

# Endogenous Receptor Agonists: Resolving Inflammation

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**Controlled resolution or the physiologic resolution of a well-orchestrated inflammatory response at the tissue level is essential to return to homeostasis. A comprehensive understanding of the cellular and molecular events that control the termination of acute inflammation is needed in molecular terms given the widely held view that aberrant inflammation underlies many common diseases. This review focuses on recent advances in the understanding of the role of arachidonic acid and  $\omega$ -3 polyunsaturated fatty acids (PUFA)–derived lipid mediators in regulating the resolution of inflammation. Using a functional lipidomic approach employing LC-MS-MS–based informatics, recent studies, reviewed herein, uncovered new families of local-acting chemical mediators actively biosynthesized during the resolution phase from the essential fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These new families of local chemical mediators are generated endogenously in exudates collected during the resolution phase, and were coined resolvins and protectins because specific members of these novel chemical families control both the duration and magnitude of inflammation in animal models of complex diseases. Recent advances on the biosynthesis, receptors, and actions of these novel anti-inflammatory and proresolving lipid mediators are reviewed with the aim to bring to attention the important role of specific lipid mediators as endogenous agonists in inflammation resolution.**

**KEYWORDS:** resolution, inflammation, neutrophil, arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), omega-3 polyunsaturated fatty acids ( $\omega$ -3 PUFA), resolvins, protectins, docosatriene, lipoxin (LX), prostaglandin (PG), human leukocytes, lipid mediators, apoptosis, chemokines, anti-inflammatory, aspirin

## INTRODUCTION

### Inflammation

The correct function of body tissues is indispensable for the proper function of the body as a whole. When tissues are injured through physical damage or are infected by exogenous microbial organisms, local and systemic responses are activated with the singular objectives to eliminate the offending factors as rapidly as possible, restore tissue integrity, and retain information about the offending agent in order to facilitate recognition and elimination on a future encounter. The outcome of these responses is a rapid physiological reaction of the body towards damage and infection, that is, inflammation. The inflammatory response effectively operates towards the removal of dead tissue and microbes, yet temporarily allows the body to deviate from homeostasis in order to recover normal functioning. Five cardinal signs of inflammation are often denoted to describe this deviation from apparent health at an ultrastructural level: *calor* (heat), *rubor* (redness), *tumor* (swelling), *dolor* (pain), and *functio laesio* (loss of tissue function)[1]. These signs are reflections of hyperemia (dilation of postcapillary venules causing increased tissue perfusion and decreased blood flow associated with tissue redness and hotness), an increase in capillary permeability (causing local fluid accumulation by exudation of serum and consequent rise in oncotic pressure), and peripheral nervous tissue stimulation by tissue swelling and increased sensitivity and perception of pain stimuli (causing increased awareness of tissue disturbance). Depending on the extent of the inflammatory response, a temporary diminution of normal organ function will result.

The inflammatory response is composed of a large number of molecular, cellular, and physiological changes that allow for the effective delivery of blood-borne leukocytes and lymphocytes to the damaged or infected tissue. Together with the local synthesis of regulatory mediators, and exudation of serum factors and acute phase proteins, a seemingly complex and multifactor, yet temporally highly scheduled, series of events takes place with the purpose to remove microbes and damaged tissue by phagocytosis, the central effector mechanism of inflammation[2]. The precise composition of components that are employed, as well as the temporal execution of cellular events during the inflammatory response by each tissue, depends on the molecular nature of microbial ligands and exposed structural components of damaged tissue. Specific molecular epitopes that “flag” tissue damage are recognized by recognition systems, such as complement, collectins, and tissue factor. Likewise, specific microbial epitopes are detected by the innate immune system via receptors localized on tissue sentinel cells, such as dendritic cells and macrophages[3]. A binary recognition of conserved microbial molecular patterns in combination with molecular components of damaged tissue has been proposed to function as an effective means to discriminate different types of damage, in the presence or absence of infection[4]. Recognition of microbial antigens also activates specific humoral and cell-mediated immunological responses targeted to inactivate particular types of microbes, and allows the building of a pool of memory lymphocytes that permits future recognition of the infectious or tissue damaging agents.

In a typical acute inflammatory response, a remarkably conserved temporal order of events appears to operate[1] (Fig. 1). After an initial increase in protein exudation, polymorphonuclear leukocytes accumulate in the inflamed tissue[5,6]. These normally circulating cells migrate to the inflamed tissue in a series of steps[7]. After first adhering to endothelial cells that line the capillaries perfusing the affected tissue, neutrophils migrate via transcellular diapedesis across the endothelium into the infected or damaged tissue[8]. Both positive cues and negative counter-regulatory signals at all steps involved in cellular migration from blood to tissue determine the magnitude of cellular infiltration and activation[9,10,11,12]. These activated neutrophils rapidly clear microorganisms and dead tissue by phagocytosis[13]. After terminating their phagocytotic function, the neutrophils die via apoptosis. Following the initial accumulation of neutrophils, a delayed infiltration of monocytes follows[1,14]. Monocytes differentiate into macrophages and on their turn remove remaining apoptotic polymorphonuclear leukocytes by nonphlogistic phagocytosis[15,16]. In this type of phagocytosis, immunomodulatory and tissue-protective mediators are released, which stop further events that maintain the evolution of inflammation. Monocyte-derived macrophages also play an important role in regulating

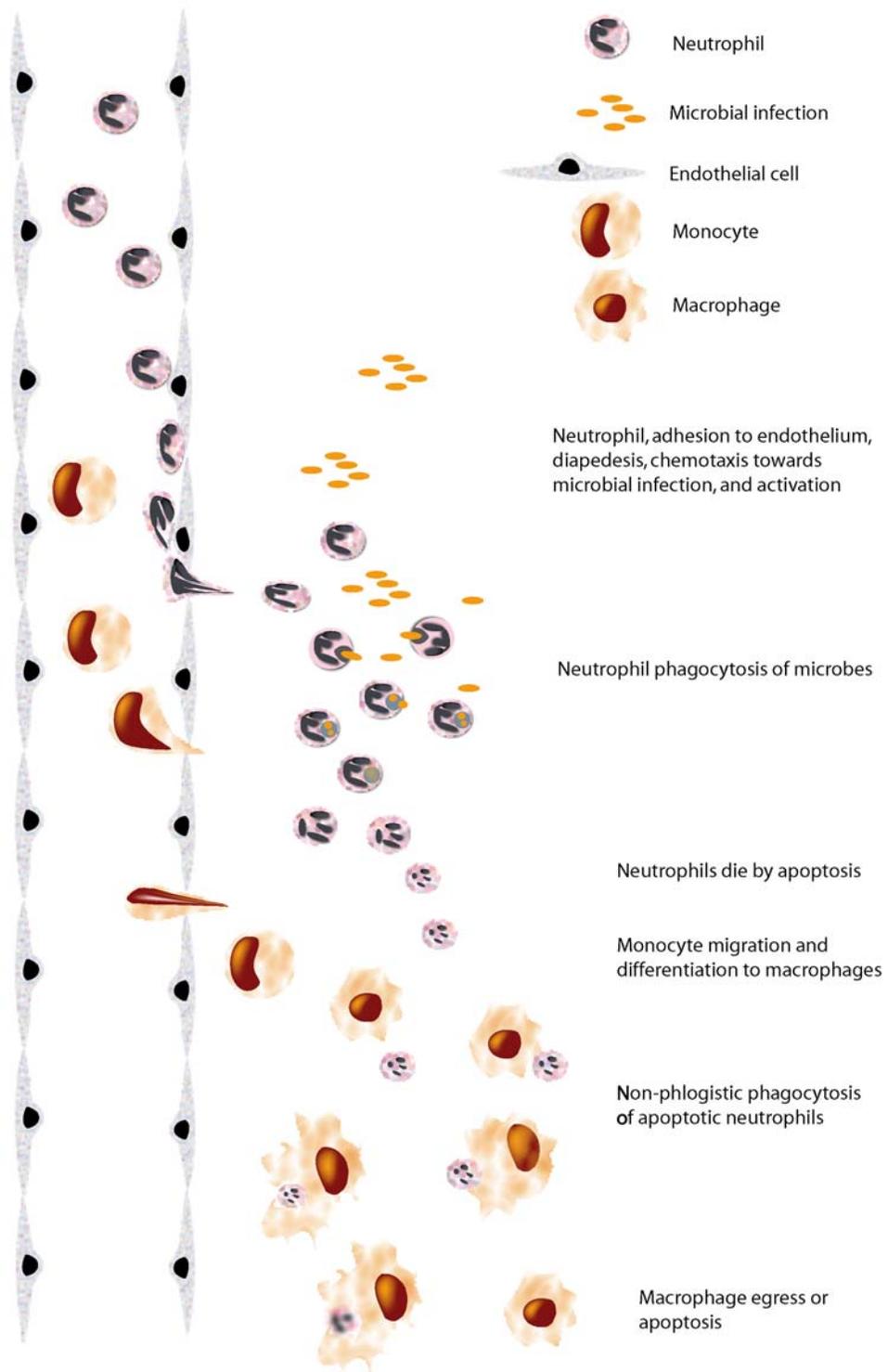


FIGURE 1. Representation of the temporal cellular events in the evolution of inflammation.

the subsequent restoration of tissue. Specific inflammatory cells may be called into action in particular types of infection; for example, eosinophils are particularly effective in eliminating infections by larger pathogens, such as helminthes. Lymphocytic inflammatory responses appear to become predominant during delayed-type hypersensitivity reactions. The preserved temporal order of events suggests that inflammation evolution is the activation of conserved elements that constitute a molecular program being executed according to the local needs for clearing the original inciting stimuli.

## Resolution of Inflammation

Effective clearance of microbial infections and damaged tissue is normally followed by resolution of inflammation. This process can be defined at the cellular level as the disappearance of accumulated polymorphonuclear leukocytes, and at macroscopic level as the reconstruction of tissue architecture and restoration of tissue function[1,17]. Complete resolution of tissues after bacterial infection will occur without loss of functional or structural damage and is directly related to the efficiency of microbial clearance[18,19,20]. Several mechanisms appear to drive the disappearance of inflammatory leukocytes, and operate in parallel or alternatively in different tissues. Apoptosis of leukocytes is one important route of elimination[21,22,23]. Cells that have completed their function as phagocytes undergo programmed cell death in response to local mediators that positively and negatively regulate the rate of apoptosis[24,25,26]. As polymorphonuclear leukocytes die, they simultaneously function as cytokine sinks that actively lower the level of proinflammatory cytokines from the inflammatory locus[27,28]. The apoptotic neutrophils are subsequently phagocytosed by macrophages (efferocytosis) in a so called nonphlogistic fashion, i.e., in the absence of further generation of proinflammatory mediators and stimulating the formation of anti-inflammatory mediators, such as transforming growth factor (TGF)- $\beta$ , lipoxin (LX)  $A_4$ , and interleukin (IL)-10[16,29,30]. Another important route of elimination of leukocytes is egress from the inflamed tissue, as shown for eosinophils in pulmonary inflammation[31]. Macrophages that have completed the elimination of apoptotic neutrophils on their turn disappear from the resolving inflammatory tissue by either apoptosis or egress via the lymphatic system[32].

Overall, an important conclusion of research into inflammation and resolution over the last 10 years is that both evolution and resolution are active components of the inflammatory response[24]. Resolution is not merely the passive dilution of inflammation, but displays the features of activation of specific molecular events that contribute to removal of inflammatory cells and restoration of tissue integrity. In view of the early activation of resolution as an integral part of the normal inflammatory response, and the execution of resolution as discrete molecular and cellular events, one can consider resolution (catabasis) as an essential characteristic of inflammation. The definition of catabasis is viewed as wider than just the decline from a state of disease, but rather the return to homeostasis, and emphasizes the cellular and molecular events involved in that return, which are likely to involve a set of conserved mechanisms[33,34]. To aid in defining the anti-inflammatory and resolution-stimulating actions of local mediators and drugs, we have provided a set of indices that define the cellular events during resolution with quantitative parameters[33]. An important conclusion that has emanated from a close observation of these measurable indices is that distinct lipid mediators that are generated at precise time points during the inflammatory response not only inhibit granulocytic inflammation, but also activate and accelerate resolution. As specific receptors for these anti-inflammatory and resolution-promoting lipid mediators have been shown to exist, it is now possible to firmly put forward the idea that specific chemical mediators function as endogenous receptor agonists stimulating the resolution of inflammation[24,35,36].

Defects in the normal development of inflammation are causal factors for and/or associated with tissue damage that underlies a large number of human diseases. Key roles for inflammation have been demonstrated in diseases as varied as Alzheimer's disease and cardiovascular disease[37], as well as cancer[38], which join the well-known inflammatory disorders, such as rheumatoid arthritis and periodontal disease[39,40,41]. Uncontrolled acute inflammatory responses, or chronic inflammation with recurrent episodes of acute inflammation, are associated with tissue damage that can cause discomfort and severely compromise normal tissue function. Inflammatory responses that are too active or do not resolve

can, consequently, instead of aiding the body to fight infections or restore tissue architecture, become harmful in themselves. The underlying mechanism of loss of tissue function as a result of inflammation is often ascribed to the situation where activated leukocytes generate reactive oxygen and nitrogen species, and release proteases at rates that damage tissue more rapidly than that it can restore[42,43]. For a normal execution of the inflammatory process, mechanisms must therefore exist that limit the extent of leukocyte accumulation during inflammation and tone down the magnitude of inflammation evolution. Lipid mediators derived from polyunsaturated fatty acids (PUFA) arachidonic acid (AA), and the  $\omega$ -3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), appear to play a particularly important role as activators of endogenous counter-regulatory, anti-inflammatory, and proresolution mechanisms. Recent studies have revealed the first molecular details of the mechanisms whereby AA- and  $\omega$ -3 PUFA-derived lipid mediators act as endogenous receptor agonists to trigger the active termination of inflammation via stimulating resolution. In the following sections, a closer look will be taken at the formation and actions of several resolution-stimulating lipid mediators.

## LIPID MEDIATORS AS AGONISTS FOR RESOLUTION

### AA-Derived Anti-Inflammatory Lipid Mediators

An important conclusion derived from studies carried out in the 1950s and 1960s that aimed to describe the chemical structure and formation of the prostaglandins, was that AA is the common endogenous precursor for the biosynthesis of a large family of bioactive lipid mediators, the eicosanoids[44,45]. AA is a substrate for both lipoxygenases and cyclooxygenases, fatty acid oxygenases that incorporate one or two molecules of molecular oxygen into a bis-allylic moiety of PUFA[45,46]. Fatty acid oxygenation by these specialized oxygenases was shown to be a required first enzymatic step in the formation of a large family of eicosanoids in animals that includes the prostaglandins, thromboxane, and leukotrienes. The generation of these lipid mediators requires the posterior modification of the primary oxygenated fatty acids by specific eicosanoid synthases, and many lipid mediators can be synthesized by a single cell type that possesses both cyclooxygenase and terminal synthase[47]. Several of the eicosanoids, such as prostaglandin (PG) E<sub>2</sub>, PGD<sub>2</sub>, leukotrienes, and thromboxane, were initially studied with respect to their role in inflammation and reproduction[48,49]. For example, PGE<sub>2</sub> exerts potent proinflammatory (proinflammatory) actions that include vasodilation, potentiation of the vascular permeability activated by histamine and bradykinin, sensitization of nerve terminals to pain stimuli, and the generation of fever during infections[50,51]. Leukotrienes are potent chemoattractants for neutrophils and mediators of vascular permeability[48]. A major focus of research on AA-derived lipid mediators has been, and still is, the understanding of their proinflammatory actions, as well as therapeutic manipulation of their biosynthesis. Although one of the prostaglandins, prostacyclin, was identified early as exerting physiological antagonistic actions to those of thromboxane in the regulation of platelet aggregation and vascular smooth muscle contraction[52], the potential anti-inflammatory or counter-regulatory actions of the eicosanoids have been surprisingly poorly explored or disregarded[53].

### *Lipoxins and Aspirin-Triggered Lipoxins*

The insight that different cell types interact, communicate, and act in concert in physiological settings, such as inflammation, did lead to studies in the beginning of the 1980s with the objective to determine whether oxygenated AA products formed in one cell type could serve as substrates in a second interacting cell type[54,55]. The demonstration that a second dioxygenation of 15S-hydroxy-eicosatetraenoic acid (15S-HETE) occurs in leukocytes, led to the description of a new class of eicosanoids, the lipoxins. Both LXA<sub>4</sub> and LXB<sub>4</sub> were isolated, their structures elucidated, and synthesized chemically[56,57]. Later studies confirmed that transcellular biosynthesis of LXA<sub>4</sub> is a primary route of eicosanoid biosynthesis in interacting cell types, such as neutrophils and epithelial cells, or platelets and neutrophils (Fig.5). LXA<sub>4</sub>

was subsequently identified to possess potent counter-regulatory actions in inflammation[57]. An important finding was that neutrophils can store 15S-HETE in an acylated form in specific phospholipids pools, and which can be rapidly released on cell stimulation and made available for further dioxygenation to form a second signal, such as LXA<sub>4</sub>, to regulate the function of the neutrophil[58]. In view of several identified cellular actions of LXA<sub>4</sub> that appeared to be inhibitory rather than stimulatory, LXA<sub>4</sub> was termed to act as a “chalone”, definable as a substance carried through the blood, which has an inhibitory effect on tissue, or organ that responds to its action. This terminology was further refined when it was discovered that LXA<sub>4</sub> does not indiscriminately inhibit cellular responses, but rather actively stimulates leukocytes and other cells via specific lipoxin binding sites[60]. The actions of LXA<sub>4</sub> more resemble that of a signal that actively “stops” neutrophil migration and activation in inflammation[61], and, on the other hand, activates in a non-phlogistic fashion monocyte migration[62]. LXA<sub>4</sub> is now known to exert potent anti-inflammatory actions that are mediated through the activation of a specific G-protein coupled seven-transmembrane domain-spanning lipoxin receptor[36,63]. In humans, there is one LXA<sub>4</sub> receptor named ALX/FPRL1, while in mice there are at least two receptors for LXA<sub>4</sub>, ALX1/Fpr-rs1 and ALX2/Fpr-rs2[36,64,65]. LXA<sub>4</sub> can be considered the first example of an endogenous amphiphilic autacoid that activates receptor-mediated molecular pathways to counter-regulate acute inflammation. The anti-inflammatory and counter-regulatory actions of LXA<sub>4</sub> operate at multiple levels in a variety of resident and mobile cell types. These include immediate actions on the regulation of signal transduction pathways activated by proinflammatory and cell growth-stimulatory mediators[66,67,68,69,70]. LXA<sub>4</sub> furthermore regulates gene transcription and transcription factor activity[71,72,73,74]. Stimulation of neutrophils and eosinophils with LXA<sub>4</sub> activates a potent inhibition of chemotaxis, adhesion and migration of these leukocytes in response to pro-inflammatory mediators[75,76,77,78]. It also potently reduces neutrophil degranulation, and regulates reactive oxygen and nitrogen species generation by leukocytes[74,79,80]. Actions of LXA<sub>4</sub> on other leukocytes include (1) the stimulation of monocyte migration, (2) stimulation of nonphlogistic phagocytosis by macrophages[81], (3) inhibition of dendritic cell migration and IL-12 formation[82], and (4) inhibition of natural killer cell cytotoxic activity[83]. In experimental animal models of inflammation, the administration of LXA<sub>4</sub> potently (low µg/kg bodyweight) reduces neutrophil accumulation in inflamed tissues, pointing to the activation of endogenous anti-inflammatory circuits by LXA<sub>4</sub>[57,84]. Moreover, transgenic mice with myeloid-selective overexpression of human ALX display a markedly reduced inflammatory infiltration of leukocytes in peritonitis, which further supports the counter-regulatory role of ALX[85]. Specific actions of LXA<sub>4</sub> have been identified on epithelial cells; in the gastrointestinal tract LXA<sub>4</sub> regulates IL-8 formation and has been found to play an important tissue protective role[72,86,87]. Moreover, LXA<sub>4</sub> acts as an endogenous receptor antagonist at the cysteinyl leukotriene receptor CysLT<sub>1</sub>[88]. Importantly, LXA<sub>4</sub> modulates vascular, respiratory, and nervous system physiology[89,90,91,92]. Taken together, a number of actions of LXA<sub>4</sub> appear to function in concert to counter-regulate inflammation and modulate physiology in order to favor resolution of inflammation. LXB<sub>4</sub> shares many of the actions of LXA<sub>4</sub>, but the study of its actions has not received as detailed consideration as LXA<sub>4</sub>. Of interest, LXB<sub>4</sub> acts via the activation of a distinct and still unknown receptor. Specific intracellular proteins such as protein kinase C[93,94] and the nuclear receptor AhR[95] have also been shown to constitute receptors for lipoxins, but the physiological relevance of these interactions remains to be investigated in full.

A diastereoisomer of LXA<sub>4</sub>, 15-*epi*-LXA<sub>4</sub>, is formed when AA is oxygenated by cyclooxygenase (COX)-2 when this enzyme is acetylated by aspirin, followed by a second oxygenation catalyzed by 5-lipoxygenase. This unique biosynthetic route permits the formation of a bioactive analogue of LXA<sub>4</sub>, named aspirin-triggered LXA<sub>4</sub> (ATL), which is more resistant to the normal routes of metabolic degradation of lipoxins *in vivo*. These routes are oxidation of LXA<sub>4</sub> to 15-oxo-LXA<sub>4</sub> by 15-hydroxyprostaglandin dehydrogenase, reduction to 13,14-dehydro-LXA<sub>4</sub> by 15-oxo prostaglandin 13-reductase/LTB<sub>4</sub>-12-hydroxy dehydrogenase, and ω-oxidation by specialized cytochrome P<sub>450</sub> enzymes[96,97]. 15-Epi-LXA<sub>4</sub> displays identical biological activities as native LXA<sub>4</sub>, and possess comparable affinity at the ALX receptor[36,98]. 15-Epi-LXA<sub>4</sub> has been taken as a lead for introducing structural modifications with the purpose to incorporate structural elements that further contribute to resist

metabolic degradation. These stable ATL analogs that resist metabolic inactivation have been proven to be equally efficacious ALX receptor agonists compared with their parent compound, and are often more potent anti-inflammatory compounds when administered *in vivo*[36,98]. Initial studies that employed the stable lipoxin analog 15-*R/S*-methyl-LXA<sub>4</sub> were key to bringing forward the concept of immunomodulation by lipoxins[99]. Administration of this compound in the mouse air pouch model not only lowered the levels of proinflammatory mediators MIP-2 and IL-1 $\beta$ , yet also stimulated the formation of IL-4, a cytokine with potent regulatory actions on inflammatory leukocytes, such as monocytes. The reorientation by LXA<sub>4</sub> of a cytokine-chemokine axis proved to be an essential propensity of lipoxins for regulating the acute inflammatory response[100]. The aspirin-triggered lipoxin analogs also potently activate the formation in epithelial cells of the microbicidal and opsonizing protein bactericidal-permeability inducing protein[101]. Recently, stimulation of nitric oxide formation by the aspirin-triggered lipoxins has been shown to account for at least part of the anti-inflammatory actions of aspirin[102].

Further modifications to the chemical structure of LXA<sub>4</sub> have been made with the aim to confer metabolic resistance to  $\beta$ -oxidation, another route of biotransformation of lipid mediators[103]. The replacement of carbon-3 in the LXA<sub>4</sub> structure with an oxygen atom has provided so-called 3-oxa lipoxin analogs that maintain efficacy as anti-inflammatory compounds after oral, topical, and systemic administration, and display enhanced pharmacokinetic properties. Selected 3-oxa-15-*epi*-LXA<sub>4</sub> analogs display increased efficacy compared to analogs that are sensitive to  $\beta$ -oxidation in particular models of inflammation, such as second-organ lung injury and dermal inflammation[84,104]. Interestingly, in spite of the development of metabolically stable lipoxin analogs, we have recently described that even after oral administration of nanogram amounts of native LXA<sub>4</sub>, systemic anti-inflammatory activity is maintained[84]. This finding likely reflects the specific and high-affinity binding by lipoxin receptors of its native ligand, recognition of which only requires localized picomolar to low nanomolar concentration. Specific lipoxin transport mechanisms, such as the voltage- and sodium-independent LXA<sub>4</sub> transporter that has been described in leukocytes[105], may potentially aid in concentrating and transporting lipoxins to their sites of action.

Importantly, the actions of LXA<sub>4</sub> and ATL are not limited to toning down or counter-regulating inflammation evolution, but also specifically stimulate resolution at several levels. By activating non-phlogistic monocytic infiltration, lipoxins facilitate the delivery of the cells that clear dying neutrophils and regulate tissue restoration[62]. Moreover, LXA<sub>4</sub> itself stimulates macrophages in their function as phagocytes of apoptotic neutrophils[81]. An early decrease in exudates levels of a range of proinflammatory cytokines and chemokines is activated by ATL, and may be explained by the recent observation that lipoxins stimulate chemokine sequestration by apoptotic neutrophils[27]. In the murine air pouch model of inflammation, LXA<sub>4</sub> is generated when neutrophils start expressing 15-lipoxygenase at the onset of resolution. At this stage, a large proportion of neutrophils are apoptotic and now complete a LXA<sub>4</sub> biosynthetic circuit together with 5-lipoxygenase that is already present in these cells[106]. In this setting, the precise temporal generation of LXA<sub>4</sub> specifically turns on resolution of inflammation. PGE<sub>2</sub> formation during the inflammatory response is critical for activating the formation of LXA<sub>4</sub> ([106], see below). Cyclooxygenase-derived prostaglandins also initiate the generation of LXA<sub>4</sub> in acid-induced acute lung injury in mice, and this action was found to be essential for the resolution of airway inflammation[107]. Additionally, macrophages exposed to apoptotic lymphocytes start to produce LXA<sub>4</sub>, which may further enhance apoptotic cell removal[29]. At the same time, this process activates the generation of TGF- $\beta$ , which can down-regulate a number of proinflammatory circuits[29]. The ATL stable analog ATLa<sub>2</sub> (16-*p*-fluorophenoxy-15-*epi*-LXA<sub>4</sub>-methyl ester) augments TGF- $\beta$  release prior to and during the resolution phase of zymosan A-stimulated peritonitis[33].

LXA<sub>4</sub> is known to regulate the proliferation of a number of cell types, including a potent inhibitory action on lung fibroblast proliferation in response to connective-tissue growth factor, and mesangial cell proliferation stimulated by platelet-derived growth factor, tumor necrosis factor (TNF)- $\alpha$ , or leukotriene (LT) D<sub>4</sub>[108,109]. LXA<sub>4</sub> furthermore reduces collagen biosynthesis and fibroblast growth induced by TGF- $\beta$ [110]. These actions indicate that lipoxins may counteract the fibrotic response, which is one of

several outcomes of tissue remodeling during inflammation. These findings most likely point to distinct temporal roles of lipid mediators such as promoting leukocyte clearance during the neutrophil-dominated resolution phase, and regulating tissue restoration after the inflammatory response resolves.

### **Prostaglandin E<sub>2</sub>**

PGE<sub>2</sub> is a ubiquitously formed eicosanoid in mammalian tissues. At least three different enzyme systems are known that can form PGE<sub>2</sub> from PGH<sub>2</sub>. Both cytosolic PGE<sub>2</sub> synthases and microsomal PGE<sub>2</sub> synthases are known, and may couple to specific cyclooxygenase-initiated biosynthetic routes[111,112,113]. The relatively widespread synthesis of PGE<sub>2</sub> matches the number of biological functions that this autacoid displays, and along with the multitude of functions is the presence of at least four PGE<sub>2</sub> (EP) receptors, EP1–4. Although PGE<sub>2</sub> is widely viewed as a proinflammatory mediator, a substantial number of studies indicate that PGE<sub>2</sub> also plays distinct roles in down-regulating immune-inflammatory responses, promotion of tissue repair, and as an activator of resolution[114]. The lung has long been known as a “privileged” site for such beneficial actions of PGE<sub>2</sub>[115]. Specific actions of PGE<sub>2</sub> in stimulating resolution of inflammation have been documented in allergic edema during infection of rats with the helminth *Angiostrongylus costaricensis*[116]. High concentrations of PGE<sub>2</sub> are formed during inflammation and specifically peak at the onset of resolution in the mouse air pouch model[106,117]. This is an essential event in establishing the complete biosynthetic pathway for LXA<sub>4</sub> in a single cell type, the apoptotic neutrophil. PGE<sub>2</sub> activates the transcription of 15-lipoxygenase in exudate neutrophils during TNF- $\alpha$ -induced inflammation. The generation of LXA<sub>4</sub> on its turn was shown to activate the resolution of inflammation[106]. Such a distinct role for PGE<sub>2</sub> in eicosanoid class switching to form LXA<sub>4</sub> during resolution does not appear to be involved in two other models of self-resolving inflammation. In zymosan-stimulated peritonitis in mouse, PGE<sub>2</sub> levels rise during the resolution interval, but is not accompanied with an increase in LXA<sub>4</sub>[33]. The LXA<sub>4</sub> concentration in the inflammatory exudate peaks during the proinflammatory phase where it may act to counterbalance LTB<sub>4</sub>-activated chemoattraction, migration, and activation of neutrophils[77]. In a second well-studied model of self-resolving inflammation, carrageenin-induced pleurisy in rat, PGE<sub>2</sub> is formed during the evolution of inflammation, but is not formed at all immediately prior to or during resolution[118]. These apparent incongruous results are perhaps providing us with the first indications of the existence of distinct types of resolution responses that are activated in particular settings of inflammation. Inflammation in the air pouch is a model for a slowly healing wound that is additionally stimulated by TNF- $\alpha$ , whereas zymosan-stimulated peritonitis and carrageenin-induced pleurisy are models of infection with minimal tissue damage. Resolving an inflammatory response to a wound vs. a sterile infection most likely also requires a different set of molecular actors in order to effectively return to homeostasis.

### **Prostaglandin D<sub>2</sub>**

PGD<sub>2</sub> is an important lipid mediator that acts on smooth muscle, inhibits platelet aggregation, influences pain sensation, and regulates our sleeping behavior[119]. Both the central nervous system and peripheral organs can synthesize PGD<sub>2</sub> via the isomerization of PGH<sub>2</sub> catalyzed by lipocalin-type and hematopoietic PGD synthases. PGD<sub>2</sub> has been shown to exert an important function in limiting neutrophil infiltration in the early phases of experimentally induced colitis in rat[120]. A specific function for PGD<sub>2</sub> in inflammation resolution has been indicated by a number of studies that have shown increased expression of the hematopoietic PGD synthase during resolution of heart inflammation after endotoxin treatment of mice[121], increased PGD<sub>2</sub> formation during resolution of peritonitis in mice[33], and a reduction of neutrophilic inflammation by local administration of hematopoietic PGD synthase-expressing fibroblasts in the murine air pouch model[122]. Furthermore, inhibition of PGD<sub>2</sub> formation, by inhibition of COX-2, impairs resolution of carrageenin-stimulated pleurisy in mice[118]. The role of PGD<sub>2</sub> in inflammation has become a subject of intense study after it was found nonenzymatic breakdown products of PGD<sub>2</sub> were

shown to display potent anti-inflammatory actions[49,123,124]. These products are prostaglandins possessing a cyclopentenone structure and include  $\text{PGJ}_2$ ,  $\Delta^{12}\text{-PGJ}_2$ , and 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$ . Specific proresolution actions of the cyclopentenones may be of particular importance in T-helper 1 (Th1)–type inflammatory reactions, where  $\text{PGD}_2$ -derived compounds regulate the intensity of delayed-type hypersensitivity responses and act as endogenous braking signals for lymphocytes to stimulate resolution[125].  $\Delta^{12}\text{-PGJ}_2$ , and 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$  also potently stimulate neutrophil apoptosis[126], their formation is triggered during phagocytosis of apoptotic neutrophils by macrophages[127], and regulate macrophage activation and proinflammatory gene expression[49]. The actions of the  $\text{PGD}_2$ -derived cyclopentenones appear to be induced independently from activation of the specific membrane receptors for  $\text{PGD}_2$ ,  $\text{DP}_1$ , or  $\text{CRTH}_2/\text{DP}_2$  receptor. Rather, their chemical reactivity permits covalent adduct formation with reactive sulfhydryl groups, a mechanism whereby these compounds regulate the activity of intracellular regulatory proteins. In particular, a number of redox-sensitive transcription factors, and their regulators, are now known to be regulated by cyclopentenone prostaglandins[128,129,130]. These include  $\text{PPAR}\gamma$ ,  $\text{Nrf2/Keap1}$ ,  $\text{NF-}\kappa\text{B}$ ,  $\text{AP-1}$ ,  $\text{H-Ras}$ , and  $\text{p53}$ . The activation of specific transcription factors subsequently triggers the transcription of genes that play regulatory roles in tissue protection and restoration during resolution[131]. Some points of controversy with regard to the cyclopentenone  $\text{PGD}_2$  products continue to provide an interesting front of research. First of all, careful studies of the biosynthesis of  $\text{PGD}_2$  products *in vivo* have indicated that the bioactive anti-inflammatory  $\text{PGD}_2$  dehydration products do not appear to be formed *in vivo* during situations where  $\text{PGD}_2$  is formed[132]. Furthermore, the use of supraphysiological concentrations of sulfhydryl-reactive products may have given experimental results that do not accurately reflect the *in vivo* situation. In contrast, mice deficient in hematopoietic  $\text{PGD}_2$  synthase display defects in resolution of T-cell-dominated inflammation in a model of delayed-type hypersensitivity. Resolution can be stimulated in these mice by administration of 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$ , indicating that  $\text{PGD}_2$ -derived cyclopentenone products do play an important role in terminating inflammation[125]. It remains a possibility that the reactive prostaglandin cyclopentenones are not detectable in their free form due to their fast rates of reaction with ubiquitous low molecular weight and protein sulfhydryl groups. Indeed, intracellular 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$  was detected in activated macrophages by monoclonal antibody specific to 15-deoxy- $\Delta^{12,14}\text{-PGJ}_2$ [133]. Taken together, the  $\text{PGD}_2$ -derived cyclopentenone products remain of interest, because their high potency and specific modes of action point to valuable therapeutic targets for stimulation of resolution. Covalent modifications of regulatory proteins by reactive cyclopentenones also indicate that not all agonists for resolution obligatorily act through reversible high-affinity interactions with cell-surface G-protein coupled receptors. Interestingly, the formation of the  $\text{PGD}_2$  dehydration products was originally found as an albumin-promoted reaction. The levels of both albumin and  $\text{PGD}_2$  are both markedly increased in inflammatory exudates before and during resolution[33]. The conditions for extracellular  $\text{PGJ}_2$  formation are therefore, at least theoretically, present, and detailed temporal studies on specific regulatory protein- $\text{PGJ}_2$  adducts may shed new light on the endogenous role of these potent  $\text{PGD}_2$ -derived anti-inflammatory compounds in resolution. Furthermore, the role of activation of the  $\text{PGD}_2$  receptors  $\text{DP}_1$  and  $\text{CRTH}_2/\text{DP}_2$  has not been addressed with respect to their involvement in resolution.

### **Prostaglandin $F_{2\alpha}$**

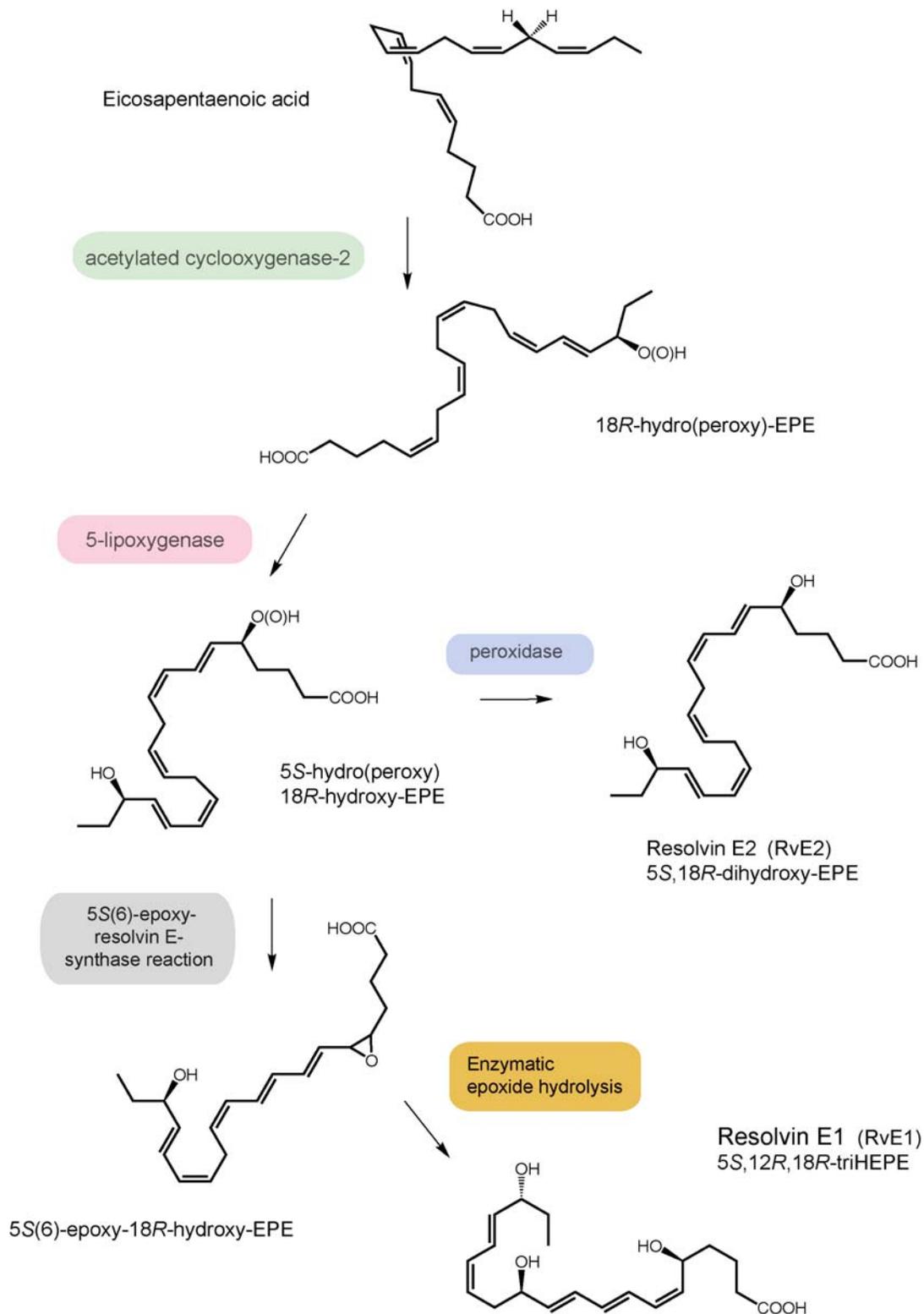
The role of  $\text{PGF}_{2\alpha}$  has been relatively little studied with respect to the resolution of inflammation.  $\text{PGF}_{2\alpha}$  can be synthesized by separate reductive routes from either  $\text{PGH}_2$  and  $\text{PGE}_2$ [134,135]. An 11-epi- $\text{PGF}_{2\alpha}$  epimer, with a different pharmacological profile from  $\text{PGF}_{2\alpha}$ , is formed by reduction from  $\text{PGD}_2$ . One recent study has indicated that  $\text{COX-2}$ -derived  $\text{PGF}_{2\alpha}$  may contribute to resolution of pleural inflammation in mice[136]. In this study, an exacerbation of murine pleural inflammation during the resolution phase after inhibition of  $\text{COX-2}$  by administration of a highly-selective cyclooxygenase-2 inhibitor was reversed by administration of the selective FP-receptor agonist fluprostenol. More detailed studies are required to demonstrate the precise role and contribution of  $\text{PGF}_{2\alpha}$  as an endogenous agonist for stimulating resolution.

## $\omega$ -3 PUFA-Derived Anti-Inflammatory/Proresolution Lipid Mediators

Studies at the beginning of the 20<sup>th</sup> century already indicated the essential roles of  $\omega$ -3 PUFA in health[137]. Many studies have since addressed the beneficial properties that underlie the protective action of EPA and DHA, the major  $\omega$ -3 PUFA in mammalian organisms[138,139,140,141]. A large randomized trial carried out with >11,000 patients with cardiovascular disease (Gruppo Italiano per lo Studio della sopravvivenza nell'Infarto miocardico study) showed that patients taking almost 1 g of  $\omega$ -3 PUFA per day displayed an approximately 45% reduction in sudden death[142,143]. Inspection of the details of this trial indicated that patients also were taking aspirin. Aspirin therapy was not taken into account for the beneficial outcomes of this trial. The human lipoxygenases (5-lipoxygenase [LO], 12-LO and 15-LO) can oxygenate  $\omega$ -3 PUFA to several monohydroxylated products. The biological importance of these lipoxygenase-derived products was not known[144,145,146]. Cyclooxygenase can oxygenate EPA to form PGH<sub>3</sub>, which can subsequently be transformed to analogs of the natural AA-derived prostaglandins. However, these prostaglandin-like compounds appear to be far less potent agonists for the specific prostaglandin receptors. DHA can also be oxygenated in a nonenzymatic fashion to isoprostane-like compounds (neuroprostanes) in the brain[147], or undergo autooxidation to racemic mixtures of monohydroxy compounds[148]. Early studies had indicated that cyclooxygenase does not oxygenate DHA[149]. In summary, several decades of research to understand the molecular basis for the essential roles of  $\omega$ -3 PUFA in human health have not provided a clear molecular mechanism to explain their regulatory and immunoprotective roles.

### **Resolvins**

Recently, we have identified novel oxygenated products derived from EPA and DHA that are generated via enzymatic pathways. Importantly, these compounds were identified first during the resolution phase of acute inflammation[150,151,152], namely, in a murine model of inflammation that spontaneously resolves, the dorsal skin air pouch[53,153]. Exudates were collected during the resolution phase and lipid mediator profiles were carefully recorded using LC-UV-MS/MS. Exudate cells from resolving air pouches that had been supplied with EPA and aspirin generated 18*R*-HEPE, 5-HEPE, and 5,12,18*R*-trihydroxy-EPE on stimulation of the cells with calcium ionophore (Fig. 2). Human endothelial cells expressing cyclooxygenase-2 incubated with aspirin and EPA formed 18*R*-HEPE. Incubation of 18*R*-HEPE with human neutrophils generated 5,12,18*R*-trihydroxy-EPE, as well as LXA<sub>5</sub>[150]. 5,12,18*R*-Trihydroxy-EPE proved to be a very potent inhibitor of human neutrophil transmigration across endothelial cells towards chemoattractants, such as LTB<sub>4</sub> and fMLP[150]. Isolated cyclooxygenase-2 treated with aspirin oxygenated EPA to form 18*R*-HEPE as well as 15*R*-HEPE. Of interest is the finding that two other commonly used anti-inflammatory drugs, acetaminophen and indomethacin, were found to also permit the oxygenation of EPA by COX-2 to form 15*R*- and 18*R*-HEPE. In summary, these initial experiments indicated that vascular endothelial cells containing COX-2 acetylated by aspirin convert EPA to 18*R*-HEPE, which is oxygenated by 5-LO in human neutrophils to form a 5(6)-epoxide-containing intermediate that undergoes epoxide hydrolysis and rearrangement to 5,12,18*R*-triHEPE (Fig. 2). This compound was named Resolvin E1 (RvE1), a name that reflects the temporal frame in which biosynthesis occurs (resolution phase), as well as the spatial cellular organization (interaction) necessary for bringing together the required biosynthetic enzymes. The complete stereochemical assignment was established using biogenic and synthetic materials and proved to be 5*S*,12*R*,18*R*-trihydroxy-6*Z*,8*E*,10*E*,14*Z*,16*E*-



**FIGURE 2.** Biosynthesis of E-series resolvins. EPA is the endogenous substrate for the formation of E-series resolvins, RvE1 and RvE2. EPA is first oxygenated by COX-2, acetylated in its catalytic center by aspirin, to form 18R-hydroperoxy-EPE, which is subsequently oxygenated by neutrophil 5-LO to form 5S-hydroperoxy-18R-HEPE. RvE1 is formed via the formation of an epoxide and subsequent hydrolysis. RvE2 is formed by reduction of the hydroperoxy group.

EPA[150,154]. RvE1 displays potent anti-inflammatory actions *in vivo*; intravenous administration of 100 ng compound reduces exudate cell numbers in the murine air pouch model[33,151,154]. In zymosan A-stimulated murine peritonitis, local administration of 300 ng RvE1 reduces exudate leukocyte numbers and activates resolution at an earlier time point, without shortening the resolution interval  $R_i$ . RvE1 specifically reduces the exudate levels of a number of proinflammatory cytokines and chemokines (IL-6, TNF- $\alpha$ , KC, JE, MIP-1 $\alpha$ , MIP-2, and RANTES) during resolution[33]. RvE1 reduces pathogen-stimulated dendritic cell IL-12 generation and migration in the spleen[154]. RvE1 also reduces *Porphyromonas gingivalis*-induced oral inflammation and alveolar bone loss during periodontitis[155], as well as has protective actions in trinitrobenzene-sulfonic acid-induced colitis in mice[156]. RvE1 binds to a G-protein coupled receptor to down-regulate the activity of NF- $\kappa$ B. This RvE1 receptor is expressed in myeloid, gastrointestinal, kidney, brain, and cardiovascular tissues[154]. Prior studies identified this receptor to be a receptor for the serum peptide chemerin, and is hence termed ChemR23[157]. It is also known as chemokine-like receptor-1. The inhibitory action of RvE1 on dendritic cell migration has been demonstrated to be mediated through ChemR23 activation[154]. Interestingly, human adherent monocytes display a marked ChemR23 expression, but neutrophils do not. This observation indicates that tissue monocytes/macrophages could substantially contribute to the resolution-promoting actions of RvE1. The ChemR23 receptor is up-regulated by the anti-inflammatory cytokine TGF- $\beta$ [158]. Given the potent actions of RvE1 on neutrophils, the existence of a second receptor for RvE1 on human neutrophils is implied.

Just as lipoxins are susceptible to metabolic degradation to regulate tissue concentrations, RvE1 is transformed by 15-hydroxy-prostaglandin dehydrogenase in the lung to form 18-oxo-RvE1, which is inactive *in vivo*.  $\omega$ -Hydroxylation of RvE1 was found to be a major route of metabolism in human neutrophils[159]. A stable analog of RvE1, 19-(*p*-fluorophenoxy)-RvE1, was synthesized to circumvent these two major routes of metabolic inactivation, and was shown to retain the anti-inflammatory properties of RvE1[159]. Recently, RvE2 (5*S*,18-dihydroxy-EPA) (Fig. 2) was identified and proved to be as potent as RvE1 to block the infiltration of neutrophils in zymosan-stimulated murine peritonitis[160].

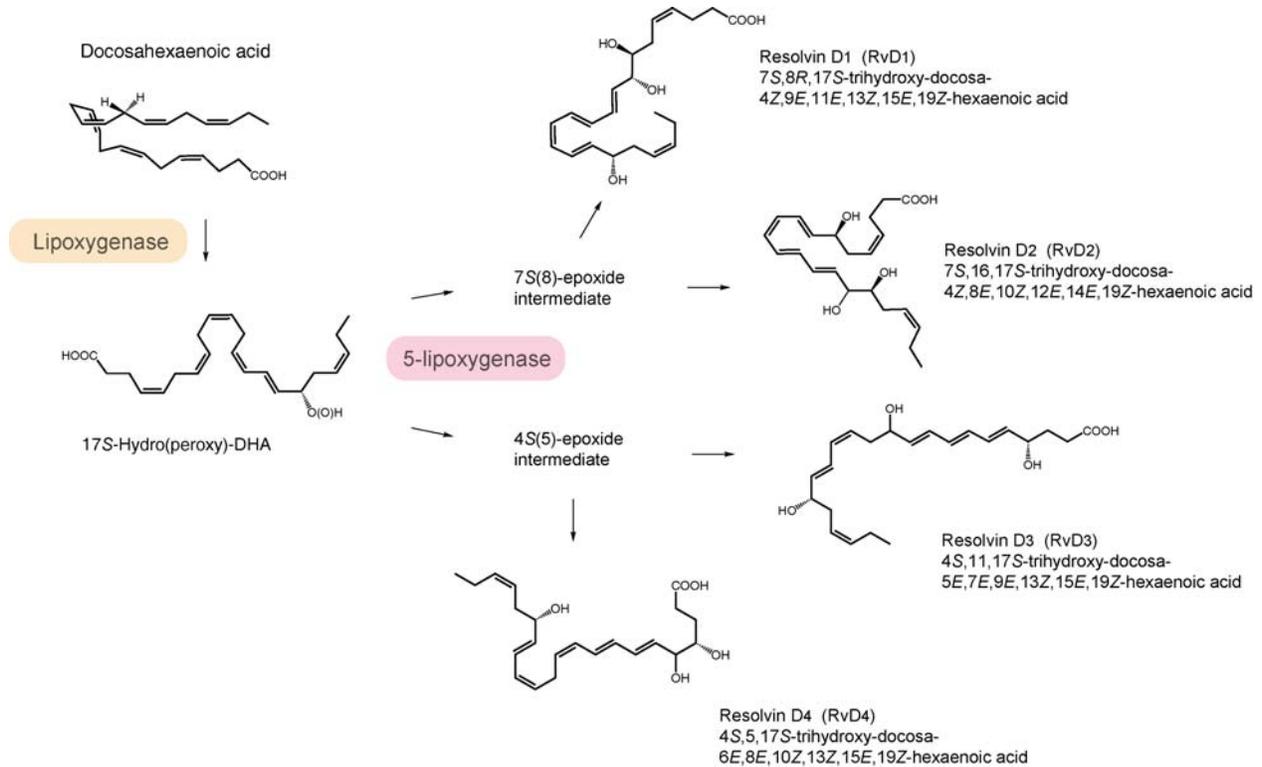
### **Aspirin-Triggered D-Series Resolvins**

Not only EPA proved to be a substrate for the generation of novel compounds that possess potent anti-inflammatory, immunoregulatory, and tissue-protective actions[161,162]. DHA was subsequently shown to be oxygenated by aspirin-acetylated COX-2 as well. Resolving exudates from mice given aspirin and DHA contained 17*R*-hydroxy-DHA (17*R*-HDHA)[151]. The same compound was formed by microvascular endothelial cells treated with aspirin. Recombinant COX-2 can convert DHA to 13*S*-hydroxy-DHA, but when acetylated by aspirin the oxygenation of DHA switches to forming the epimeric 17*R*-hydroperoxy-DHA. This aspirin-triggered biosynthetic pathway has been shown to operate at sites of exudate formation (murine air pouch model) and in brain. 5-LO in human neutrophils can further oxygenate 17*R*-HDHA to form 4-hydroperoxy-17*R*-HDHA and 7-hydroperoxy-17*R*-HDHA. Both of these two intermediates can undergo further transformations to the corresponding 4,17*R*- and 7,17*R*-dihydroxylated compounds via reduction of the hydroperoxy group, as well as to trihydroxylated compounds formed via an intermediate epoxy group, and subsequent spontaneous or epoxide hydrolase-catalyzed hydrolysis (Fig. 3). Potent inhibitory actions by these novel aspirin-triggered DHA-derived bioactive products (aspirin-triggered D-series resolvins) were demonstrated on IL-1 $\beta$  secretion by glioma cells, and on neutrophil infiltration in zymosan A-stimulated peritonitis and the murine air pouch model[151].

### **Protectins and 17*S* D-Series Resolvins**

Interestingly, neither aspirin nor exogenous DHA was required for the *in vivo* formation of D-series resolvins that are hydroxylated at the C17 position as the *S*-stereoisomers (Fig. 3)[152]. Release of endogenous DHA can be demonstrated during the inflammatory response[33], most probably via the stimulated deacylation of DHA from intracellular phospholipid pools[163]. Endogenous DHA can be

converted via lipoxygenase-initiated mechanisms *in vivo* to the 17*S* alcohol-containing series of resolvins (Fig. 3) and to compounds that possess a docosatriene structure (Fig. 4)[152,161]. One specific DHA-derived lipid mediator, 10,17*S*-docosatriene, was termed protectin D1 (PD1). When it is generated in neural tissue[164], this compound is termed neuroprotectin D1 (NPD1). The complete stereochemistry

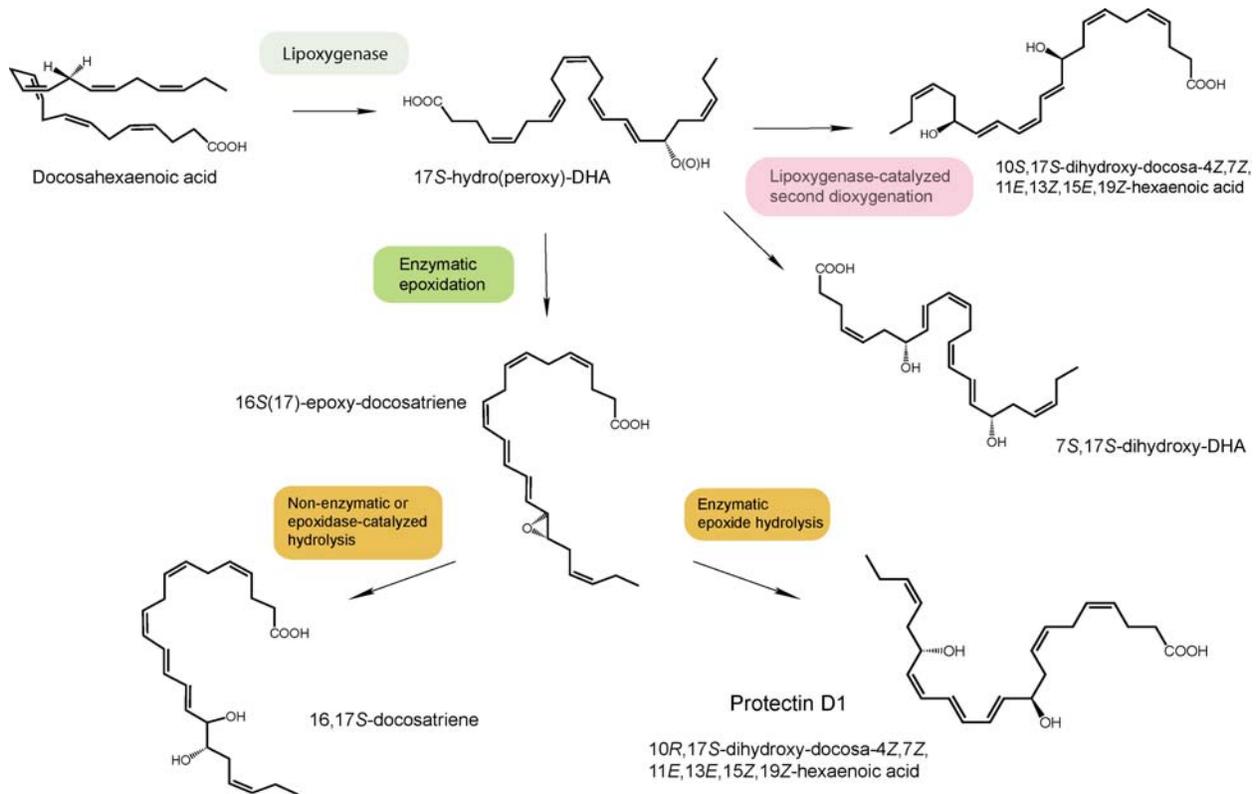


**FIGURE 3.** Biosynthesis of D-series resolvins. DHA is the endogenous substrate for the formation of novel D-series resolvins. These lipid mediators are formed by oxygenation via the action of a lipoxygenase at the carbon-17 position forming 17*S*-hydroperoxy-DHA, followed by a second oxygenation step catalyzed by neutrophil 5-LO. Note that acetylated COX-2 transforms DHA to 17*R*-hydroperoxy-DHA allowing the formation of the corresponding 17*R* D-series resolvins (aspirin-triggered resolvins).

and double bond configuration of PD1 has recently been established. This docosatriene-containing structure is formed from 17*S*-hydroperoxy-DHA via an intermediate epoxide that opens via hydrolysis and subsequent rearrangement to form (*in vivo*) 10*R*,17*S*-dihydroxy-docosa-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-hexaenoic acid[164]. PD1 formation has been demonstrated in brain, blood, Th2-skewed lymphocytes, after ischemia/reperfusion in kidney, and during the resolution phase of zymosan A-stimulated inflammation[33,152,161,165]. Potent tissue-protective and anti-inflammatory actions are exerted by PD1. PD1 reduces neutrophil accumulation in murine peritonitis after intravenous administration of 100 ng compound[152]. Neutrophil transmigration across endothelial cells was reduced approximately 50% by 10 nM PD1, whereas the  $\Delta$ 15-trans isomer of PD1 was inactive. Potent protective actions afforded by this lipid mediator have been determined in experimental models of stroke[161], and in the protection of retinal epithelial cells from oxidative stress[161,162]. Furthermore, a markedly reduced formation of PD1 and decreased 15-LO expression has been found in Alzheimer's disease brain tissue[41]. Both 17*S*-hydroxy-DHA and NPD1 have been shown to potently reduce TNF- $\alpha$ -stimulated IL-1 $\beta$  gene transcription in human glial cells[152].

The potent and stereospecific actions of PD1 strongly suggest that PD1 acts through a yet unidentified receptor. A further indication to the existence of a specific PD1 receptor is the observation that the

inhibitory actions of PD1 are additive with those of RvE1 *in vivo*[164]. An explicit role for PD1 in resolution of inflammation has been exposed[33]; the formation of PD1 is activated specifically during the resolution phase of murine peritonitis. Local administration of 300 ng PD1 prior to initiation of zymosan A-stimulated peritonitis reduced maximal neutrophil infiltration (decreased  $\phi_{max}$ ), shortened the resolution interval (decreased  $R_i$ ), and activated resolution at an earlier time point (decreased  $T_{max}$ ). Furthermore, like RvE1, PD1 reduced proinflammatory cytokine levels specifically during the resolution phase in this model of inflammation[33].



**FIGURE 4.** Biosynthesis of PD1. 17S-Hydroperoxy-DHA, generated by oxygenation of DHA, can also be transformed to a 16S(17)-epoxy-docosatriene intermediate that, via hydrolysis, leads to the formation of a 10R,17S-dihydroxy-triene-containing lipid mediator named PD1, as well as a 16,17S-docosatriene. A second lipoxygenation-catalyzed dioxygenation of 17S-hydroperoxy-DHA leads to the formation of the double-dioxygenated 10S,17S-dihydroxy geometric isomer of PD1, as well as 7,17S-dihydroxy-DHA. Note that aspirin-acetylated COX-2 can oxygenate DHA to form 17R-hydroperoxy-DHA allowing the generation of the corresponding 17R-epimeric aspirin-triggered products.

D-series resolvins with protective actions are also formed during inflammation. In response to bilateral ischemia/reperfusion of mouse kidney injury, small amounts of 17S-DHA and RvD2 (7S,16,17S-trihydroxy-DHA) were found in kidney tissue and in plasma[166]. On intravenous and subcutaneous administration of DHA, the formation of these products was markedly increased, and the formation of RvD1 (7S,8,17S-trihydroxy-DHA) and lower levels of RvD3 (Fig. 3), RvD5, and RvD6[167] were activated as well. Administration of RvD1, RvD2, and RvD3 prior to and during ischemia afforded kidney tissue protection, both functionally and morphologically; exerted a marked anti-inflammatory action; and reduced the subsequent development of interstitial fibrosis[166]. The generation of RvD1 in brain has been demonstrated after an ischemic insult to murine brain[161].

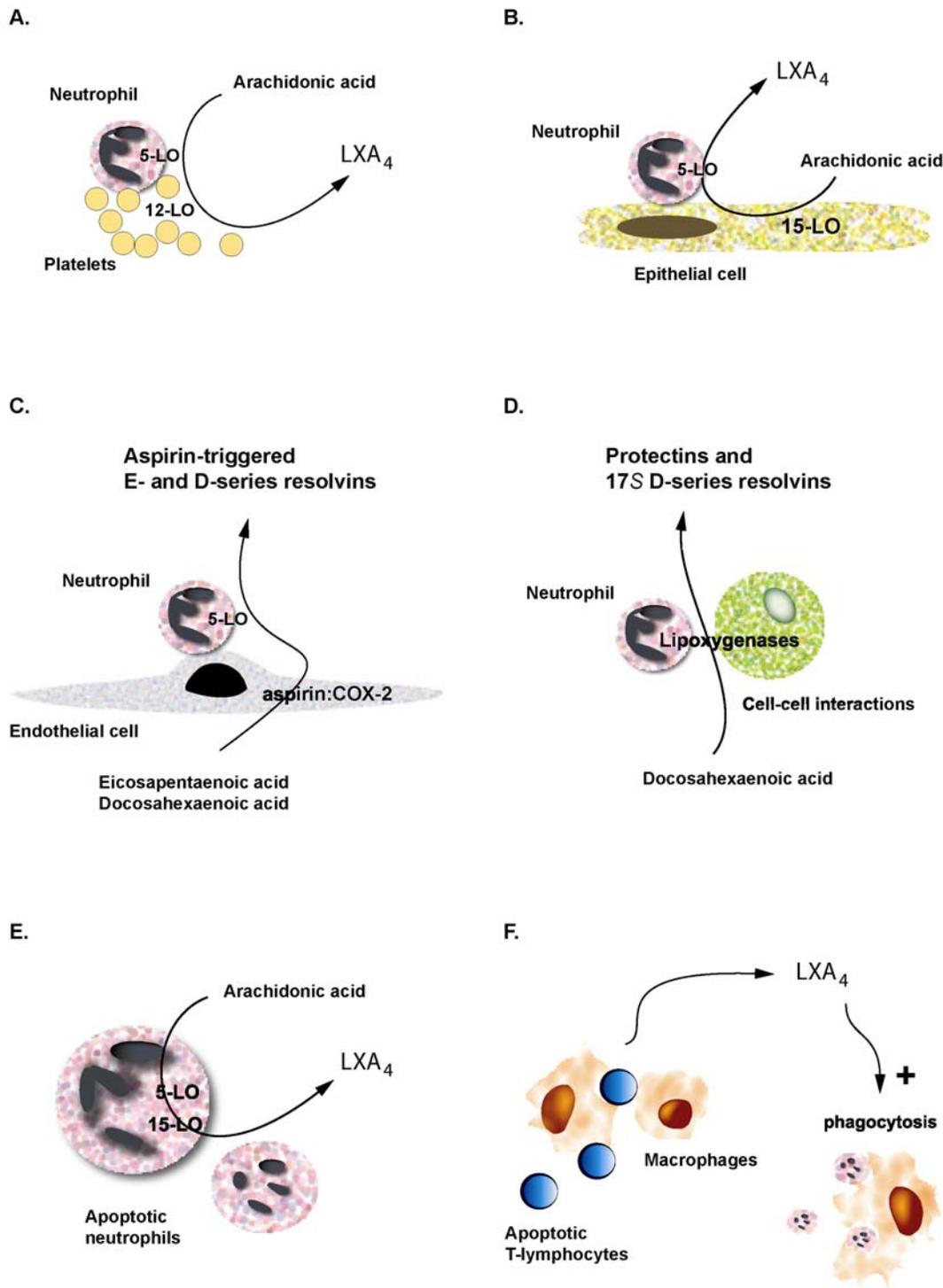
Taken together, a number of recent studies have now revealed that both EPA and DHA are endogenous precursors for the generation of a new and large family of oxygenated products that possess potent protective anti-inflammatory and resolution-stimulating actions. These actions are mediated via the

activation of specific receptors, of which ChemR23 is the first identified receptor. Further support for the role of EPA and DHA as endogenous precursors for the synthesis of protective resolvins and protectins has recently been demonstrated employing transgenic Fat-1 mice that are able to synthesize  $\omega$ -3 PUFA endogenously. These mice form resolvins and protectins endogenously and display a reduced inflammatory response in colitis compared to wild-type mice that are essentially dependent on dietary sources of EPA and DHA[168,169]. It is important to stress that lipid mediators of the resolvins and protectin family exert their action at picomolar to nanomolar concentrations[150,151,152,161,162], whereas EPA- and DHA-derived prostaglandin-like products, which have been characterized in earlier studies, are far less potent or devoid of biological action[144,149,170]. It is of interest that microbial organisms also possess the capacity to form oxygenated fatty acids that could feed into endogenous biosynthetic circuits forming resolvins. For instance, EPA can be converted by microbial cytochrome P<sub>450</sub> to form 18R-HEPE, which can subsequently be transformed to RvE1 by neutrophil 5-LO. Similarly, LTB<sub>5</sub> can be transformed *in vitro* to RvE1 by this cytochrome P<sub>450</sub> [150,171]. This route of biosynthesis was useful in the biogenic synthesis of RvE1. Whether this route is used *in vivo* in certain biological settings remains of interest. Symbiotic and pathogenic microbes have developed biosynthetic routes in coevolution with their natural hosts, and have learned to exploit the formation of anti-inflammatory, host-protective, and immunomodulatory biosynthetic routes for their survival[171,172,173].

## SUMMARY AND CONCLUSION

A physiologically normal inflammatory response can be viewed as having defined temporal phases of inflammation evolution and resolution. A number of studies in the field have now led to the idea that the inflammatory response comprises a number of programmed events that are executed in a temporally defined fashion. Several important checkpoints in inflammation can be assigned that activate the next stage of the response. It is important to note that different components may activate the employment of subsets of molecular components, or possibly in a different temporal order, depending on the original molecular stimulus that initiated inflammation. For example, we have seen that in acute inflammation initiated by administration of TNF- $\alpha$  in the mouse air pouch, resolution on inflammation turns on when apoptotic neutrophils start expressing 15-LO, which in concert with already present 5-LO completes the formation of a LXA<sub>4</sub> biosynthetic circuit[106]. In zymosan A-initiated murine peritonitis, LXA<sub>4</sub> appears to play a role during the evolution of inflammation, possible as a counteracting signal to regulate the magnitude of neutrophil infiltration[33]. Yet, in this model, the proresolving docosatriene PD1 is specifically formed during resolution. Together with the resolution-promoting and accelerating actions of resolvins and protectins, these findings point to central roles for endogenous lipid mediators in the activation of resolution. Delineating the different “programs” of inflammation is an important and interesting aim for future investigations, as therapeutic intervention in inflammation may need to beget precision in order to target specific components of the inflammatory response.

Inflammation underlies and accompanies a majority of the diseases that afflict human beings. Yet, treatment of inflammatory disease is generally limited to the use of compounds that antagonize the evolution of inflammation. It still remains a major challenge to treat chronic or recurrent inflammatory diseases. It is only recently that we have started to consider that the stimulation of inflammation resolution may constitute a viable therapeutic approach for treatment of inflammatory disease. We have learned that in experimental models of inflammation, resolution of inflammation is not merely the termination of inflammation, but displays discrete molecular and cellular changes that point to the active progression of inflammation to the healthy state. If the view is taken that resolution is the execution of a program that forms an essential part of the acute inflammatory response, then it follows that the temporally defined generation of pro- and anti-inflammatory and proresolution lipid mediators is an integral part of this program. Our growing appreciation that these mediators exert their biological actions



**FIGURE 5.** Generation and actions of anti-inflammatory/pro-resolution lipid mediators during acute inflammation and resolution. The formation of anti-inflammatory and pro-resolution lipid mediators is characterized by heterotypic cellular interactions that bring together the required fatty acid oxygenases permitting transcellular biosynthesis. (A) Biosynthesis of LXA<sub>4</sub> by transformation of AA via oxygenation by neutrophil 5-LO and platelet 12-LO. (B) Biosynthesis of LXA<sub>4</sub> by transformation of AA via sequential oxygenation by epithelial cell 15-LO and neutrophil 5-LO. (C) Formation of aspirin-triggered E- and D-series resolvins from the  $\omega$ -3 PUFA EPA and DHA. (D) Formation of protectins and D-series resolvins from DHA via sequential oxygenation steps involving neutrophil lipoxygenases and other inflammatory cells lipoxygenases. (E) Formation of LXA<sub>4</sub> by apoptotic neutrophils expressing both 5- and 15-LO[106]. (F) Formation of LXA<sub>4</sub> by macrophages that are exposed to apoptotic lymphocytes[29]. The formed LXA<sub>4</sub> contributes to the nonphlogistic nature of apoptotic cell removal by phagocytosis, and LXA<sub>4</sub> itself can stimulate the phagocytosis of apoptotic neutrophils[81].

via the activation of specific receptors indicates that agonist-receptor interactions are critical regulatory events in the progression of the normal inflammatory response. Possibly, defects in the generation of the discussed proresolution lipid mediators, their agonist-receptor interactions, and subsequent signaling actions, underlie inflammatory disease. This puts forward the very interesting prospect for active modulation of life-threatening acute inflammation or chronic inflammatory disease through activation of specific endogenous resolution circuits.

## ACKNOWLEDGMENTS

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## REFERENCES

1. Cotran, R.S., Kumar, V., and T., C. (1999) *Robbins Pathologic Basis of Disease*. W.B. Saunders, Philadelphia.
2. Metchnikoff, E. (1893) *Lectures on Comparative Pathology of Inflammation*. New York.
3. Medzhitov, R. and Janeway, C.J. (2000) Innate immune recognition: mechanisms and pathways. *Immunol. Rev.* **173**, 89–97.
4. Nathan, C. (2006) Neutrophils and immunity: challenges and opportunities. *Nat. Rev. Immunol.* **6**, 173–182.
5. Kolaczowska, E., Shahzidi, S., Seljelid, R., van Rooijen, N., and Plytycz, B. (2002) Early vascular permeability in murine experimental peritonitis is mediated by residential peritoneal macrophages and mast cells: crucial involvement of macrophage-derived cysteinyl-leukotrienes. *Inflammation* **26**, 61–70.
6. Dahlén, S.E., Björk, J., Hedqvist, P., Arfors, K.E., Hammarstrom, S., Lindgren, J.Å., and Samuelsson, B. (1981) Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules: in vivo effects with relevance to the acute inflammatory response. *Proc. Natl. Acad. Sci. U. S. A.* **78**, 3887–3891.
7. Springer, T.A. (1994) Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* **76**, 301–314.
8. Luster, A.D., Alon, R., and von Andrian, U.H. (2005) Immune cell migration in inflammation: present and future therapeutic targets. *Nat. Immunol.* **6**, 1182–1190.
9. Louis, N.A., Hamilton, K.E., and Colgan, S.P. (2005) Lipid mediator networks and leukocyte transmigration. *Prostaglandins Leukot. Essent. Fatty Acids* **73**, 197–202.
10. Serhan, C.N. (1994) Eicosanoids in leukocyte function. *Curr. Opin. Hematol.* **1**, 69–77.
11. Graves, D.T. and Jiang, Y. (1995) Chemokines, a family of chemotactic cytokines. *Crit. Rev. Oral Biol. Med.* **6**, 109–118.
12. Marasco, W.A., Phan, S.H., Krutzsch, H., Showell, H.J., Feltner, D.E., Nairn, R., Becker, E.L., and Ward, P.A. (1984) Purification and identification of formyl-methionyl-leucyl-phenylalanine as the major peptide neutrophil chemotactic factor produced by *Escherichia coli*. *J. Biol. Chem.* **259**, 5430–5439.
13. Segal, A.W. (1981) The antimicrobial role of the neutrophil leukocyte. *J. Infect.* **3**, 3–17.
14. Ryan, G.B. and Majno, G. (1977) Acute inflammation. A review. *Am. J. Pathol.* **86**, 183–276.
15. Van Furth, R., Diesselhoff-den Dulk, M.C., and Mattie, H. (1973) Quantitative study on the production and kinetics of mononuclear phagocytes during an acute inflammatory reaction. *J. Exp. Med.* **138**, 1314–1330.
16. Huynh, M.L., Fadok, V.A., and Henson, P.M. (2002) Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF- $\beta$ 1 secretion and the resolution of inflammation. *J. Clin. Invest.* **109**, 41–50.
17. Willoughby, D.A., Moore, A.R., Colville-Nash, P.R., and Gilroy, D. (2000) Resolution of inflammation. *Int. J. Immunopharmacol.* **22**, 1131–1135.
18. Metlay, J.P., Atlas, S.J., Borowsky, L.H., and Singer, D.E. (1998) Time course of symptom resolution in patients with community-acquired pneumonia. *Respir. Med.* **92**, 1137–1142.
19. White, A.J., Gompertz, S., Bayley, D.L., Hill, S.L., O'Brien, C., Unsal, I., and Stockley, R.A. (2003) Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* **58**, 680–685.

20. Kobayashi, S.D., Voyich, J.M., Somerville, G.A., Braughton, K.R., Malech, H.L., Musser, J.M., and DeLeo, F.R. (2003) An apoptosis-differentiation program in human polymorphonuclear leukocytes facilitates resolution of inflammation. *J. Leukoc. Biol.* **73**, 315–322.
21. Walker, A., Ward, C., Taylor, E.L., Dransfield, I., Hart, S.P., Haslett, C., and Rossi, A.G. (2005) Regulation of neutrophil apoptosis and removal of apoptotic cells. *Curr. Drug Targets Inflamm. Allergy* **4**, 447–454.
22. Savill, J.S., Wyllie, A.H., Henson, J.E., Walport, M.J., Henson, P.M., and Haslett, C. (1989) Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. *J. Clin. Invest.* **83**, 865–875.
23. Haslett, C. (1992) Resolution of acute inflammation and the role of apoptosis in the tissue fate of granulocytes. *Clin. Sci. (Lond.)* **83**, 639–648.
24. Serhan, C.N. and Savill, J. (2005) Resolution of inflammation: the beginning programs the end. *Nat. Immunol.* **6**, 1191–1197.
25. Savill, J. and Haslett, C. (1995) Granulocyte clearance by apoptosis in the resolution of inflammation. *Semin. Cell Biol.* **6**, 385–393.
26. Ward, C., Walker, A., Dransfield, I., Haslett, C., and Rossi, A.G. (2004) Regulation of granulocyte apoptosis by NF- $\kappa$ B. *Biochem. Soc. Trans.* **32**, 465–467.
27. Ariel, A., Fredman, G., Sun, Y.P., Kantarci, A., Van Dyke, T.E., Luster, A.D., and Serhan, C.N. (2006) Apoptotic neutrophils and T cells sequester chemokines during immune response resolution through modulation of CCR5 expression. *Nat. Immunol.* **7**(11), 1209–1216.
28. McKimmie, C.S. and Graham, G.J. (2006) Leucocyte expression of the chemokine scavenger D6. *Biochem. Soc. Trans.*, **34**, 1002–1004.
29. Freire-de-Lima, C.G., Xiao, Y.Q., Gardai, S.J., Bratton, D.L., Schiemann, W.P., and Henson, P.M. (2006) Apoptotic cells, through transforming growth factor- $\beta$ , coordinately induce anti-inflammatory and suppress pro-inflammatory eicosanoid and NO synthesis in murine macrophages. *J. Biol. Chem.* **281**, 38376–38384.
30. Lucas, M., Stuart, L.M., Savill, J., and Lacy-Hulbert, A. (2003) Apoptotic cells and innate immune stimuli combine to regulate macrophage cytokine secretion. *J. Immunol.* **171**, 2610–2615.
31. Uller, L., Persson, C.G., and Erjefält, J.S. (2006) Resolution of airway disease: removal of inflammatory cells through apoptosis, egression or both? *Trends Pharmacol. Sci.* **27**, 461–466.
32. Cao, C., Lawrence, D.A., Strickland, D.K., and Zhang, L. (2005) A specific role of integrin Mac-1 in accelerated macrophage efflux to the lymphatics. *Blood* **106**, 3234–3241.
33. Bannenberg, G.L., Chiang, N., Ariel, A., Arita, M., Tjonahen, E., Gotlinger, K.H., Hong, S., and Serhan, C.N. (2005) Molecular circuits of resolution: formation and actions of resolvins and protectins. *J. Immunol.* **174**, 4345–4355.
34. Serhan, C.N. (2006) Resolution phases of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. *Annu. Rev. Immunol.* **25**, 101–137.
35. Serhan, C.N. (2002) Endogenous chemical mediators in anti-inflammation and pro-resolution. *Curr. Med. Chem.* **1**, 177–192.
36. Takano, T., Fiore, S., Maddox, J.F., Brady, H.R., Petasis, N.A., and Serhan, C.N. (1997) Aspirin-triggered 15-epi-lipoxin A<sub>4</sub> (LXA<sub>4</sub>) and LXA<sub>4</sub> stable analogues are potent inhibitors of acute inflammation: evidence for anti-inflammatory receptors. *J. Exp. Med.* **185**, 1693–1704.
37. Hansson, G., Robertson, A.K.L., and Soderberg-Naucler, C. (2006) Inflammation and atherosclerosis. *Annu. Rev. Pathol. Mech. Dis.* **1**, 297–329.
38. Erlinger, T.P., Platz, E.A., Rifai, N., and Helzlsouer, K.J. (2004) C-reactive protein and the risk of incident colorectal cancer. *JAMA* **291**, 585–590.
39. Nathan, C. (2002) Points of control in inflammation. *Nature* **420**, 846–852.
40. Van Dyke, T.E. and Serhan, C.N. (2003) Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. *J. Dent. Res.* **82**, 82–90.
41. Lukiw, W.J., Cui, J.G., Marcheselli, V.L., Bodker, M., Botkjaer, A., Gotlinger, K., Serhan, C.N., and Bazan, N.G. (2005) A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J. Clin. Invest.* **115**, 2774–2783.
42. Weiss, S.J. (1989) Tissue destruction by neutrophils. *N. Engl. J. Med.* **320**, 365–376.
43. Dallegri, F. and Ottonello, L. (1997) Tissue injury in neutrophilic inflammation. *Inflamm. Res.* 382–391.
44. Bergström, S. (1982) The prostaglandins: from the laboratory to the clinic. In *Les Prix Nobel: Nobel Prizes, Presentations, Biographies and Lectures*. Almqvist & Wiksell, Stockholm. pp. 129–148.
45. Samuelsson, B. (1982) From studies of biochemical mechanisms to novel biological mediators: prostaglandin endoperoxides, thromboxanes and leukotrienes. In *Les Prix Nobel: Nobel Prizes, Presentations, Biographies and Lectures*. Almqvist & Wiksell, Stockholm. pp. 153–174.
46. Cristopher, J., Pistorius, E., and Axelrod, B. (1970) Isolation of an isozyme of soybean lipoxygenase. *Biochim. Biophys. Acta* **198**, 12–19.
47. Ueno, N., Takegoshi, Y., Kamei, D., Kudo, I., and Murakami, M. (2005) Coupling between cyclooxygenases and terminal prostanoid synthases. *Biochem. Biophys. Res. Commun.* **338**, 70–76.
48. Samuelsson, B. (1983) Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. *Science* **220**, 568–575.
49. Lawrence, T., Willoughby, D.A., and Gilroy, D.W. (2002) Anti-inflammatory lipid mediators and insights into the

- resolution of inflammation. *Nat. Rev. Immunol.* **2**, 787–795.
50. Engblom, D., Saha, S., Engström, L., Westman, M., Audoly, L.P., Jakobsson, P.J., and Blomqvist, A. (2003) Microsomal prostaglandin E synthase-1 is the central switch during immune-induced pyresis. *Nat. Neurosci.* **6**, 1137–1138.
  51. Dinarello, C.A. (2004) Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. *J. Endotoxin Res.* **10**, 201–222.
  52. Bunting, S., Moncada, S., and Vane, J.R. (1983) The prostacyclin-thromboxane A<sub>2</sub> balance: pathophysiological and therapeutic implications. *Br. Med. Bull.* **39**, 271–276.
  53. Gilroy, D.W., Lawrence, T., Perretti, M., and Rossi, A.G. (2004) Inflammatory resolution: new opportunities for drug discovery. *Nat. Rev. Drug Discov.* **3**, 401–416.
  54. Marcus, A.J., Safier, L.B., Broekman, M.J., Ullman, H.L., Islam, N., Sorrell, T.C., Serhan, C.N., Weissmann, G., Oglesby, T.D., and Gorman, R.R. (1984) Production of metabolic products of arachidonic acid during cell-cell interactions. *J. Allergy Clin. Immunol.* **74**, 338–342.
  55. Maclouf, J.A. and Murphy, R.C. (1988) Transcellular metabolism of neutrophil-derived leukotriene A<sub>4</sub> by human platelets. A potential cellular source of leukotriene C<sub>4</sub>. *J. Biol. Chem.* **263**, 174–181.
  56. Serhan, C.N., Hamberg, M., and Samuelsson, B. (1984) Lipoxins: novel series of biologically active compounds formed from arachidonic acid in human leukocytes. *Proc. Natl. Acad. Sci. U. S. A.* **81**, 5335–5339.
  57. Serhan, C.N. (1994) Lipoxin biosynthesis and its impact in inflammatory and vascular events. *Biochim. Biophys. Acta* **1212**, 1–25.
  58. Brezinski, M.E. and Serhan, C.N. (1990) Selective incorporation of (15*S*)-hydroxyeicosatetraenoic acid in phosphatidylinositol of human neutrophils: agonist-induced deacylation and transformation of stored hydroxyeicosanoids. *Proc. Natl. Acad. Sci. U. S. A.* **87**, 6248–6252.
  59. Serhan, C.N. (1991) In *Advances in Rheumatology and Inflammation*. Vol. 1. Hedqvist, P., Kalden, J.R., Muller-Peddinghaus, R., and Robinson, D.R., Eds. Eular, Basel. pp. 141–153.
  60. Fiore, S., Ryeom, S.W., Weller, P.F., and Serhan, C.N. (1992) Lipoxin recognition sites. Specific binding of labeled lipoxin A<sub>4</sub> with human neutrophils. *J. Biol. Chem.* **267**, 16168–16176.
  61. Brady, H.R., Papayianni, A., and Serhan, C.N. (1995) Potential vascular roles for lipoxins in the "stop programs" of host defense and inflammation. *Trends Cardiovasc. Med.* **5**, 186–192.
  62. Maddox, J.F. and Serhan, C.N. (1996) Lipoxin A<sub>4</sub> and B<sub>4</sub> are potent stimuli for human monocyte migration and adhesion: selective inactivation by dehydrogenation and reduction. *J. Exp. Med.* **183**, 137–146.
  63. Fiore, S., Maddox, J.F., Perez, H.D., and Serhan, C.N. (1994) Identification of a human cDNA encoding a functional high affinity lipoxin A<sub>4</sub> receptor. *J. Exp. Med.* **180**, 253–260.
  64. Vaughn, M.W., Proske, R.J., and Haviland, D.L. (2002) Identification, cloning, and functional characterization of a murine lipoxin A<sub>4</sub> receptor homologue gene. *J. Immunol.* **169**, 3363–3369.
  65. Wada, K., Arita, M., Nakajima, A., Katayama, K., Kudo, C., Kamisaki, Y., and Serhan, C.N. (2006) Leukotriene B<sub>4</sub> and lipoxin A<sub>4</sub> are regulatory signals for neural stem cell proliferation and differentiation. *FASEB J.* **20**, 1785–1792.
  66. Ohira, T., Bannenberg, G., Arita, M., Takahashi, M., Ge, Q., Van Dyke, T.E., Stahl, G.L., Serhan, C.N., and Badwey, J.A. (2004) A stable aspirin-triggered lipoxin A<sub>4</sub> analog blocks phosphorylation of leukocyte-specific protein 1 in human neutrophils. *J. Immunol.* **173**, 2091–2098.
  67. Bonnans, C., Mainprice, B., Chanez, P., Bousquet, J., and Urbach, V. (2003) Lipoxin A<sub>4</sub> stimulates a cytosolic Ca<sup>2+</sup> increase in human bronchial epithelium. *J. Biol. Chem.* **278**, 10879–10884.
  68. Machado, F.S., Johndrow, J.E., Esper, L., Dias, A., Bafica, A., Serhan, C.N., and Aliberti, J. (2006) Anti-inflammatory actions of lipoxin A<sub>4</sub> and aspirin-triggered lipoxin are SOCS-2 dependent. *Nat. Med.* **12**, 330–334.
  69. Levy, B.D., Petasis, N.A., and Serhan, C.N. (1997) Polyisoprenyl phosphates in intracellular signalling. *Nature* **389**, 985–990.
  70. McMahan, B., Stenson, C., McPhillips, F., Fanning, A., Brady, H.R., and Godson, C. (2000) Lipoxin A<sub>4</sub> antagonizes the mitogenic effects of leukotriene D<sub>4</sub> in human renal mesangial cells. Differential activation of MAP kinases through distinct receptors. *J. Biol. Chem.* **275**, 27566–27575.
  71. Qiu, F.H., Devchand, P.R., Wada, K., and Serhan, C.N. (2001) Aspirin-triggered lipoxin A<sub>4</sub> and lipoxin A<sub>4</sub> up-regulate transcriptional corepressor NAB1 in human neutrophils. *FASEB J.* **15**, 2736–2738.
  72. Gewirtz, A.T., McCormick, B., Neish, A.S., Petasis, N.A., Gronert, K., Serhan, C.N., and Madara, J.L. (1998) Pathogen-induced chemokine secretion from model intestinal epithelium is inhibited by lipoxin A<sub>4</sub> analogs. *J. Clin. Invest.* **101**, 1860–1869.
  73. Fiore, S., Antico, G., Aloman, M., and Sodin-Semrl, S. (2005) Lipoxin A<sub>4</sub> biology in the human synovium. Role of the ALX signaling pathways in modulation of inflammatory arthritis. *Prostaglandins Leukot. Essent. Fatty Acids* **73**, 189–196.
  74. Jozsef, L., Zouki, C., Petasis, N.A., Serhan, C.N., and Filep, J.G. (2002) Lipoxin A<sub>4</sub> and aspirin-triggered 15-epi-lipoxin A<sub>4</sub> inhibit peroxynitrite formation, NF-κB and AP-1 activation, and IL-8 gene expression in human leukocytes. *Proc. Natl. Acad. Sci. U. S. A.* **99**, 13266–13271.
  75. Lee, T.H., Horton, C.E., Kyan-Aung, U., Haskard, D., Crea, A.E., and Spur, B.W. (1989) Lipoxin A<sub>4</sub> and lipoxin B<sub>4</sub> inhibit chemotactic responses of human neutrophils stimulated by leukotriene B<sub>4</sub> and N-formyl-L-methionyl-L-leucyl-L-phenylalanine. *Clin. Sci. (Lond.)* **77**, 195–203.
  76. Papayianni, A., Serhan, C.N., and Brady, H.R. (1996) Lipoxin A<sub>4</sub> and B<sub>4</sub> inhibit leukotriene-stimulated interactions of human neutrophils and endothelial cells. *J. Immunol.* **156**, 2264–2272.

77. Colgan, S.P., Serhan, C.N., Parkos, C.A., Delp-Archer, C., and Madara, J.L. (1993) Lipoxin A<sub>4</sub> modulates transmigration of human neutrophils across intestinal epithelial monolayers. *J. Clin. Invest.* **92**, 75–82.
78. Fiore, S. and Serhan, C.N. (1995) Lipoxin A<sub>4</sub> receptor activation is distinct from that of the formyl peptide receptor in myeloid cells: inhibition of CD11/18 expression by lipoxin A<sub>4</sub>-lipoxin A<sub>4</sub> receptor interaction. *Biochemistry* **34**, 16678–16686.
79. Gewirtz, A.T., Fokin, V.V., Petasis, N.A., Serhan, C.N., and Madara, J.L. (1999) LXA<sub>4</sub>, aspirin-triggered 15-epi-LXA<sub>4</sub>, and their analogs selectively downregulate PMN azurophilic degranulation. *Am. J. Physiol.* **276**, C988–994.
80. Gilroy, D.W. (2005) New insights into the anti-inflammatory actions of aspirin-induction of nitric oxide through the generation of epi-lipoxins. *Mem. Inst. Oswaldo Cruz* **100(Suppl 1)**, 49–54.
81. Godson, C., Mitchell, S., Harvey, K., Petasis, N.A., Hogg, N., and Brady, H.R. (2000) Lipoxins rapidly stimulate nonphlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages. *J. Immunol.* **200**, 1663–1667.
82. Aliberti, J., Hieny, S., Reis e Sousa, C., Serhan, C.N., and Sher, A. (2002) Lipoxin-mediated inhibition of IL-12 production by DCs: a mechanism for regulation of microbial immunity. *Nat. Immunol.* **3**, 76–82.
83. Ramstedt, U., Serhan, C.N., Nicolaou, K.C., Webber, S.E., Wigzell, H., and Samuelsson, B. (1987) Lipoxin A-induced inhibition of human natural killer cell cytotoxicity: studies on stereospecificity of inhibition and mode of action. *J. Immunol.* **138**, 266–270.
84. Bannenberg, G., Moussignac, R.L., Gronert, K., Devchand, P.R., Schmidt, B.A., Guilford, W.J., Bauman, J.G., Subramanyam, B., Perez, H.D., Parkinson, J.F., and Serhan, C.N. (2004) Lipoxins and novel 15-epi-lipoxin analogs display potent anti-inflammatory actions after oral administration. *Br. J. Pharmacol.* **143**, 43–52.
85. Devchand, P.R., Arita, M., Hong, S., Bannenberg, G., Moussignac, R.L., Gronert, K., and Serhan, C.N. (2003) Human ALX receptor regulates neutrophil recruitment in transgenic mice: roles in inflammation and host defense. *FASEB J.* **17**, 652–659.
86. Gronert, K., Gewirtz, A., Madara, J.L., and Serhan, C.N. (1998) Identification of a human enterocyte lipoxin A<sub>4</sub> receptor that is regulated by interleukin (IL)-13 and interferon- $\gamma$  and inhibits tumor necrosis factor  $\alpha$ -induced IL-8 release. *J. Exp. Med.* **187**, 1285–1294.
87. Wallace, J.L., de Lima, O.M., Jr., and Fiorucci, S. (2005) Lipoxins in gastric mucosal health and disease. *Prostaglandins Leukot. Essent. Fatty Acids* **73**, 251–255.
88. Gronert, K., Martinsson-Niskanen, T., Ravasi, S., Chiang, N., and Serhan, C.N. (2001) Selectivity of recombinant human leukotriene D(4), leukotriene B(4), and lipoxin A(4) receptors with aspirin-triggered 15-epi-LXA(4) and regulation of vascular and inflammatory responses. *Am. J. Pathol.* **158**, 3–9.
89. Dahlen, S.E., Raud, J., Serhan, C.N., Bjork, J., and Samuelsson, B. (1987) Biological activities of lipoxin A include lung strip contraction and dilation of arterioles in vivo. *Acta Physiol. Scand.* **130**, 643–647.
90. Badr, K.F., Serhan, C.N., Nicolaou, K.C., and Samuelsson, B. (1987) The action of lipoxin-A on glomerular microcirculatory dynamics in the rat. *Biochem. Biophys. Res. Commun.* **145**, 408–414.
91. Tamaoki, J., Tagaya, E., Yamawaki, I., and Konno, K. (1995) Lipoxin A<sub>4</sub> inhibits cholinergic neurotransmission through nitric oxide generation in the rabbit trachea. *Eur. J. Pharmacol.* **287**, 233–238.
92. Svensson, C.I., Zattoni, M., and Serhan, C.N. (2007) Lipoxins and aspirin-triggered lipoxin inhibit inflammatory pain processing. *J. Exp. Med.* **204**, 245–252.
93. Hansson, A., Serhan, C.N., Haeggstrom, J., Ingelman-Sundberg, M., and Samuelsson, B. (1986) Activation of protein kinase C by lipoxin A and other eicosanoids. Intracellular action of oxygenation products of arachidonic acid. *Biochem. Biophys. Res. Commun.* **134**, 1215–1222.
94. Shearman, M.S., Naor, Z., Sekiguchi, K., Kishimoto, A., and Nishizuka, Y. (1989) Selective activation of the  $\gamma$ -subspecies of protein kinase C from bovine cerebellum by arachidonic acid and its lipoxygenase metabolites. *FEBS Lett.* **243**, 177–182.
95. Schaldach, C.M., Riby, J., and Bjeldanes, L.F. (1999) Lipoxin A<sub>4</sub>: a new class of ligand for the Ah receptor. *Biochemistry* **38**, 7594–7600.
96. Clish, C.B., Levy, B.D., Chiang, N., Tai, H.H., and Serhan, C.N. (2000) Oxidoreductases in lipoxin A<sub>4</sub> metabolic inactivation: a novel role for 15-oxoprostaglandin 13-reductase/leukotriene B<sub>4</sub> 12-hydroxydehydrogenase in inflammation. *J. Biol. Chem.* **275**, 25372–25380.
97. Sumimoto, H., Isobe, R., Mizukami, Y., and Minakami, S. (1993) Formation of a novel 20-hydroxylated metabolite of lipoxin A<sub>4</sub> by human neutrophil microsomes. *FEBS Lett.* **315**, 205–210.
98. Maddox, J.F., Hachicha, M., Takano, T., Petasis, N.A., Fokin, V.V., and Serhan, C.N. (1997) Lipoxin A<sub>4</sub> stable analogs are potent mimetics that stimulate human monocytes and THP-1 cells via a G-protein-linked lipoxin A<sub>4</sub> receptor. *J. Biol. Chem.* **272**, 6972–6978.
99. Pouliot, M. and Serhan, C.N. (1999) Lipoxin A<sub>4</sub> and aspirin-triggered 15-epi-LXA<sub>4</sub> inhibit tumor necrosis factor- $\alpha$ -initiated neutrophil responses and trafficking: novel regulators of a cytokine-chemokine axis relevant to periodontal diseases. *J. Periodontal Res.* **34**, 370–373.
100. Parkinson, J.F. (2006) Lipoxin and synthetic lipoxin analogs: an overview of anti-inflammatory functions and new concepts in immunomodulation. *Inflamm. Allergy Drug Targets* **5**, 91–106.
101. Canny, G., Levy, O., Furuta, G.T., Narravula-Alipati, S., Sisson, R.B., Serhan, C.N., and Colgan, S.P. (2002) Lipid mediator-induced expression of bactericidal/ permeability-increasing protein (BPI) in human mucosal epithelia. *Proc. Natl. Acad. Sci. U. S. A.* **99**, 3902–3907.
102. Gilroy, D.W. (2005) The role of aspirin-triggered lipoxins in the mechanism of action of aspirin. *Prostaglandins Leukot.*

- Essent. Fatty Acids* **73**, 203–210.
103. Guilford, W.J. and Parkinson, J.F. (2005) Second-generation  $\beta$ -oxidation resistant 3-oxa-lipoxin A<sub>4</sub> analogs. *Prostaglandins Leukot. Essent. Fatty Acids* **73**, 245–250.
  104. Guilford, W.J., Bauman, J.G., Skuballa, W., Bauer, S., Wei, G.P., Davey, D., Schaefer, C., Mallari, C., Terkelsen, J., Tseng, J.L., Shen, J., Subramanyam, B., Schottelius, A.J., and Parkinson, J.F. (2004) Novel 3-oxa lipoxin A<sub>4</sub> analogues with enhanced chemical and metabolic stability have anti-inflammatory activity in vivo. *J. Med. Chem.* **47**, 2157–2165.
  105. Simchowitz, L., Fiore, S., and Serhan, C.N. (1994) Carrier-mediated transport of lipoxin A<sub>4</sub> in human neutrophils. *Am. J. Physiol.* **267**, C1525–1534.
  106. Levy, B.D., Clish, C.B., Schmidt, B., Gronert, K., and Serhan, C.N. (2001) Lipid mediator class switching during acute inflammation: signals in resolution. *Nat. Immunol.* **2**, 612–619.
  107. Fukunaga, K., Kohli, P., Bonnans, C., Fredenburgh, L.E., and Levy, B.D. (2005) Cyclooxygenase 2 plays a pivotal role in the resolution of acute lung injury. *J. Immunol.* **174**, 5033–5039.
  108. Wu, S.H., Wu, X.H., Lu, C., Dong, L., and Chen, Z.Q. (2006) Lipoxin A<sub>4</sub> inhibits proliferation of human lung fibroblasts induced by connective tissue growth factor. *Am. J. Respir. Cell Mol. Biol.* **34**, 65–72.
  109. McMahon, B., Mitchell, D., Shattock, R., Martin, F., Brady, H.R., and Godson, C. (2002) Lipoxin, leukotriene, and PDGF receptors cross-talk to regulate mesangial cell proliferation. *FASEB J.* **16**, 1817–1819.
  110. Sato, Y., Kitasato, H., Murakami, Y., Endo, H., Kondo, H., Inoue, M., and Hayashi, I. (2004) Down-regulation of lipoxin A<sub>4</sub> receptor by thromboxane A<sub>2</sub> signalling in RAW246.7 cells in vitro and bleomycin-induced lung fibrosis in vivo. *Biomed. Pharmacother.* **58**, 351–358.
  111. Murakami, M. and Kudo, I. (2004) Recent advances in molecular biology and physiology of the prostaglandin E<sub>2</sub>-biosynthetic pathway. *Prog. Lipid Res.* **43**, 3–35.
  112. Park, J.Y., Pillinger, M.H., and Abramson, S.B. (2006) Prostaglandin E<sub>2</sub> synthesis and secretion: the role of PGE2 synthases. *Clin. Immunol.* **119**, 229–240.
  113. Jakobsson, P.J., Thoren, S., Morgenstern, R., and Samuelsson, B. (2002) Characterization of microsomal, glutathione dependent prostaglandin E synthase. *Adv. Exp. Med. Biol.* **507**, 287–291.
  114. Raud, J., Dahlen, S.E., Sydbom, A., Lindbom, L., and Hedqvist, P. (1988) Enhancement of acute allergic inflammation by indomethacin is reversed by prostaglandin E<sub>2</sub>: apparent correlation with in vivo modulation of mediator release. *Proc. Natl. Acad. Sci. U. S. A.* **85**, 2315–2319.
  115. Vancheri, C., Mastruzzo, C., Sortino, M.A., and Crimi, N. (2004) The lung as a privileged site for the beneficial actions of PGE<sub>2</sub>. *Trends Immunol.* **25**, 40–46.
  116. Bandeira-Melo, C., Serra, M.F., Diaz, B.L., Cordeiro, R.S., Silva, P.M., Lenzi, H.L., Bakhle, Y.S., Serhan, C.N., and Martins, M.A. (2000) Cyclooxygenase-2-derived prostaglandin E<sub>2</sub> and lipoxin A<sub>4</sub> accelerate resolution of allergic edema in *Angiostrongylus costaricensis*-infected rats: relationship with concurrent eosinophilia. *J. Immunol.* **164**, 1029–1036.
  117. Masferrer, J.L., Zweifel, B.S., Manning, P.T., Hauser, S.D., Leahy, K.M., Smith, W.G., Isakson, P.C., and Seibert, K. (1994) Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic. *Proc. Natl. Acad. Sci. U. S. A.* **91**, 3228–3232.
  118. Gilroy, D.W., Colville-Nash, P.R., Willis, D., Chivers, J., Paul-Clark, M.J., and Willoughby, D.A. (1999) Inducible cyclooxygenase may have anti-inflammatory properties. *Nat. Med.* **5**, 698–701.
  119. Urade, Y. and Hayaishi, O. (2000) Prostaglandin D synthase: structure and function. *Vitam. Horm.* **58**, 89–120.
  120. Ajuebor, M.N., Singh, A., and Wallace, J.L. (2000) Cyclooxygenase-2-derived prostaglandin D<sub>2</sub> is an early anti-inflammatory signal in experimental colitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **279**, G238–244.
  121. Schuligoi, R., Grill, M., Heinemann, A., Peskar, B.A., and Amann, R. (2005) Sequential induction of prostaglandin E and D synthases in inflammation. *Biochem. Biophys. Res. Commun.* **335**, 684–689.
  122. Murakami, Y., Akaoshi, T., Hayashi, I., Endo, H., Hashimoto, A., Kono, S., Kondo, H., Kawai, S., Inoue, M., and Kitasato, H. (2003) Inhibition of monosodium urate monohydrate crystal-induced acute inflammation by retrovirally transfected prostaglandin D synthase. *Arthritis Rheum.* **48**, 2931–2941.
  123. Jiang, C., Ting, A.T., and Seed, B. (1998) PPAR- $\gamma$  agonists inhibit production of monocyte inflammatory cytokines. *Nature* **391**, 82–86.
  124. Ricote, M., Li, A.C., Willson, T.M., Kelly, C.J., and Glass, C.K. (1998) The peroxisome proliferator-activated receptor- $\gamma$  is a negative regulator of macrophage activation. *Nature* **391**, 79–82.
  125. Trivedi, S.G., Newson, J., Rajakariar, R., Jacques, T.S., Hannon, R., Kanaoka, Y., Eguchi, N., Colville-Nash, P., and Gilroy, D.W. (2006) Essential role for hematopoietic prostaglandin D<sub>2</sub> synthase in the control of delayed type hypersensitivity. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 5179–5184.
  126. Ward, C., Dransfield, I., Murray, J., Farrow, S.N., Haslett, C., and Rossi, A.G. (2002) Prostaglandin D<sub>2</sub> and its metabolites induce caspase-dependent granulocyte apoptosis that is mediated via inhibition of  $\text{I}\kappa\text{B}\alpha$  degradation using a peroxisome proliferator-activated receptor- $\gamma$ -independent mechanism. *J. Immunol.* **168**, 6232–6243.
  127. Lawrence, T., Gilroy, D.W., Colville-Nash, P.R., and Willoughby, D.A. (2001) Possible new role for NF- $\kappa\text{B}$  in the resolution of inflammation. *Nat. Med.* **7**, 1291–1297.
  128. Kim, E.H. and Surh, Y.J. (2006) 15-Deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub> as a potential endogenous regulator of redox-sensitive transcription factors. *Biochem. Pharmacol.* **72**, 1516–1528.
  129. Oliva, J.L., Pérez-Sala, D., Castrillo, A., Martínez, N., Cañada, F.J., Boscá, L., and Rojas, J.M. (2003) The cyclopentenone 15-deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub> binds to and activates H-Ras. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 4772–4777.

130. Renedo, M., Gayarre, J., García-Domínguez, C., Pérez-Rodríguez, A., Prieto, A., Cañada, F., Rojas, J., and Pérez-Sala, D. (2007) Modification and activation of Ras proteins by electrophilic prostanoids with different structure are site-selective. *Biochemistry* **47**, 6607–6616.
131. Mochizuki, M., Ishii, Y., Itoh, K., Iizuka, T., Morishima, Y., Kimura, T., Kiwamoto, T., Matsuno, Y., Hegab, A.E., Nomura, A., Sakamoto, T., Uchida, K., Yamamoto, M., and Sekizawa, K. (2005) Role of 15-deoxy  $\Delta^{12,14}$  prostaglandin  $J_2$  and Nrf2 pathways in protection against acute lung injury. *Am. J. Respir. Crit. Care Med.* **171**, 1260–1266.
132. Bell-Parikh, L.C., Ide, T., Lawson, J.A., McNamara, P., Reilly, M., and FitzGerald, G.A. (2003) Biosynthesis of 15-deoxy- $\Delta^{12,14}$ -PGJ<sub>2</sub> and the ligation of PPAR $\gamma$ . *J. Clin. Invest.* **112**, 945–955.
133. Shibata, T., Kondo, M., Osawa, T., Shibata, N., Kobayashi, M., and Uchida, K. (2002) 15-deoxy- $\Delta^{12,14}$ -prostaglandin  $J_2$ . A prostaglandin  $D_2$  metabolite generated during inflammatory processes. *J. Biol. Chem.* **277**, 10459–10466.
134. Watanabe, K. (2002) Prostaglandin F synthase. *Prostaglandins Other Lipid Mediat.* **68–69**, 401–407.
135. Burgess, J.R. and Reddy, C.C. (1997) Isolation and characterization of an enzyme from sheep seminal vesicles that catalyzes the glutathione-dependent reduction of prostaglandin  $H_2$  to prostaglandin  $F_{2\alpha}$ . *Biochem. Mol. Biol. Int.* **41**, 217–226.
136. Colville-Nash, P.R., Gilroy, D.W., Willis, D., Paul-Clark, M.J., Moore, A.R., and Willoughby, D.A. (2005) Prostaglandin  $F_{2\alpha}$  produced by inducible cyclooxygenase may contribute to the resolution of inflammation. *Inflammopharmacology* **12**, 473–476.
137. Burr, G.O. and Burr, M.M. (1973) Nutrition classics from The Journal of Biological Chemistry 82:345-67, 1929. A new deficiency disease produced by the rigid exclusion of fat from the diet. *Nutr. Rev.* **31**, 248–249.
138. Lands, W.E.M. (1987) In *AOCS Short Course on Polyunsaturated Fatty Acids and Eicosanoids*. Lands, W.E.M., Ed. American Oil Chemists' Society, Champaign, IL.
139. Bazan, N.G. (1990) Supply of n-3 polyunsaturated fatty acids and their significance in the central nervous system. In *Nutrition and the Brain*. Wurtman, R.J. and Wurtman, J.J., Ed. Raven Press, New York. pp. 1–22.
140. Simopoulos, A.P., Leaf, A., and Salem, N.J. (1999) Workshop on the essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. *J. Am. Coll. Nutr.* **18**, 487–489.
141. Salem, N., Jr., Litman, B., Kim, H.Y., and Gawrisch, K. (2001) Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids* **36**, 945–959.
142. GISSI-Prevenzione\_Investigators (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* **354**, 447–455.
143. Marchioli, R., Barzi, F., Bomba, E., Chieffo, C., Di Gregorio, D., Di Mascio, R., Franzosi, M.G., Geraci, E., Levantesi, G., Maggioni, A.P., Mantini, L., Marfisi, R.M., Mastrogiuseppe, G., Mininni, N., Nicolosi, G.L., Santini, M., Schweiger, C., Tavazzi, L., Tognoni, G., Tucci, C., and Valagussa, F. (2002) Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* **105**, 1897–1903.
144. Lee, T.H., Mencia-Huerta, J.M., Shih, C., Corey, E.J., Lewis, R.A., and Austen, K.F. (1984) Effects of exogenous arachidonic, eicosapentaenoic, and docosahexaenoic acids on the generation of 5-lipoxygenase pathway products by ionophore-activated human neutrophils. *J. Clin. Invest.* **74**, 1922–1933.
145. Hamberg, M. and Samuelsson, B. (1967) On the specificity of the oxygenation of unsaturated fatty acids catalyzed by soybean lipoxidase. *J. Biol. Chem.* **242**, 5329–5335.
146. Sawazaki, S., Salem, N., Jr., and Kim, H.Y. (1994) Lipoygenation of docosahexaenoic acid by the rat pineal body. *J. Neurochem.* **62**, 2437–2447.
147. Reich, E.E., Zackert, W.E., Brame, C.J., Chen, Y., Roberts, L.J., 2nd, Hachey, D.L., Montine, T.J., and Morrow, J.D. (2000) Formation of novel D-ring and E-ring isoprostane-like compounds (D4/E4-neuroprostanes) in vivo from docosahexaenoic acid. *Biochemistry* **39**, 2376–2383.
148. VanRollins, M. and Murphy, R.C. (1984) Autooxidation of docosahexaenoic acid: analysis of ten isomers of hydroxydocosahexaenoate. *J. Lipid Res.* **25**, 507–517.
149. Corey, E.J., Shih, C., and Cashman, J.R. (1983) Docosahexaenoic acid is a strong inhibitor of prostaglandin but not leukotriene biosynthesis. *Proc. Natl. Acad. Sci. U. S. A.* **80**, 3581–3584.
150. Serhan, C.N., Clish, C.B., Brannon, J., Colgan, S.P., Chiang, N., and Gronert, K. (2000) Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. *J. Exp. Med.* **192**, 1197–1204.
151. Serhan, C.N., Hong, S., Gronert, K., Colgan, S.P., Devchand, P.R., Mirick, G., and Moussignac, R.-L. (2002) Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med.* **196**, 1025–1037.
152. Hong, S., Gronert, L., Devchand, P.R., Moussignac, R.-L., and Serhan, C.N. (2003) Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. *J. Biol. Chem.* **278**, 14677–14687.
153. Winyard, P.G. and Willoughby, D.A., Eds. (2003) *Inflammation Protocols*. Humana, Totowa, NJ.
154. Arita, M., Bianchini, F., Aliberti, J., Sher, A., Chiang, N., Hong, S., Yang, R., Petasis, N.A., and Serhan, C.N. (2005) Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *J. Exp. Med.* **201**, 713–722.
155. Hasturk, H., Kantarci, A., Ohira, T., Arita, M., Ebrahimi, N., Chiang, N., Petasis, N.A., Levy, B.D., Serhan, C.N., and

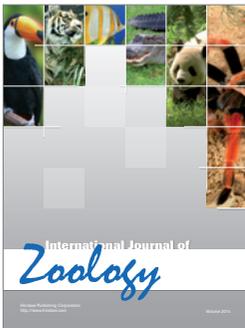
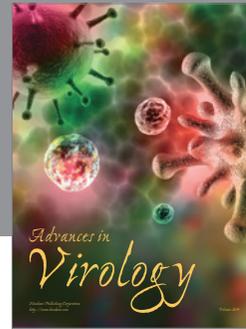
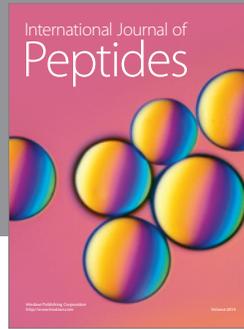
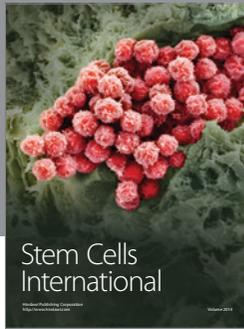
- Van Dyke, T.E. (2006) RvE1 protects from local inflammation and osteoclast-mediated bone destruction in periodontitis. *FASEB J.* **20**, 401–403.
156. Arita, M., Yoshida, M., Hong, S., Tjonahen, E., Glickman, J.N., Petasis, N.A., Blumberg, R.S., and Serhan, C.N. (2005) Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 7671–7676.
157. Wittamer, V., Franssen, J.D., Vulcano, M., Mirjolet, J.F., Le Poul, E., Migeotte, I., Brezillon, S., Tyldesley, R., Blanpain, C., Dethoux, M., Mantovani, A., Sozzani, S., Vassart, G., Parmentier, M., and Communi, D. (2003) Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. *J. Exp. Med.* **198**, 977–985.
158. Zabel, B.A., Ohyama, T., Zuniga, L., Kim, J.Y., Johnston, B., Allen, S.J., Guido, D.G., Handel, T.M., and Butcher, E.C. (2006) Chemokine-like receptor 1 expression by macrophages in vivo: regulation by TGF- $\beta$  and TLR ligands. *Exp. Hematol.* **34**, 1106–1114.
159. Arita, M., Oh, S.F., Chonan, T., Hong, S., Elangovan, S., Sun, Y.P., Uddin, J., Petasis, N.A., and Serhan, C.N. (2006) Metabolic inactivation of resolvin E1 and stabilization of its anti-inflammatory actions. *J. Biol. Chem.* **281**, 22847–22854.
160. Tjonahen, E., Oh, S.F., Siegelman, J., Elangovan, S., Percarpio, K.B., Hong, S., Arita, M., and Serhan, C.N. (2006) Resolvin E2: identification and anti-inflammatory actions: pivotal role of human 5-lipoxygenase in resolvin E series biosynthesis. *Chem. Biol.* **13**, 1193–1202.
161. Marcheselli, V.L., Hong, S., Lukiw, W.J., Tian, X.H., Gronert, K., Musto, A., Hardy, M., Gimenez, J.M., Chiang, N., Serhan, C.N., and Bazan, N.G. (2003) Novel docosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. *J. Biol. Chem.* **278**, 43807–43817.
162. Mukherjee, P.K., Marcheselli, V.L., Serhan, C.N., and Bazan, N.G. (2004) Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 8491–8496.
163. Birbes, H., Pageaux, J.F., Fayard, J.M., Lagarde, M., and Laugier, C. (1998) Protein kinase C inhibitors stimulate arachidonic and docosahexaenoic acids release from uterine stromal cells through a Ca<sup>2+</sup>-independent pathway. *FEBS Lett.* **432**, 219–224.
164. Serhan, C.N., Gotlinger, K., Hong, S., Lu, Y., Siegelman, J., Baer, T., Yang, R., Colgan, S.P., and Petasis, N.A. (2006) Anti-inflammatory actions of neuroprotectin D1/protectin D1 and its natural stereoisomers: assignments of dihydroxy-containing docosatrienes. *J. Immunol.* **176**, 1848–1859.
165. Ariel, A., Li, P.L., Wang, W., Tang, W.X., Fredman, G., Hong, S., Gotlinger, K.H., and Serhan, C.N. (2005) The docosatriene protectin D1 is produced by T<sub>H</sub>2 skewing and promotes human T cell apoptosis via lipid raft clustering. *J. Biol. Chem.* **280**, 43079–43086.
166. Duffield, J.S., Hong, S., Vaidya, V.S., Lu, Y., Fredman, G., Serhan, C.N., and Bonventre, J.V. (2006) Resolvin D series and protectin D1 mitigate acute kidney injury. *J. Immunol.* **177**, 5902–5911.
167. Serhan, C.N., Gotlinger, K., Hong, S., and Arita, M. (2004) Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their aspirin-triggered endogenous epimers: an overview of their protective roles in catabasis. *Prostaglandins Other Lipid Mediat.* **73**, 155–172.
168. Hudert, C.A., Weylandt, K.H., Lu, Y., Wang, J., Hong, S., Dignass, A., Serhan, C.N., and Kang, J.X. (2006) Transgenic mice rich in endogenous omega-3 fatty acids are protected from colitis. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 11276–11281.
169. Xia, S., Lu, Y., Wang, J., He, C., Hong, S., Serhan, C.N., and Kang, J.X. (2006) Melanoma growth is reduced in fat-1 transgenic mice: impact of omega-6/omega-3 essential fatty acids. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 12499–12504.
170. Terano, T., Salmon, J.A., and Moncada, S. (1984) Biosynthesis and biological activity of leukotriene B<sub>5</sub>. *Prostaglandins* **27**, 217–232.
171. Arita, M., Clish, C.B., and Serhan, C.N. (2005) The contributions of aspirin and microbial oxygenase to the biosynthesis of anti-inflammatory resolvins: novel oxygenase products from omega-3 polyunsaturated fatty acids. *Biochem. Biophys. Res. Commun.* **338**, 149–157.
172. BannenberG, G.L., Aliberti, J., Hong, S., Sher, A., and Serhan, C. (2004) Exogenous pathogen and plant 15-lipoxygenase initiate endogenous lipoxin A<sub>4</sub> biosynthesis. *J. Exp. Med.* **199**, 515–523.
173. Aliberti, J. and Bafica, A. (2005) Anti-inflammatory pathways as a host evasion mechanism for pathogens. *Prostaglandins Leukot. Essent. Fatty Acids* **73**, 283–288.

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