

## **LIPID MEDIATORS IN INFLAMMATION**

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## **ABSTRACT**

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

## **INFLAMMATION AND ITS ONSET**

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

## **RESOLUTION OF INFLAMMATION**

It is important to distinguish between inflammatory resolution and inflammatory onset. At onset, local release/activation of soluble mediators (e.g. complement, vasoactive amines, cytokines, lipids) from histiocytes and stromal cells and up-regulation of cell adhesion molecules on the microvascular endothelium collectively facilitate extravascular leukocyte accumulation manifesting in Celsus' cardinal signs of inflammation - heat, redness, swelling and pain (Rudolph Virchoff added loss of function in the 19<sup>th</sup> century)(4). This well-characterised phase of the inflammatory response is routinely targeted using drugs including NSAIDS and anti-TNF $\alpha$  that inhibit or antagonise the action of these inflammatory drivers forming the mainstay for treating chronic inflammatory disease. Resolution, however, switches inflammation off. In-as-much as onset is orchestrated by a host of sequentially released mediators, resolution is an active process that is no longer considered a passive event where the response was hitherto thought to simply fizzle out(5, 6). For instance, a critical requirement for the inflammatory response to switch off is the elimination of the injurious agents that initiated it in the first place. Failure to achieve this first step will lead to chronic inflammation as exemplified by chronic granulomatous disease, which results from a failure of the phagocytic NADPH oxidase enzyme system to produce superoxide and kill invading infections leading to a predisposition to recurrent bacterial and fungal infections and the development of inflammatory granulomas(7). Successfully dispensing with the inciting stimulus will signal a cessation of pro-inflammatory mediator synthesis and lead to their catabolism. This will halt further leukocyte recruitment and edema formation. These are probably the very earliest determinants for the resolution of acute inflammation, the outcome of which signals the next stage of cell clearance. The clearance phase of resolution, be it polymorphonuclear leukocyte (PMN)- or eosinophil-driven or adaptive (lymphocyte mediated) in nature, also has a number of mutually dependent steps. The clearance routes available to inflammatory leukocytes include systemic recirculation or local death by

apoptosis/necrosis of influxed PMNs, eosinophils or lymphocytes followed by their phagocytosis or efferocytosis by recruited monocyte-derived macrophages. Once phagocytosis is complete, macrophages can leave the inflamed site by lymphatic drainage with evidence that a small population may die locally by apoptosis(8).

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

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

### **RESOLUTION: A DYNAMIC PROCESS WITH CHECKS AND BALANCES**

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

In other words, while it is recognized that pro-inflammatory mediators generated in the inflamed tissue drive acute inflammation, there is also the systemic and local production of endogenous mediators that counter-balance these pro-inflammatory events. These internal checks-and-balances have evolved to avert development of pathologies such as those

highlighted above. Lipid mediators derived from polyunsaturated fatty acids (PUFA), such as arachidonic acid (AA) and the omega-3 PUFA eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), are synthesised during normal cell haemostasis or, more often, after cell activation and in conditions of stress, functioning as activators of counter-regulatory, anti-inflammatory and pro-resolution mechanisms. Interestingly, these immuno-modulatory effects are also found with a family of lipids, called prostanoids, which help to drive some of the cardinal signs of inflammation (heat, redness, swelling, pain and loss of function). As the role of lipids in inflammation is diverse, this review aims to provide an update of AA/DHA/EPA-derived signaling molecules that not only drive acute inflammation but also counter-regulate its severity and bring about its timely resolution.

## **AA METABOLISM AND THE INFLAMMATORY RESPONSE**

AA is a 20-carbon fatty acid and the main eicosanoid precursor and is a constituent of all cells. Although not freely available, stimulation by various cellular agonists including receptor-mediated agonists (i.e. formyl peptide [fMLP], interleukin-8 [IL-8], and platelet activating factor [PAF]), microorganisms, phagocytic particles, non-specific stimuli such as damage or injury (11) activates several phospholipase enzymes (predominantly PLA<sub>2</sub>), which releases AA from membrane phospholipid stores. Once in the cytosol, AA can be metabolised via three principal pathways to form an important family of oxygenated products, collectively termed eicosanoids that are released from the source cell and act at nanomolar concentrations in an autocrine/paracrine manner on target cells. Prostaglandins (PGs) and thromboxane (collectively termed prostanoids), formed by cyclooxygenase (COX); leukotrienes (LTs) and lipoxins (LXs) by lipoxygenases (LOX) (12, 13); and epoxyeicosatrienic acids (EETs) by cytochrome P450 enzymes (14) are members of the eicosanoid family.

## **CYCLOOXYGENASE**

COX is a bifunctional enzyme that acts successively as a bis-dioxygenase and peroxidase to carry out a complex free radical reaction. It begins by catalysing the bisoxygenation and cyclisation of AA to form the hydroperoxy arachidonate metabolite PGG<sub>2</sub> (15). After which the peroxidase element of the enzyme reduces the carbon 15 position hydroperoxide to its corresponding alcohol to form PGH<sub>2</sub> (16, 17). There are two main isoforms involved in the conversion of AA, COX-1 and COX-2. While COX-1 is constitutively expressed in most cells and tissues, COX-2 is rapidly induced when cells are challenged with inflammatory stimuli (18). Although not exclusive, it is generally accepted that COX-1 is involved in cellular housekeeping functions necessary for normal physiological activity whereas COX-2 acts primarily at sites of inflammation. Formation of biologically active prostanoids from PGH<sub>2</sub> occurs through the actions of a set of synthases that are expressed in a tissue and cell type-selective fashion. These synthases include prostaglandin D synthase (PGDS) (19) prostaglandin E synthase (PGES) (20), prostaglandin F synthase (PGFS) (21), prostaglandin I synthase (PGIS) (22), and thromboxane A synthase (TXAS) (23), which form PGE<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub> (also known as prostacyclin) and TXA<sub>2</sub> respectively. It is the differential expression of these enzymes within cells that determines the profile of prostanoid production. For example, mast cells predominantly produce PGD<sub>2</sub> while macrophages produce PGE<sub>2</sub> and TXA<sub>2</sub>. Moreover, alterations in the profile of prostanoid synthesis can occur upon cell activation such that resting macrophages produce TXA<sub>2</sub> in excess of PGE<sub>2</sub>, but upon cell activation this ratio changes to favor PGE<sub>2</sub> (24). Several biochemical mechanisms have been proposed to explain this altered synthetic profile. Firstly, it has been suggested that physical compartmentalisation of COX-1 and COX-2 with specific terminal synthases could link the



activity of these enzymes with the synthesis of specific prostanoid end products (25). Secondly, some of the synthases are inducible and their expression may be regulated by environmental signals. For example, expression of the glutathione-dependent isoform of PGE-synthase is enhanced by IL-1 $\beta$  (26). Finally, it has been proposed that differences in substrate affinity and kinetics of PGE-synthase and TXA-synthase account for different production profiles of resting and activated monocytes (27). There is also evidence that the two COX isoforms may preferentially contribute to the synthesis of distinct prostanoids. For instance, in primary peritoneal macrophages, expressing all terminal synthases, COX-1 yields a balance of prostanoids (i.e. PGE<sub>2</sub>, PGD<sub>2</sub>, PGI<sub>2</sub> and TXA<sub>2</sub>) while COX-2 preferentially generates only PGE<sub>2</sub> and PGI<sub>2</sub> (28).

The biological effect of prostanoids is initiated by binding to specific cell-surface receptors. Currently there are nine known prostanoid receptors in mice and man: the PGD receptors DP1 and DP2, the PGE<sub>2</sub> receptors, EP1, EP2, EP3 and EP4; the PGF receptor, FP; the PGI receptor, IP; and the TXA receptor, TP. In addition, there are splice variants of the EP3, FP and TP receptors differentiated only in their C-terminal tails. All belong to the G-protein coupled receptor (GPCR) superfamily of seven transmembrane spanning proteins, with the exception of DP2 (also known as CRTH2), which is a member of the chemoattractant receptor family (29-31). The IP, DP1, EP2 and EP4 receptors signal through G<sub>s</sub> resulting in an increased intracellular cAMP, whereas the EP3 receptor couples to G<sub>i</sub> to reduce cAMP. EP1, FP and TP receptors signal through G<sub>q</sub> to induce calcium mobilization.

## **PROSTANOIDS**

In the mid 1930s potent bioactive compounds in human semen were identified as prostanoids (32). Today it is appreciated that prostanoids are generated in most tissues and cells,

modulating a wide range of biological processes such as smooth muscle tone (33-35), vascular permeability (36, 37), hyperalgesia (38), fever (39-41), and platelet aggregation (42). Indeed, the clinical importance of prostanoids is emphasised by the fact that prostanoid biosynthesis is the target of non-steroidal anti-inflammatory drugs (NSAIDs), one of the most widely used classes of pharmacotherapeutic agents for the treatment of chronic inflammatory diseases emphasizes the clinical importance of these lipids

The more widely studied prostanoids, PGE<sub>2</sub> and PGI<sub>2</sub>, both enhance vasodilation(43), oedema formation and vascular permeability particularly in the presence of histamine, bradykinin and 5-HT (44-49). Genetic depletion of their respective receptors (IP, EP2 and EP3) in mice significantly reduced pleural exudation after insult with carrageenin or zymosan (50, 51). PGE<sub>2</sub> is also one of the most potent pyretic agents known with elevated concentrations found in cerebrospinal fluid taken from patients with bacterial or viral infections (52). Indeed, a number of lines of evidence from EP-deficient mice have shown that the febrile response to PGE<sub>2</sub> occurs through the action of PGE<sub>2</sub> on the EP3 receptor present on sensory neurons in the periphery and brain (53-56). This has been postulated to cause an increase in thermogenesis through activation of brown adipose tissue and reduced passive heat loss through the skin by tail artery vasoconstriction (57-61). Although none of the COX-metabolites overtly cause pain, PGI<sub>2</sub> and PGE<sub>2</sub> cause peripheral and central hyperalgesia when bound to IP, EP1, EP3 and EP4 receptors, respectively, by reducing the threshold of nociceptor sensory neurons to stimulation (34, 38, 62-70).

In addition, prostanoids play an important role in protecting against oxidative injury in cardiac tissue (71) and in maintaining cardiovascular (CV) homeostasis. Indeed, the protective effect has been highlighted/demonstrated in clinical studies undertaken with NSAIDs, which found

that COX-2-specific inhibitors increase the risk of stroke, myocardial infarction (MI), thrombosis, systemic and pulmonary hypertension, congestive heart failure, and sudden cardiac death (72, 73). Furthermore, deleting specific prostanoid synthases and receptors result in an augmentation of ischemia/reperfusion injury (74) as well as exacerbating the decline in cardiac function after MI(75, 76). The maintenance of CV health is dependent on a very fine balance between vasodilatory PGI<sub>2</sub> and pro-thrombotic TXA<sub>2</sub> (77, 78), where PGI<sub>2</sub> functions to counterbalance the actions of TXA<sub>2</sub> (73). Indeed, PGI<sub>2</sub> released from endothelial cells and in synergy with NO prevent TXA<sub>2</sub>-induced platelet aggregation and thrombosis (42, 79, 80). TXA<sub>2</sub> is derived from platelet COX-1 causing platelet aggregation and vascular smooth muscle contraction (81-83). Clinical CV diseases, such as unstable angina, MI and stroke can be a result of overproduction of TXA<sub>2</sub>. Importantly, the cardio-protective properties of aspirin can be attributed to the covalent inhibition of COX-1 (84).

As well as having ‘pro-inflammatory’ properties, many prostanoids also exert immunosuppressive effects through upregulation of intracellular cAMP (85-87). For example, PGE<sub>2</sub> and PGI<sub>2</sub> reduce the ability of inflammatory leukocytes to phagocytose and kill microorganisms (88-93), as well as inhibit the production of downstream pro-inflammatory mediators (94-100) while, in contrast, enhancing the production of IL-10 and IL-6 (101, 102). Indeed, in a number of conditions associated with increased susceptibility to infection, including cancer (103), aging (104) and cystic fibrosis (105, 106) overexpression of PGE<sub>2</sub> has been reported. Interestingly, during the onset phase of inflammation, PGE<sub>2</sub> indirectly results in pro-resolution effects by switching on the transcription of enzymes required for the generation of LXs (107), resolvins (Rvs) and protectins (PDs) (108-111), other classes of bioactive lipids that are potent pro-resolution mediators..

As well as eliciting immuno-modulatory and anti-inflammatory effects in the same manner as described for PGE<sub>2</sub> and PGI<sub>2</sub> via ligation to DP1, PGD<sub>2</sub> can also act independently of DP1 and DP2 receptor activation when non-enzymatically dehydrated into biologically active prostaglandins of the J2 series (e.g. PGJ<sub>2</sub>, Δ12,14-PGJ<sub>2</sub> and 15-deoxy-Δ12,14-PGJ<sub>2</sub> [15d-PGJ<sub>2</sub>]) (112-116). These so called cyclopentenone PGs form covalent attachments with reactive sulphhydryl groups on intracellular regulatory proteins, which enables modulation of their function (117-119). For instance, 15d-PGJ<sub>2</sub> upon ligation to the nuclear receptor PPAR-γ (120), decreases pro-inflammatory cytokine release and modifies gene expression (121, 122) as well as directly inhibiting the actions of IκB kinase (IKK), which is responsible for the activation of NF-κB (123-125). 15d-PGJ<sub>2</sub>, independently of PPAR-γ, can preferentially inhibit monocyte rather than neutrophil trafficking through differential regulation of cell-adhesion molecule and chemokine expression (8, 126-128); regulate macrophage activation and pro-inflammatory gene expression (129); and induce leukocyte apoptosis through a caspase-dependent mechanism (8, 115, 130-133). Moreover, it has been shown that PGD<sub>2</sub>-derived compounds function as endogenous breaking signals for lymphocytes to stimulate resolution (134).

## **LIPOXYGENASE**

LOX enzymes, including 5-, 12-, or 15-LOX in leukocytes, platelets and endothelial cells, respectively, metabolise AA. The generation of the slow-reacting substances of anaphylaxis (LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>: potent mediators of the allergic response) (135) and LTB<sub>4</sub>, a powerful polymorphonuclear (PMN) leukocyte (i.e. neutrophils and eosinophils) chemoattractant (136, 137) is elicited by Leukocyte 5-LOX. Due to its involvement in LT synthesis, 5-LOX has received the most attention in inflammation research. Therefore, the remainder of this section will concentrate specifically on this pathway.

Once activated, 5-LOX converts AA into a hydroperoxide by inserting molecular oxygen into AA at positions 5 aided by the 5-LOX activating protein (FLAP). Termed 5-hydroperoxyeicosatetraenoic acid (5-HPETE), this intermediate is then rapidly reduced to 5-hydroxyeicosatetraenoic acid (5-HETE). 5-HPETE can also be converted by removal of water to an unstable 5,6-epoxide containing a conjugated triene structure called LTA<sub>4</sub>, which is then converted to either LTB<sub>4</sub> by insertion of a hydroxyl group at carbon-12 (C-12) through the action of LTA<sub>4</sub> hydrolase (138, 139) or LTC<sub>4</sub> by addition of the glutathionyl group at C-6 by  $\gamma$ -glutamyl-S-transferase (140). In most cases LTB<sub>4</sub> and 5-HETE are subsequently secreted from the cell by an unidentified protein carrier (141). LTC<sub>4</sub> is also exported, but by the ATP-dependent multidrug resistance proteins (142), including MRP1 and MRP2. After export, LTC<sub>4</sub> is metabolised by the cleavage of glutamic acid by  $\gamma$ -glutamyl transpeptidase to form LTD<sub>4</sub>, which can be further modified by removal of a glycine by cysteinyl glycinease to produce LTE<sub>4</sub>. Unlike COX, 5-LOX is inactive in quiescent cells but becomes enzymatically functional after cell activation by increases in intracellular calcium (143) enhanced by ATP (144), or by phosphorylation, which can occur without an increase in calcium (145).

Heptahelical receptors of the rhodopsin class located on the outer leaflet of the plasma membrane of structural and inflammatory cells mediate the effects of LTs (146, 147). To date, four subtypes have been described, B leukotriene receptor 1 and 2 (BLT1 and BLT2), and cysteinyl leukotriene receptor 1 and 2 (cys-LT1 and cys-LT2). Once LTs have bound, a signal is sent via a G-protein in the cytoplasm to increase intracellular calcium and block formation of cAMP, which then alters various cellular activities, ranging from motility to transcriptional activation. While Cys-LT1 mediates broncho-constriction, mucus secretion, and oedema accumulation in airways (148), Cys-LT2 contributes to inflammation, vascular permeability

and tissue fibrosis in lungs (149, 150). Indeed, overexpression of Cys-LT1 is seen in patients with asthma or chronic rhinosinusitis who have aspirin sensitivity (151). In contrast, BLT1 is a high-affinity receptor for LTB<sub>4</sub>, mediating all of its chemo-attractant and pro-inflammatory properties (147). Although BLT2 acts in a similar fashion to BLT1, LTB<sub>4</sub> affinity towards BLT1 is much higher. Interestingly, studies employing both *in vitro* and a murine model of inflammation demonstrate that LTB<sub>4</sub> ligates and activates the anti-inflammatory nuclear receptor PPAR- $\alpha$  (152-155).

## **LEUKOTRIENES IN INFLAMMATION**

LTs are generated at sites of infection/inflammation primarily by inflammatory cells, including PMNs, macrophages and mast cells and play a critical role in the inflammatory response by acting as pro-inflammatory lipid mediators. Physiologically, each of the 5-LOX-derived compounds has a distinct role in driving different phases of inflammation. For example, LTB<sub>4</sub> attracts and activates neutrophils, monocytes, and lymphocytes, a hallmark of tissue inflammation (147, 156, 157), whereas LTD<sub>4</sub> is a potent chemoattractant for eosinophils (158). The cysteinyl LTs (LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>) on the other hand increase vascular permeability and plasma leakage, leading to oedema that is characteristic of inflammation (159-163). Pathologically, LTs contribute to a variety of inflammatory and allergic diseases, such as rheumatoid arthritis, inflammatory bowel disease (IBD), psoriasis, allergic rhinitis, bronchial asthma, cancer, atherosclerosis and osteoarthritis (164). This can be seen in asthmatic patients where antileukotriene therapy (i.e. 5-LOX inhibition by zileuton and CysLT1 blockage by montelukast or zafirlukast) resulted in benefitted from improved pulmonary function, symptoms, and overall quality of life (165-167).

The role of LTs in CV disease has been the subject of intense investigation. In atherosclerotic lesions for example, 5-LOX activity/levels are associated with the severity of the lesion (168) and plaque instability (169). Furthermore, both LTB<sub>4</sub> and cysLTs participate in the development of atherosclerotic lesions in animals and *in vitro*. LTB<sub>4</sub> increases recruitment of monocytes and their differentiation to foam cells (170), as well as intimal hyperplasia (171). CysLTs on the other hand enhance the recruitment of leukocytes into the arterial wall and contribute to thrombosis and vascular remodeling (172, 173). Interestingly in humans, the incidences of strokes and MI in certain populations has been linked to variants of the genes that encode FLAP and LTA<sub>4</sub> hydrolase, which cause an overproduction of LTs (174-176). Indeed, upon treatment with a FLAP inhibitor (veliflapon), a potent biomarker of inflammation, C-reactive protein, was reduced in one population of patients with a history of MI and one of the variants mentioned above (177). Despite their pathophysiologic role, it has now become apparent that LTs are important participants in the host response against infection (178). For instance, 5-LOX-deficient mice or pharmacological inhibition of LT synthesis caused increased mortality and reduced microbial clearance after challenge with a variety of microbes (e.g. bacteria, mycobacteria, fungi, parasites(179-184). Similarly, LT-deficient alveolar macrophages also displayed impaired phagocytosis and intracellular killing of bacteria, an effect that could be overcome with the exogenous introduction of LTB<sub>4</sub> or cysLTs (180, 185). Interestingly, LT deficiency is also a feature of a number of clinical conditions that are associated with impaired microbial clearance (Human immunodeficiency virus [HIV] infection, malnutrition, cigarette smoking, vitamin D deficiency and post-bone marrow transplantation) (186-191). It is believed that LTs enhance microbicidal activities in leukocytes by upregulating production of nitric oxide (192, 193) and the secretion of microbial peptides (194) as well as activating NADPH oxidase to generate ROI (185). Recently, it has been demonstrated that LTB<sub>4</sub> may also possess anti-inflammatory properties

through ligation to PPAR- $\alpha$  in its parent cell (155). It has been suggested that this activation in turn leads to its own catabolism thus facilitating resolution of the inflammatory process. This hypothesis/theory/stipulation is conceivable /further demonstrates how inflammation is such a finely balanced process that is invoked when required, yet limited and resolved when it is no longer needed.

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

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

5-oxo-ETE acts via OXE receptor (OXE-R), a distinct orphan G-protein coupled receptor (GPCR) (202, 203) that is most highly expressed in human peripheral leukocytes, lungs, kidney, liver and spleen (204, 205). The relative expression of OXE-R in eosinophils, neutrophils and macrophages is 200:6:1 (205). OXE-R, once coupled to a G<sub>i/o</sub>-protein (197, 206, 207), activates a number of distinct intracellular signaling pathways including PLC $\beta$



(208), PI3K and Akt (206, 208, 209), PKC $\delta/\zeta$  (210), as well as ERK-1/2 and cPLA<sub>2</sub> (210, 211), which, in turn, could lead to further production of AA-derived metabolites. OXE-R may also inhibit the cascade mediated by adenylyl cyclase and cAMP (204).

## **5-OXO-ETE AND INFLAMMATION**

5-oxo-ETE is produced by eosinophils, neutrophils, basophils and monocytes and like other inflammatory lipids it acts in an autocrine manner. In addition to its most potent property as a chemoattractant for eosinophils (200), 5-oxo-ETE also induces calcium mobilisation, actin polymerisation, CD11b expression, and L-selectin shedding (201). Furthermore, 5-oxo-ETE induces degranulation and superoxide production in leukocytes primed with cytokines such as granulocyte macrophage-colony stimulating factor (GM-CSF) and TNF- $\alpha$ , an effect not mirrored in naive cells (207, 211). In addition 5-oxo-ETE stimulates human monocytes to secrete GM-CSF (212), which is a potent survival factor for eosinophils. In prostrate tumour cells this lipid prevents apoptosis/proliferation (213, 214).

## **LIPOXINS – BIOSYNTHESIS AND RECEPTORS**

Lipoxins (LXs) are a series of trihydroxytetraene-containing bioactive eicosanoids that were first isolated from human leukocytes in the mid 1980's (13). However, in contrast to LTs and 5-oxo-ETEs, which are manufactured by intracellular biosynthesis, LXs are generated through cell-cell interactions by a process known as transcellular biosynthesis. In different human cell types, during the first biosynthetic step of LX biosynthesis, LOX inserts molecular oxygen into AA. This can be achieved by two major routes - the first pathway involves the oxygenation of AA at C-15 by 15-LOX in eosinophils, monocytes, or epithelial cells (found in the respiratory tract, gastrointestinal tract and oral cavity), yielding 15S-HPETE. Following secretion, 15S-HPETE is taken up by either PMNs or monocytes and rapidly converted into

5,6-epoxytetraene by 5-LOX, which is hydrolysed within these recipient cells by either LXA<sub>4</sub> or LXB<sub>4</sub> hydrolase to bioactive LXA<sub>4</sub> or LXB<sub>4</sub>. Interestingly, this process also markedly reduces the formation of LTs, which requires 5-LOX to convert AA into LTA<sub>4</sub> (215-217). Moreover, it has been found that the 15*S*-HETE synthesised via this pathway can also be esterified and stored within the membranes of neutrophils, specifically inositol-containing phospholipids. Upon cell stimulation, 15*S*-HETE is rapidly released and transformed to a second signal, such as LXA<sub>4</sub>, to regulate the function of the neutrophil (218). The second major route of LX biosynthesis occurs in a LTA<sub>4</sub>-dependent manner, involving peripheral blood platelet-leukocyte interactions. Leukocyte 5-LOX converts AA into LTA<sub>4</sub>, which is released, taken up by adherent platelets, and subsequently transformed to LXA<sub>4</sub> and LXB<sub>4</sub> via the LX synthase activity of human 12-LOX (219). A third unorthodox route of LX generation occurs after the exogenous administration of aspirin (but not other conventional NSAIDs), which irreversibly acetylates COX-2 in endothelial cells and other cell types. Rather than COX-2 converting AA into PGG<sub>2</sub>, acetylation causes the transformation of AA into 15*R*-HETE (C-15 alcohol carried in the *R*-configuration). This is then rapidly metabolised in a transcellular manner by adherent leukocyte, vascular endothelial or epithelial 5-LOX to form 15 epimeric-LX (15-epi-LXs) or aspirin-triggered LXs (ATL) that carry their C-15 alcohol in the *R* configuration rather than 15*S* native LX. ATL's share many of the anti-inflammatory/pro-resolution characteristics of the native LXs.

LXA<sub>4</sub> and 15-epi-LXs elicit their multi-cellular responses via ALX (FPRL1 receptor), a specific G-protein-coupled receptor (GPCR) isolated and cloned in human, mouse and rat tissues (220-222). Human ALX was subsequently identified and cloned in several types of leukocytes, including monocytes (223) and T cells (224), as well as resident cells such as macrophages, synovial fibroblasts (225) and intestinal epithelial cells (226). One of the

functions attributed to ALX is in mediating the multi-cellular responses of LXA<sub>4</sub> and 15-epi-LXs. Studies in transgenic models have shown its selectivity towards LXA<sub>4</sub> and 15-epi-lipoxin A<sub>4</sub> (not for LXB<sub>4</sub>, LTB<sub>4</sub>, LTD<sub>4</sub> or PGE<sub>2</sub>) with high affinity (K<sub>d</sub> = 1.7nM) [231]. ALX also has the ability to interact with other small peptides/proteins such as Ac2-26 and glucocorticoid-derived annexin-1, which carry out similar anti-inflammatory effects as LXs and 15-epi-LXs. Evidence that the protective effects of LXs and 15-epi-LXs were both ligand- and receptor-dependent arose from studies in transgenic mice over-expressing human ALX (227-229). In a zymosan-induced peritonitis model, infiltration of neutrophils was also substantially diminished in transgenic mice compared to their wild-type equivalents (227) with the site of lipoxin action being the leukocyte/endothelial interface mediated by the generation of nitric oxide's anti-adhesive properties (230).

ALX activation inhibits NADPH oxidase assembly, which, in turn, reduces superoxide anion generation by neutrophils through accumulation of polyisoprenoid presqualene diphosphate (PSDP) (231). Indeed, it has been demonstrated that inhibition of pro-inflammatory genes such as neutrophil chemoattractant IL-8 occurs via an ALX-dependent peroxynitrite-mediated signaling pathway (232). Moreover, peroxynitrite-induction of IL-8 in response to LPS, TNF- $\alpha$  or IL- $\beta$  in human leukocytes occurs via a NF $\kappa$ B and AP-1 dependent pathway (233, 234). 15-epi-LX analogues also regulate an ALX-dependent p38/MAPK cascade, known to promote chemotaxis by inhibiting leukocyte-specific AP-1 phosphorylation and activation (235). In addition to ALX, LXs also function as partial agonists to a subclass of rhodopsin receptors (CysLT1) more commonly activated by LTs, mediating bioactions in several tissues and cell types other than leukocytes (221, 236). At nanomolar concentrations LXA<sub>4</sub> has been shown to compete for binding with LTD<sub>4</sub> on mesangial cells (236) and human umbilical vein endothelial cells (HUVECs) (222, 237) as well as opposing the pro-inflammatory effects of

LTD<sub>4</sub>. There is also evidence that another intracellular receptor, the Ah receptor (AhR) mediates the bioactions of LXs. This receptor is a ligand activated transcription factor that controls several of the biologic actions of LXs, such as increasing the expression of suppressor of cytokine signalling 2 (SOCS-2) (238-240).

## **LIPOXINS IN INFLAMMATION**

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

At sites of inflammation, macrophages are stimulated by lipoxins to ingest and clear apoptotic neutrophils (249), which appears to be coupled to changes in the actin cytoskeleton (250). Furthermore, lipoxins elevate the levels of the anti-inflammatory cytokine TGF- $\beta$ 1, which, in

turn, down-regulates a number of pro-inflammatory pathways (251-253). It is believed that these lipid mediators are generated *in situ* when neutrophils express 5-LOX at the onset of resolution as they begin to apoptose (107). LXs may also counteract the fibrotic response and thus improve tissue remodelling by reducing the proliferation of fibroblasts and mesangial cells induced by a number of factors, including connective-tissue growth factor, platelet-derived growth factor, TNF- $\alpha$ , LTD<sub>4</sub> and TGF- $\beta$  (254-257). 15-epi-LXs exert the same biological effects as endogenously produced LXs, but with additional benefits that increase vasorelaxation (258), and induce endothelial cell production of anti-inflammatory nitric oxide synthesis (230, 259). Moreover, 15-epi-lipoxin A<sub>4</sub> has been found to inhibit TNF- $\alpha$ -induced IL-1 $\beta$  in periodontitis *in vivo* (260, 261), dampen SOCS-2 signalling (262) and inhibition of TNF- $\alpha$ -induced IL-8 gene expression (226). Not surprisingly, both LXs and 15-epi-LXs have been identified and proven to exert beneficial effects in various experimental models of inflammation and human diseases, such as glomerulonephritis (263, 264), ischemia/reperfusion injury (246, 254), cystic fibrosis (265), periodontitis (266), acute pleuritis (230), asthma (267), wound healing processes in the eye (268), colitis, inflammation-induced hyperalgesia in rats, various cutaneous inflammation models (269), and microbial infection in mice (238, 270, 271).

### **OMEGA-3 POLYUNSATURATED FATTY ACID PATHWAY**

Omega-3 polyunsaturated fatty acids ( $\omega$ 3-PUFA) have long been known to be important in not only in maintaining organ function and health but also in reducing the incidence of infection and inflammation (110, 111, 272-275). A clinical trial (GISSI-Prevenzione) assessing the benefits of aspirin with and without  $\omega$ -3 PUFA supplementation in patients recovering from myocardial infarctions revealed a significant decrease in mortality in the group taking the supplement (276). More recent evaluations have confirmed the importance

of  $\omega$ -3 PUFA in reducing CV disease, and inflammation associated with it (277, 278). It was initially hypothesised that fish oils demonstrate their anti-thrombotic, immuno-regulatory and anti-inflammatory bioactions by inhibiting PGs and LTs synthesis (279). However, current opinion is that it is likely that a series of novel compounds derived from EPA and DHA are responsible for eliciting these immuno-modulatory effects. First identified in the resolving exudate of a mouse dorsal air pouch or peritonitis model using lipidomic and bio-informatic analysis (110, 111, 280, 281), these naturally occurring bioactive lipid mediators are termed resolvins, Rvs (derived from ‘resolution phase interaction products’), protectins (PDs) and maresins (derived from ‘macrophage mediator in resolving inflammation’). All these  $\omega$ -3 PUFA-derived products possess a plethora of stereospecific and potent anti-inflammatory and immuno-regulatory actions that are protective *in vitro* and *in vivo* (282, 283).

## **RESOLVINS AND PROTECTINS**

Rvs can be generated from either EPA or DHA and are therefore categorised as either members of the E-series (from EPA) or D-series (from DHA). Rvs of both series were first isolated *in vivo* from murine dorsal air pouches treated with aspirin and EPA or DHA. Transcellular formation of E-series Rvs can occur with the conversion of EPA to 18R-hydroxyeicosapentanoic acid (18R-HEPE) by endothelial cells expressing COX-2 treated with aspirin. As with 15R-HETE in 15-epi-LX formation, 18R-HEPE can be released from endothelial cells to neighboring leukocytes for subsequent conversion by 5-LOX to either RvE1 or RvE2, via a 5(6) epoxide-containing intermediate (110, 284). This interaction is blocked by selective COX-2 inhibition but not by indomethacin or paracetamol (110). RvE1 is spontaneously produced in healthy subjects, with levels increasing after treatment with either aspirin or EPA (285). D-series Rvs, aspirin-triggered RvD1 (AT-RvD1) and RvD1 are synthesised via a pathway involving sequential oxygenations, initiated by 15-LOX or aspirin-

acetylated COX-2 in the microvascular, respectively, followed by 5-LOX in human neutrophils with an epoxide containing intermediate. For AT-RvD1s, DHA is initially converted to epimeric 17*R*-hydroxydocosahexaenoic acid (17*R*-HDHA). In the absence of aspirin, however, DHA is enzymatically converted to 17*S*-HDHA (108). Interestingly, generation of E-series Rvs can also be mediated by microbial and mammalian cytochrome P450 enzymes, which convert EPA into 18-HEPE. 18-HEPE can then be transformed by human neutrophils into either RvE1 or RvE2 (110). Hence, it is possible that microbes at sites of infection may contribute to the production of Rvs in a similar pathway.

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

## **RESOLVINS AND PROTECTINS IN INFLAMMATION**

One of the broader immunomodulatory properties of RvE1 is its ability to inhibit neutrophil and dendritic cell accumulation at sites of inflammation by blocking trans-endothelial migration as well as enhancing their clearance from mucosal epithelial cells (110, 285, 287).

Other bioactions of RvE1 includes inhibition of neutrophil ROI in response to TNF- $\alpha$  and bacterial peptide, fMLP (288), abrogation of LTB<sub>4</sub>-BLT1 signalling via NF- $\kappa$ B and thus the production of pro-inflammatory cytokines and chemokines (251, 289, 290), stimulation of macrophages to ingest apoptotic neutrophils (291), enhancement of the percentage of phagocytes present in the lymph nodes (292) and upregulation of the CC-chemokine receptor 5 (CCR5) on late apoptotic neutrophils (10), which terminates chemokine signalling, and inhibition of dendritic cells migration. More recently, RvE1 has been demonstrated to regulate the leukocyte pro-inflammatory cell surface markers, such as L-selectin, whilst selectively disrupting TX-mediated platelet aggregation (293), adding further mechanistic insight into its anti-inflammatory/pro-resolution properties. In disease states, RvE1 suppresses *Porphyromonas gingivalis*-induced oral inflammation and alveolar bone loss during periodontitis (294), demonstrates protective actions in trinitrobenzene-sulphonic acid-induced colitis in mice (272), as well as causing re-epithelisation of mouse cornea after thermal-injury (268). Overall, RvE1 initiates resolution of inflammation and causes decreased numbers of PMNs at sites of inflammation early during the response, reviewed in (283).

Structure-activity assays have elucidated that RvE1 binds to an orphan G-protein coupled receptor belonging to the same cluster as ALX (ChemR23), with a high affinity ( $K_d = 48.3\text{nm}$ ). This coupling down-regulates the activity of NF- $\kappa$ B and hence TNF- $\alpha$  synthesis, as well as initiating signalling pathways involved in initiating mitogen-activated protein kinase (MAPK) (285). Indeed, ChemR23 activation has been demonstrated to inhibit one of the most prominent RvE1 actions, dendritic cell migration (285). Although it has been found in myeloid, gastro-intestinal, kidney, brain, and CV tissue, the percentage of ChemR23 expression is highly variable. For example, it has been demonstrated that ChemR23 is markedly increased on the surface of human monocytes but less so on neutrophils by anti-



inflammatory mediators such as TGF- $\beta$  (295). Like ALX, ChemR23 acts as a receptor towards peptide ligands, including chemerin that also act as anti-inflammatory mediators (296). RvE1 also appears to interact with the LTB<sub>4</sub> receptor, BLT1 and act as a partial antagonist preventing neutrophil activation (289). Therefore, it can be concluded that RvE1 couples to two distinct receptors to both suppress pro-inflammatory mechanisms and enhance resolution pathways.

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

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

reduced bacterial load and pro-inflammatory cytokines, which subsequently led to increased survival and improved health (298).

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

## **MARESINS**

Maresins (MaR) were identified in 2008 after 17S-D series Rvs, PDs as well as 14S-hydroxydocosahexaenoic acid (14S-HDHA) were isolated from the resolution phase of mouse peritonitis were added to stimulated resident peritoneal macrophages (281). Macrophages then convert these intermediates to novel dihydroxy-containing products, which possesses potent anti-inflammatory and pro-resolving properties. Although the exact biosynthetic pathway is yet to be elucidated a hypothetical scheme was proposed. It is thought that DHA is

converted to 14*S*-hydroperoxydocosaehaenoic acid (14*S*-HPDHA; maresin, MaR1) via 12- or 15-LOX, followed by either reduction to 14*S*-HDHA and/or via double dioxygenation (e.g. sequential 12-LOX-5-LOX) to generate a metabolome of MaR1, 7*S*,14*S*-dihydroxydocosaehaenoic acid (7*S*,14*S*-diHDHA). Though maresins have only been recently it has been reported that, as with Rvs and PD1, MaR1 block the infiltration of PMNs, whilst stimulating macrophage phagocytosis of apoptotic PMNs/zymosan (281). Its metabolome 7*S*,14*S*-diHDHA was active but less potent.

### **CYTOCHROME P450**

In the last decade, interest into a third less well-characterised pathway of AA metabolism, cytochrome P450 (CYP) has been rekindled. CYP are families of membrane-bound, haeme-containing enzymes found in the liver, brain, kidneys, lung, heart and the CV system, thought initially to be involved in catalysing NADPH-dependent oxidation of drugs, chemical and carcinogens (309, 310). It is now well-appreciated that CYPs also catalyse the conversion of fatty acids including AA into products which have been denoted epoxyeicosatrienoic acids (EETs), hydroxyeicosatetraenoic acids (HETEs) and dihydroxyeicosatrienoic acids (DHETs) (311). For instance, AA is metabolised in the vascular endothelium by CYP epoxygenase to EETs (312), which can then be converted by epoxide hydrolase to the respective regioisomer of DHETs (311). In the vascular smooth muscle, AA is catalysed by CYP hydroxylases to 20-HETE (313). Indeed, one particular member, CYP4F3 is highly expressed in PMNs catalysing the  $\omega$ -hydroxylation of LTs (314). However, it is unknown whether CYP4F3 is the source of 20-HETE produced by PMNs (315). These metabolites play a large and complex role in maintaining renal, cardiac, and pulmonary homeostasis by regulating aspects such as vascular tone and reactivity, renal and pulmonary functions, ion transport, and growth

responses (316-318). Interestingly, they have also been demonstrated to exert potent anti-inflammatory actions (319-321), detailed below.

### **CYTOCHROME P450-DERIVED PRODUCTS AND INFLAMMATION**

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

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

## **SUMMARY**

Studies on inflammation and its resolution have advanced our understanding of leukocyte trafficking, efferocytosis and pro-inflammatory leukocyte clearance as well as immune-suppressive eicosanoids, specialised immune-regulatory cells and cytokine catabolism. These pathways converge on the termination of acute inflammatory responses and contribute to the notion that chronic inflammation is avoided and wounds healed in an appropriate manner(329, 330). Implicit therein is that tolerance is not compromised making the host susceptible to autoimmunity. AA metabolites were once considered pro-inflammatory due to the effective usage of NSAIDs in the treatment of chronic inflammatory diseases. While NSAIDs have been a valuable treatment in terms of anti-inflammation and pain relief, they have recently unmasked beneficial properties of some LOX and COX products. Thus, our understanding of eicosanoids in physiology and pathology has come a long way since the earliest observations of Kurzrok and Lieb(331). Hence, PGs may drive oedema but prevent leukocyte trafficking, while at the same time elevating cAMP and impairing bacterial

phagocytosis and killing. However,  $LTB_4/D_4$  oppose/prevents the immune suppressive actions of  $PGE_2$ , with 5-LOX metabolites thus enhancing macrophage antimicrobial functions/roles, including the phagocytosis of IgG-opsonized targets via the  $Fc\gamma R$ . COX/LOX derived lipoxins, resolvins and protectins attenuate innate immune responses, aid/ameliorate/promote resolution and are proving beneficial in experimental sepsis. Thus, the role of eicosanoids in inflammation is most likely dependant on the phase of the response during which they are synthesised, tissues affected and the nature of the inciting stimulus with some AA metabolites counteracting the bio-action of others but also triggering the synthesis of other families of eicosanoids that terminate inflammation. And while eicosanoids act diversely in acute inflammation, their role in chronic, non-resolving inflammation may be far more complex. That notwithstanding it now appears that not all eicosanoids are bad as some attenuate innate immune-mediated functions and accelerate/facilitate their timely resolution. This offers a more accurate strategy in treating diseases driven by over-exuberant inflammation.

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