagocytose and kill microorganisms (88–93), as well as inhibit the production of downstream proinflammatory mediators (94–100) while, in contrast, enhancing the production of IL-10 and IL-6 (101, 102). Indeed, in a number of conditions associated with increased susceptibility to infection, including cancer (103), aging (104), and cystic fibrosis (105, 106), overexpression of PGE₂ has been reported. Interestingly, during the onset phase of inflammation, PGE₂ indirectly results in proresolution effects by switching on the transcription of enzymes required for the generation of LXs (107), resolvins (Rvs), and protectins (PDs) (108–111), other classes of bioactive lipids that are potent proresolution mediators.

As well as elicits immunomodulatory and anti-inflammatory effects in the same manner as described for PGE₂ and PGI₂ via ligation to DP1, PGD₂ can also
act independently of DP1 and DP2 receptor activation when nonenzymatically dehydrated into biologically active prostaglandins of the J₂ series (e.g., PGJ₂, Δ₁₂,₁₄-PGJ₂, and 15-deoxy-A₁₂,₁₄-PGJ₂ [15d-PGJ₂]) (112–116). These so called cyclopentenone PGs form covalent attachments with reactive sulfhydryl groups on intracellular regulatory proteins, which enables modulation of their function (117–119). For instance, 15d-PGJ₂, upon ligation to the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-γ (120), decreases proinflammatory cytokine release and modifies gene expression (121, 122), as well as directly inhibiting the actions of IkB kinase (IKK), which is responsible for the activation of NF-κB (123–125). 15d-PGJ₂, independently of PPAR-γ, can preferentially inhibit monocyte rather than neutrophil trafficking through differential regulation of cell adhesion molecule and chemokine expression (8, 126–128); regulate macrophage activation and proinflammatory gene expression (129); and induce leukocyte apoptosis through a caspase-dependent mechanism (8, 115, 130–133). Moreover, it has been shown that PGD₂-derived compounds function as endogenous breaking signals for lymphocytes to stimulate resolution (134).

LIPOXYGENASE

LOX enzymes, including 5-, 12-, and 15-LOX in leukocytes, platelets, and endothelial cells, respectively, metabolize AA. The generation of the slow-reacting substances of anaphylaxis (LTCA₄, LTD₄, and LTE₄—potent mediators of the allergic response) (135) and LTB₄, a powerful PMN (i.e., neutrophils and eosinophils) chemoattractant (136, 137), is elicited by leukocyte 5-LOX. Due to its involvement in LT synthesis, 5-LOX has received the most attention in inflammation research. Therefore, the remainder of this section will concentrate specifically on this pathway.

Once activated, 5-LOX converts AA into a hydroperoxide by inserting molecular oxygen into AA at position 5, aided by the 5-LOX activating protein (FLAP). Termed 5-hydroperoxyeicosatetraenoic acid (5-HPETE), this intermediate is then rapidly reduced to 5-hydroxyeicosatetraenoic acid (5-HETE). 5-HPETE can also be converted by removal of water to an unstable 5,6-epoxide containing a conjugated triene structure called LTA₄, which is then converted to either LTB₄ by insertion of a hydroxyl group at carbon-12 (C-12) through the action of LTA₄ hydrolase (138, 139) or LTC₄ by addition of the glutathionyl group at C-6 by γ-glutamyl-S-transferase (140). In most cases, LTB₄ and 5-HETE are subsequently secreted from the cell by an unidentified protein carrier (141). LTC₄ is also exported, but by the ATP-dependent multidrug resistance proteins (142), including MRP1 and MRP2. After export, LTC₄ is metabolized by the cleavage of glutamic acid by γ-glutamyl transpeptidase to form LTD₄, which can be further modified by removal of a glycine by cysteiny1 glycine to produce LTE₄. Unlike COX, 5-LOX is inactive in quiescent cells but becomes enzymatically functional after cell activation by increases in intracellular calcium (143), enhanced by ATP (144), or by phosphorylation, which can occur without an increase in calcium (145).

Heptahelical receptors of the rhodopsin class located on the outer leaflet of the plasma membrane of structural and inflammatory cells mediate the effects of LTs (146, 147). To date, four subtypes have been described, BLT1 receptors 1 and 2 (BLT1 and BLT2) and cysteinyl LT receptors 1 and 2 (CysLT1 and CysLT2). Once LTs have bound, a signal is sent via a G protein in the cytoplasm to increase intracellular calcium and block formation of cAMP, which then alters various cellular activities, ranging from motility to transcriptional activation. While CysLT1 mediates bronchoconstriction, mucus secretion, and edema accumulation in airways (148), CysLT2 contributes to inflammation, vascular permeability, and tissue fibrosis in lungs (149, 150). Indeed, overexpression of CysLT1 is seen in patients with asthma or chronic rhinosinusitis who have aspirin sensitivity (151). In contrast, BLT1 is a high-affinity receptor for LTB₄, mediating all of its chemoattractant and proinflammatory properties (147). Although BLT2 acts in a similar fashion to BLT1, LTB₄ affinity toward BLT1 is much higher. Interestingly, studies employing both an in vitro and a murine model of inflammation demonstrate that LTB₄ ligates and activates the anti-inflammatory nuclear receptor PPAR-α (152–155).

LTs IN INFLAMMATION

LTs are generated at sites of infection/inflammation primarily by inflammatory cells, including PMNs, macrophages, and mast cells, and play a critical role in the inflammatory response by acting as proinflammatory lipid mediators. Physiologically, each of the 5-LOX-derived compounds has a distinct role in driving different phases of inflammation. For example, LTB₄ attracts and activates neutrophils, monocytes, and lymphocytes, a hallmark of tissue inflammation (147, 156, 157), whereas LTD₄ is a potent chemoattractant for eosinophils (158). The cysteiny1 LTs (LTC₄, LTD₄, and LTE₄),
on the other hand, increase vascular permeability and plasma leakage, leading to edema that is characteristic of inflammation (159–163). Pathologically, LTs contribute to a variety of inflammatory and allergic diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, allergic rhinitis, bronchial asthma, cancer, atherosclerosis, and osteoarthritis (164). This can be seen in asthmatic patients, in whom antileukotriene therapy (i.e., 5-LOX inhibition by zileuton and CysLT1 blockage by montelukast or zafirlukast) resulted in improved pulmonary function, symptoms, and overall quality of life (165–167).

The role of LTs in CV disease has been the subject of intense investigation. In atherosclerotic lesions, for example, 5-LOX activity and levels are associated with the severity of the lesion (168) and plaque instability (169). Furthermore, both LTB4 and CysLTs participate in the development of atherosclerotic lesions in animals and in vitro. LTB4 increases recruitment of monocytes and their differentiation to foam cells (170), as well as intimal hyperplasia (171). CysLTs, on the other hand, enhance the recruitment of leukocytes into the arterial wall and contribute to thrombosis and vascular remodeling (172, 173). Interestingly, in humans, the incidences of strokes and MI in certain populations have been linked to variants of the genes that encode FLAP and LTA4 hydrolase, which cause an overproduction of LTs (174–176). Indeed, upon treatment with a FLAP inhibitor (velilaplon), a potent biomarker of inflammation, C-reactive protein, was reduced in one population of patients with a history of MI and one of the variants mentioned above (177). Despite their pathophysiologic role, it has now become apparent that LTs are important participants in the host response against infection (178). For instance, 5-LOX-deficient mice or pharmacological inhibition of LT synthesis caused increased mortality and reduced microbial clearance after challenge with a variety of microbes (e.g., bacteria, mycobacteria, fungi, and parasites) (179–184). Similarly, LT-deficient alveolar macrophages also displayed impaired phagocytosis and intracellular killing of bacteria, an effect that could be overcome with the exogenous introduction of LTB4 or CysLTs (180, 185). Interestingly, LT deficiency is also a feature of a number of clinical conditions that are associated with impaired microbial clearance (HIV infection, malnutrition, cigarette smoking, vitamin D deficiency, and post-bone marrow transplantation) (186–191). It is believed that LTs enhance microbicidal activities in leukocytes by upregulating production of nitric oxide (192, 193) and the secretion of microbial peptides (194), as well as activating NADPH oxidase to generate reactive oxygen intermediates (185). Recently it has been demonstrated that LTB4 may also possess anti-inflammatory properties through ligation to PPAR-α in its parent cell (155). It has been suggested that this activation in turn leads to its own catabolism, thus facilitating resolution of the inflammatory process. This hypothesis/theory/stipulation is conceivable and further demonstrates how inflammation is such a finely balanced process that is invoked when required, yet limited and resolved when it is no longer needed.

5-OXO-6,8,11,14-EICOSATETRAENOIC ACID

5-LOX activity also results in the generation of 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE), which has potent biological activities that have only recently become appreciated, including eosinophil activation and chemotraction. It is formed by the oxidation of 5S-HETE by 5-hydroxyeicosanoid dehydrogenase (5-HEDH), a microsomal enzyme widely distributed in both inflammatory and structural cells, including leukocytes and platelets (195). 5-HEDH, however, cannot generate 5-oxo-ETE without NADP+, which is available in large quantities during the respiratory burst, neutrophil apoptosis, and oxidative stress (196, 197). Other endogenously occurring PUFAs (sebaleic acid, mead acid, and EPA) can also be converted to analogous 5-oxo-fatty acids following oxidation by 5-LOX-forming products that are also granulocyte chemoattractants (198–200). Furthermore, both enzymatic and nonenzymatic pathways can further modify 5-oxo-ETE to produce several additional eicosanoids (201).

5-oxo-ETE acts via the OXE receptor (OXE-R), a distinct orphan GPCR (202, 203) that is most highly expressed in human peripheral leukocytes, lungs, kidney, liver, and spleen (204, 205). The relative expression of OXE-R in eosinophils, neutrophils, and macrophages is 200:6:1 (205). OXE-R, once coupled to a G protein (197, 206, 207), activates a number of distinct intracellular signaling pathways including PLC-β (208), phosphatidylinositol 3-kinase, and Akt (206, 208, 209); protein kinase C-δζ (210); as well as extracellular signal-regulated kinase-1/2 and cytosolic PLA2 (210, 211), which, in turn, could lead to further production of AA-derived metabolites. OXE-R may also inhibit the cascade mediated by adenyl cyclase and cAMP (204).

5-OXO-ETE AND INFLAMMATION

5-oxo-ETE is produced by eosinophils, neutrophils, basophils, and monocytes, and like other inflammatory
Lipid Mediators in Inflammation

Lipids, it acts in an autocrine manner. In addition to its most potent property as a chemoattractant for eosinophils (200), 5-oxo-ETE also induces calcium mobilization, actin polymerization, CD11b expression, and L-selectin shedding (201). Furthermore, 5-oxo-ETE induces degranulation and superoxide production in leukocytes primed with cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF-α, an effect not mirrored in naive cells (207, 211). In addition, 5-oxo-ETE stimulates human monocytes to secrete GM-CSF (212), which is a potent survival factor for eosinophils. In prostate tumor cells, this lipid prevents apoptosis/proliferation (213, 214).

**LXs—Biosynthesis and Receptors**

LXs are a series of trihydroxytetrane-containing bioactive eicosanoids that were first isolated from human leukocytes in the mid-1980s (13). However, in contrast to LTs and 5-oxo-ETEs, which are manufactured by intracellular biosynthesis, LXs are generated through cell-cell interactions by a process known as transcellular biosynthesis. In different human cell types, during the first biosynthetic step of LX biosynthesis, LOX inserts molecular oxygen into AA. This can be achieved by two major routes—the first pathway involves the oxygenation of AA at C-15 by 15-LOX in eosinophils, monocytes, or epithelial cells (found in the respiratory tract, gastrointestinal tract, and oral cavity), yielding 15S-HPETE. Following secretion, 15S-HPETE is taken up by either PMNs or monocytes and rapidly converted into 5,6-epoxytetrane by 5-LOX, which is hydrolyzed within these recipient cells by either LXA₄ or LXB₄ hydrolase to bioactive LXA₄ or LXB₄. Interestingly, this process also markedly reduces the formation of LTs, which requires 5-LOX to convert AA into LTA₄ (215–217). Moreover, it has been found that the 15S-HETE synthesized via this pathway can also be esterified and stored within the membranes of neutrophils, specifically inositol-containing phospholipids. Upon cell stimulation, 15S-HETE is rapidly released and transformed to a second signal, such as LXA₄, to regulate the function of the neutrophil (218). The second major route of LX biosynthesis occurs in an LTA₄-dependent manner, involving peripheral blood platelet-leukocyte interactions. Leukocyte 5-LOX converts AA into LTA₄, which is released, taken up by adherent platelets, and subsequently transformed to LXA₄ and LXB₄ via the LX synthase activity of human 12-LOX (219). A third unorthodox route of LX generation occurs after the exogenous administration of aspirin (but not other conventional NSAIDs), which irreversibly acetylates COX-2 in endothelial cells and other cell types. Rather than COX-2 converting AA into PGG₂, acetylation causes the transformation of AA into 15R-HETE (C-15 alcohol carried in the R-configuration). This is then rapidly metabolized in a transcellular manner by adherent leukocyte, vascular endothelial or epithelial 5-LOX to form 15-epimeric-LXs (15-epi-LXs) or aspirin-triggered LXs (ATLs) that carry their C-15 alcohol in the R-configuration rather than 15S native LX. ATLs share many of the anti-inflammatory/proresolovation characteristics of the native LXs.

LXA₄ and 15-epi-LXs elicit their multicellular responses via ALX (formyl peptide receptor-like-1 [FPRL1] receptor), a specific GPCR isolated and cloned in human, mouse, and rat tissues (220–222). Human ALX was subsequently identified and cloned in several types of leukocytes, including monocytes (223) and T cells (224), as well as resident cells such as macrophages, synovial fibroblasts (225), and intestinal epithelial cells (226). One of the functions attributed to ALX is in mediating the multicellular responses of LXA₄ and 15-epi-LXs. Studies in transgenic models have shown its selectivity toward LXA₄ and 15-epi-LPA₄ (not for LXB₄, LTB₄, LTD₄, or PGE₂) with high affinity (Kᵩ [dissociation constant] = 1.7 nM) (231). ALX also has the ability to interact with other small peptides/proteins such as Ac2-26 and glucocorticoid-derived annexin-1, which carry out similar anti-inflammatory effects as LXs and 15-epi-LXs. Evidence that the protective effects of LXs and 15-epi-LXs are both ligand and receptor dependent arose from studies in transgenic mice overexpressing human ALX (227–229). In a zymosan-induced peritonitis model, infiltration of neutrophils was also substantially diminished in transgenic mice compared to their wild-type equivalents (227), with the site of lipoxin action being the leukocyte/endothelial interface mediated by the generation of nitric oxide’s anti-adhesive properties (230).

ALX activation inhibits NADPH oxidase assembly, which, in turn, reduces superoxide anion generation by neutrophils through accumulation of polyisoprenoid presqualene diphosphate (231). Indeed, it has been demonstrated that inhibition of proinflammatory genes such as neutrophil chemoattractant IL-8 occurs via an ALX-dependent peroxynitrite-mediated signaling pathway (232). Moreover, peroxynitrite induction of IL-8 in response to lipopolysaccharide, TNF-α, or IL-β in human leukocytes occurs via an NF-κB- and activator protein 1 (AP1)-dependent pathway (233, 234). 15-epi-LX analogs also regulate an ALX-dependent p38/mitogen-activated protein kinase cascade known to promote chemotaxis by inhibiting leukocyte-specific AP1 phos-
phorylation and activation (235). In addition to ALX, Lxs also function as partial agonists to a subclass of rhodopsin receptors (CysLT1) more commonly activated by LTs, mediating bioactions in several tissues and cell types other than leukocytes (221, 236). At nanomolar concentrations, LXA4 has been shown to compete for binding with LTD4 on mesangial cells (236) and human umbilical vein endothelial cells (222, 237) as well as opposing the proinflammatory effects of LTD4. There is also evidence that another intracellular receptor, the Ah receptor, mediates the bioactions of LXs. This receptor is a ligand-activated transcription factor that controls several of the bio logical actions of LXs, such as increasing the expression of suppressor of cytokine signaling 2 (SOCS2) (238–240).

**LXs IN INFLAMMATION**

Lxs are anti-inflammatory at nanomolar concentrations, controlling both granulocyte (neutrophil and eosinophil) and monocyte entry to sites of inflammation. Yet while they inhibit the transmigration of neutrophils and eosinophils down a chemokine gradient into inflamed sites (241–244), they promote noninflammatory infiltration of monocytes required for resolution and wound healing (245), without inducing neutrophil degranulation or release of other reactive oxygen species (232). Indeed, the ability of LXs to diminish neutrophil trafficking was corroborated when an analog of 15-epi-LX was intravenously administered to BLT1 knockout mice, which have dramatically elevated neutrophils in the lungs after high limb ischemia/reperfusion (246). Furthermore, research in our laboratory has uncovered in humans that 15-epi-Lxs regulate PMN influx in forearm blisters, accounting for low-dose aspirin’s anti-inflammatory properties (247). Our additional work on resolving inflammation has revealed that humans fall into two categories, those who resolve their acute inflammatory responses in an immediate manner and those who show a more delayed or prolonged healing process, with the severity and duration controlled by endogenous epi-LX/ALX expression (248).

At sites of inflammation, macrophages are stimulated by LXs to ingest and clear apoptotic neutrophils (249), which appears to be coupled to changes in the actin cytoskeleton (250). Furthermore, LXs elevate the levels of the anti-inflammatory cytokine transforming growth factor β1 (TGF-β1), which, in turn, downregulates a number of proinflammatory pathways (251–253). It is believed that these lipid mediators are generated in situ when neutrophils express 5-LOX at the onset of reso-
lution as they begin to apoptose (107). LXs may also counteract the fibrotic response and thus improve tissue remodeling by reducing the proliferation of fibroblasts and mesangial cells induced by a number of factors, including connective tissue growth factor, platelet-derived growth factor, TNF-α, LTD4, and TGF-β (254–257). 15-Epi-Lxs exert the same biological effects as endogeneously produced LXs, but with additional benefits that increase vasorelaxation (258), and induce endothelial cell production of anti-inflammatory nitric oxide synthesis (230, 259). Moreover, 15-epi-LPA4 has been found to inhibit TNF-α-induced IL-1β in periodontitis in vivo (260, 261), dampen SOCS2 signaling (262), and inhibit TNF-α-induced IL-8 gene expression (226). Not surprisingly, both LXs and 15-epi-Lxs have been identified and proven to exert beneficial effects in various experimental models of inflammation and human diseases, such as glomerulonephritis (263, 264), ischemia/reperfusion injury (246, 254), cystic fibrosis (265), periodontitis (266), acute pleuritis (230), asthma (267), wound healing processes in the eye (268), colitis, inflammation-induced hyperalgesia in rats, various cutaneous inflammation models (269), and microbial infection in mice (238, 270, 271).

**OMEGA-3 PUFA PATHWAY**

Omega-3 PUFAs have long been known to be important not only in maintaining organ function and health but also in reducing the incidence of infection and inflammation (110, 111, 272–275). A clinical trial (GISSI-Prevenzione) assessing the benefits of aspirin with and without omega-3 PUFA supplementation in patients recovering from MIs revealed a significant decrease in mortality in the group taking the supplement (276). More-recent evaluations have confirmed the importance of omega-3 PUFAs in reducing CV disease and inflammation associated with it (277, 278). It was initially hypothesized that fish oils demonstrate their anti-thrombotic, immunoregulatory, and anti-inflammatory bioactions by inhibiting PG and LT synthesis (279). However, current opinion is that it is likely that a series of novel compounds derived from EPA and DHA are responsible for eliciting these immunomodulatory effects. First identified in the resolving exudate of a mouse dorsal air pouch or peritonitis model using lipidomic and bioinformatic analysis (110, 111, 280, 281), these naturally occurring bioactive lipid mediators are termed resolvins (Rv; derived from “resolution phase interaction products”), protectins (PDs), and maresins (MaRs; derived from “macrophage mediator in resolving in-
flammation”). All these omega-3 PUFA-derived products possess a plethora of stereospecific and potent anti-inflammatory and immunoregulatory actions that are protective in vitro and in vivo (282, 283).

**Rvs AND PDs**

Rvs can be generated from either EPA or DHA and are therefore categorized as either members of the E-series (from EPA) or D-series (from DHA). Rvs of both series were first isolated in vivo from murine dorsal air pouches treated with aspirin and EPA or DHA. Transcellular formation of E-series Rvs can occur with the conversion of EPA to 18R-hydroxyicosapentaenoic acid (18R-HEPE) by endothelial cells expressing COX-2 treated with aspirin. As with 15R-HETE in 15-epi-LX formation, 18R-HEPE can be released from endothelial cells to neighboring leukocytes for subsequent conversion by 5-LOX to either RvE1 or RvE2, via a 5(6)-epoxide-containing intermediate (110, 284). This interaction is blocked by selective COX-2 inhibition but not by indomethacin or paracetamol (110). RvE1 is spontaneously produced in healthy subjects, with levels increasing after treatment with either aspirin or EPA (285). D-series Rvs, aspirin-triggered RvD1 (AT-RvD1), and RvD1 are synthesized via a pathway involving sequential oxygenations, initiated by 15-LOX or aspirin-acetylated COX-2 in the microvasculature respectively, followed by 5-LOX in human neutrophils with an epoxide-containing intermediate. For AT-RvD1s, DHA is initially converted to epimeric 17R-hydroxydocosahexaenoic acid (17R-HDHA). In the absence of aspirin, however, DHA is enzymatically converted to 17S-HDHA (108). Interestingly, generation of E-series Rvs can also be mediated by microbial and mammalian CYP enzymes, which convert EPA into 18-HEPE. 18-HEPE can then be transformed by human neutrophils into either RvE1 or RvE2 (110). Hence, it is possible that microbes at sites of infection may contribute to the production of Rvs in a similar pathway.

DHA also serves as a precursor for the biosynthesis of PDs enzymatically converted by 15-LOX to a 17S-hydroperoxide-containing intermediate. Subsequently, this intermediate is rapidly converted by human leukocytes into a 16(17)-epoxide that is enzymatically converted in these cells to a 10,17-dihydroxy-containing compound (108, 286). PDs are distinguished by the presence of a conjugated triene double bond and by their potent bioactivity. One specific DHA-derived lipid mediator, 10,17S-docosatriene, was termed protectin D1 (PD1). When generated in neural tissue, however, this compound is called neuroprotectin D1 (NPD1). Moreover, PD1 exhibits tissue-specific bioactivity, as in humans this lipid is synthesized by peripheral blood mononuclear cells and Th2 CD4⁺ T cells, while in mice it has been isolated from exudates and brain cells, human microglial cells (111), and in peripheral blood (108).

**Rvs AND PDs IN INFLAMMATION**

One of the broader immunomodulatory properties of RvE1 is its ability to inhibit neutrophil and dendritic cell accumulation at sites of inflammation by blocking transendothelial migration as well as enhancing their clearance from mucosal epithelial cells (110, 285, 287). Other bioactions of RvE1 include inhibition of neutrophil reactive oxygen intermediates in response to TNF-α and the bacterial peptide fMLP (288); abrogation of LTB₄-BLT1 signaling via NF-κB, and thus the production of proinflammatory cytokines and chemokines (251, 289, 290); stimulation of macrophages to ingest apoptotic neutrophils (291); enhancement of the percentage of phagocytes present in the lymph nodes (292); upregulation of CCR5 on late apoptotic neutrophils (10), which terminates chemokine signaling; and inhibition of dendritic cell migration. More recently, RvE1 has been demonstrated to regulate the leukocyte proinflammatory cell surface markers, such as L-selectin, while selectively disrupting TX-mediated platelet aggregation (293), adding further mechanistic insight into its anti-inflammatory/proresolution properties. In disease states, RvE1 suppresses Porphyromonas gingivalis-induced oral inflammation and alveolar bone loss during periodontitis (294), demonstrates protective actions in trinitrobenzene-sulfonic acid-induced colitis in mice (272), as well as causing reepithelization of mouse cornea after thermal injury (268). Over all, RvE1 initiates resolution of inflammation and causes decreased numbers of PMNs at sites of inflammation early during the response (reviewed in reference 283).

Structure-activity assays have elucidated that RvE1 binds to an orphan GPCR belonging to the same cluster as ALX (ChemR23), with a high affinity (Kᵦ = 48.3 nm). This coupling downregulates the activity of NF-κB and hence TNF-α synthesis, as well as initiating signaling pathways involved in initiating mitogen-activated protein kinase (283). Indeed, ChemR23 activation has been demonstrated to inhibit one of the most prominent RvE1 actions, dendritic cell migration (285). Although it has been found in myeloid, gastrointestinal, kidney, brain, and CV tissue, the percentage of ChemR23 expression is...
highly variable. For example, it has been demonstrated that ChemR23 is markedly increased on the surface of human monocytes but less so on neutrophils by anti-inflammatory mediators such as TGF-β (295). Like ALX, ChemR23 acts as a receptor toward peptide ligands, including chemerin, that also act as anti-inflammatory mediators (296). RvE1 also appears to interact with the LTβ receptor, BLT1, and acts as a partial antagonist preventing neutrophil activation (289). Therefore, it can be concluded that RvE1 couples to two distinct receptors to both suppress proinflammatory mechanisms and enhance resolution pathways.

RvE2 is a second member of the EPA-derived family of E-series resolvins but is structurally distinct from RvE1. In human PMNs, it is generated at higher concentrations than RvE1, but is equipotent when given intravenously and additive when administered alongside RvE1 (292). As with RvE1, RvE2 suppresses PMN migration into the peritoneum after zymosan (292). Although it is still unclear what receptor RvE2 couples to, its identification is the subject of ongoing research.

D-series Rvs are derived from DHA and comprise four bioactive compounds, RvD1, RvD2, RvD3, and RvD4 (108). Like RvE1, RvD1/D2 exerts both anti-inflammatory and proresolution properties by blocking neutrophil infiltration, while in contrast enhancing macrophage phagocytosis of apoptotic PMNs (297–299). The latter occurs via the binding of RvD1 to either ALX or an orphan receptor, GPR32, present on the surface of both PMNs and monocytes, the expression of which is upregulated by inflammatory agonists, such as zymosan and GM-CSF (297). Interestingly, a member of the D-series Rvs has also been shown to contain microbicidal properties in septic mice initiated by cecal ligation and puncture. RvD2, whose receptor is GPR18 (300), in addition to blocking peritoneal PMN accumulation, markedly reduced bacterial load and proinflammatory cytokines, which subsequently led to increased survival and improved health (298).

As mentioned above, besides D-series Rvs, DHA also acts as a precursor for the biosynthesis of PDs. One member, PD1, has been demonstrated to be synthesized by microglial (111), peripheral blood mononuclear cells, and Th2 CD4⁺ T cells (108, 286). Similarly to Rvs, PD1 exerts potent immunoregulatory effects that include inhibiting neutrophil migration and Toll-like receptor-mediated activation (301), suppression of Th2 inflammatory cytokines and proinflammatory lipid mediators (302), as well as the upregulation of CCR5 on PMNs (10). PD1 also blocks T-cell migration in vivo and promotes T-cell apoptosis (303). In disease states, PD1 has been proven to be protective in experimental models of ischemic stroke (109), oxidative stress (304–306), asthma (302), ischemia/reperfusion renal injury (301), and Alzheimer’s disease (307). Indeed, Alzheimer’s patients given DHA-rich dietary supplements have reduced production of IL-1β, IL-6, and granulocyte CSF in peripheral blood mononuclear cells (308). As with RvE2, a receptor has yet to be identified. It is likely, however, that it couples to a distinct receptor to RvE1, as its anti-inflammatory effects are additive with those of RvE1 in vivo.

MARESINS
MaRs were identified in 2008 after 17S-D-series Rvs, PDs, as well as 14S-HDHA were isolated from the resolution phase of mouse peritonitis and were added to stimulated resident peritoneal macrophages (281). Macrophages then convert these intermediates to novel dihydroxy-containing products, which possess potent anti-inflammatory and proresolving properties. Although the exact biosynthetic pathway has yet to be elucidated, a hypothetical scheme was proposed. It is thought that DHA is converted to 14S-hydroperoxydocosahexaenoic acid (14S-HPDHA; maresin, MaR1) via 12- or 15-LOX, followed by reduction to 14S-HDHA and/or via double dioxygenation (e.g., sequential 12-LOX–5-LOX) to generate a metabolome of MaR1, 7S,14S-dihydroxydocasahexaenoic acid (7S,14S-diHDHA). Though MaRs have only been recently identified, it has been reported that, as with Rvs and PD1, MaR1 blocks the infiltration of PMNs, while stimulating macrophage phagocytosis of apoptotic PMNs/zymosan (281). Its metabolome 7S,14S-diHDHA was active but less potent.

CYTOCHROME P450
In the last decade, interest in a third, less well-characterized pathway of AA metabolism, CYP, has been rekindled. CYPs are families of membrane-bound, heme-containing enzymes found in the liver, brain, kidneys, lung, heart, and CV system, thought initially to be involved in catalyzing NADPH-dependent oxidation of drugs, chemicals, and carcinogens (309, 310). It is now well appreciated that CYPs also catalyze the conversion of fatty acids including AA into products that have been denoted EETs, HETEs, and dihydroxyicosatrienoic acids (DHETs) (311). For instance, AA is metabolized in the vascular endothelium by CYP epoxygenase to EETs (312), which can then be converted by epoxide hydrolase to the respective regioisomer of DHETs (311). In
the vascular smooth muscle, AA is catalyzed by CYP hydroxylases to 20-HETE (313). Indeed, one particular member, CYP4F3, is highly expressed in PMNs catalyzing the \( \omega \)-hydroxylation of LTs (314). However, it is unknown whether CYP4F3 is the source of 20-HETE produced by PMNs (315). These metabolites play a large and complex role in maintaining renal, cardiac, and pulmonary homeostasis by regulating aspects such as vascular tone and reactivity, renal and pulmonary functions, ion transport, and growth responses (316–318). Interestingly, they have also been demonstrated to exert potent anti-inflammatory actions (319–321), detailed below.

**CYP-DERIVED PRODUCTS AND INFLAMMATION**

EETs catalyzed by CYPs 2C8, 2C9, and 2J2 prevent the adhesion of PMNs to the vascular wall by suppressing the expression of cell adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, on the surface of endothelial cells in response to cytokines (TNF-\( \alpha \) and IL-1\( \alpha \)) and lipopolysaccharide (316, 321). Mechanistically, this is associated with inhibiting the activation of the transcription factor NF-kB via the inhibitor of NF-kB kinase (IKK) (321). As a consequence, EETs may therefore have the propensity to downregulate various cytokine-induced proinflammatory signaling pathways downstream of NF-kB activation. Indeed, it was recently reported that EETs display hyperalgesic bioactions during experimental inflammatory pain (319, 320). It was also shown that EETs could directly activate PPAR-\( \gamma \) in endothelial cells (322), with EET-mediated anti-inflammatory effects demonstrated to be blocked by PPAR-\( \gamma \) antagonists (322). EETs released from platelets have been shown to exert anti-thrombotic properties by inhibiting platelet aggregation induced by AA and vascular injury (323–325). It was also demonstrated that EETs could act in a profibrinolytic manner by increasing the expression of tissue plasminogen activator in a cAMP-dependent mechanism, thus suggesting that they could play an important role in controlling the fibrinolytic balance in the vessel wall (326). It was suggested that the anti-inflammatory properties of EETs occurred through their ligation to a cell surface receptor. It was reported that EETs bind with high affinity to an “EET receptor” on the surface of a monocytesc cell line, belonging to a specific class of GPCRs (327). The identity of this receptor and its role, if any, in initiating the immunomodulatory actions of EETs have yet to be determined.

CYP hydroxylase metabolites also exhibit anti-inflammatory properties. Similarly to EETs, 16-HETE can also block the adhesion of leukocytes to the endothelium (315). In fact, it also suppresses the synthesis of LTs as well as inhibiting rises in cerebrospinal fluid pressure (index of tissue damage and swelling) in a thromboembolic model of stroke in rabbits (315). Furthermore, 20-HETE and 16-HETE released from PMNs in response to factors that activate phospholipase (platelet-activating factor, calcium, and thrombin) also inhibit TX-induced platelet aggregation (328). Therefore, it can be surmised that not only do metabolites of CYPs maintain renal and CV health, but they also regulate other multiple signaling pathways including inflammation, fibrinolysis, platelet aggregation, and cellular injury.

**SUMMARY**

Studies on inflammation and its resolution have advanced our understanding of leukocyte trafficking, effecrocytosis, and proinflammatory leukocyte clearance, as well as immune-suppressive eicosanoids, specialized immune-regulatory cells, and cytokine catabolism. These pathways converge on the termination of acute inflammatory responses and contribute to the notion that chronic inflammation is avoided and wounds healed in an appropriate manner (329, 330). Implicit therein is that tolerance is not compromised, making the host susceptible to autoimmunity. AA metabolites were once considered proinflammatory due to the effective usage of NSAIDs in the treatment of chronic inflammatory diseases. While NSAIDs have been a valuable treatment in terms of anti-inflammation and pain relief, they have recently unmasked beneficial properties of some LOX and COX products. Thus, our understanding of eicosanoids in physiology and pathology has come a long way since the earliest observations of Kurzrok and Lieb (331). Hence, PGs may drive edema but prevent leukocyte trafficking, while at the same time elevating cAMP and impairing bacterial phagocytosis and killing. However, LTs oppose the immune-suppressive actions of PGE\(_2\), with 5-LOX metabolites thus enhancing macrophage antimicrobial functions and roles, including the phagocytosis of IgG-opsonized targets via the Fc\( \gamma \)R. COX/LOX-derived LXs, Rvs, and PCs attenuate innate immune responses, ameliorate or promote resolution, and are proving beneficial in experimental sepsis. Thus, the role of eicosanoids in inflammation is most likely dependent on the phase of the response during which they are synthesized, the tissues affected, and the nature of the inciting stimulus, with some AA metabolites...
counteracting the bioaction of others but also triggering the synthesis of other families of eicosanoids that terminate inflammation. And while eicosanoids act diversely in acute inflammation, their role in chronic, nonresolving inflammation may be far more complex. That notwithstanding, it now appears that not all eicosanoids are bad, as some attenuate innate immune-mediated functions and accelerate or facilitate their timely resolution. This offers a more accurate strategy in treating diseases driven by overexuberant inflammation.

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Lipid Mediators in Inflammation


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