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Review

Specialized pro-resolving lipid mediators in the inflammatory response: An update

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ABSTRACT

A new genus of specialized pro-resolving mediators (SPM) which include several families of distinct local mediators (lipoxins, resolvins, protectins, and maresins) are actively involved in the clearance and regulation of inflammatory exudates to permit restoration of tissue homeostasis. Classic lipid mediators that are temporally regulated are formed from arachidonic acid, and novel local mediators were uncovered that are biosynthesized from ω-3 poly-unsaturated fatty acids, such as eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid. The biosynthetic pathways for resolvins are constituted by fatty acid lipoxygenases and cyclooxygenase-2 via transcellular interactions established by innate immune effector cells which migrate from the vasculature to inflamed tissue sites. SPM provide local control over the execution of an inflammatory response towards resolution, and include recently recognized actions of SPM such as tissue protection and host defense. The structural families of the SPM do not resemble classic eicosanoids (PG or LT) and are novel structures that function uniquely via pro-resolving cellular and molecular targets. The extravasation of inflammatory cells expressing SPM biosynthetic routes are matched by the temporal provision of essential fatty acids from circulation needed as substrate for the formation of SPM. The present review provides an update and overview of the biosynthetic pathways and actions of SPM, and examines resolution as an integrated component of the inflammatory response and its return to homeostasis via biochemically active resolution mechanisms.

1. The inflammatory response

The inflammatory response is a local reaction of the vasculature towards a disturbance of tissue homeostasis incurred by damage to tissue structure and infection [1–3]. Changes in local blood vessel perfusion and permeability permit the directional extravasation of circulating leukocytes that achieve tissue disinfection, and of a range of plasma proteins which play distinct roles in regulating the inflammatory process. Structural alterations of tissue structure that activate the inflammatory response can be brought about by a variety of energetic interactions between a tissue and an exogenous force that tears, shears, or wears on its integrity, *e.g.* radiation (sunlight), heat (a burn), a cut (a bite), enzymatic proteolysis (some allergens), and chemical modification. Superimposed infections by exogenous microorganisms are sensed by an array of innate immune receptors (toll-like receptors and C-type lectins), triggering the mounting of a granulocyte-dominated acute inflammatory response, as well as by adaptive immune responses that are appropriate for elimination of the inciting stimulus [4–7].

Exposure to noxious insults and infections is effectively minimized by learned behavior, through involuntary local and centrally mediated neural reflexes, and by conscious avoidance following their sensation. If tissue integrity is breached regardless, the inflammatory response is activated rapidly (within minutes). The principal objectives of this response are the delivery of blood-borne phagocytes (neutrophils and monocytes) to the affected tissue in order to increase the local tissue concentration of cells that can remove the inciting tissue-damaging stimulus, as well as the regulation of antigen-specific adaptive immune responses [8,9]. The directed migration of blood-borne leukocytes to the inflammatory locus, a transient increase in vascular permeability which facilitates plasma exudation, and phagocytosis of microbes and dying cells are central events during the pro-inflammatory phase of the inflammatory response (Fig. 1) [8,10,11]. Of importance, the acute inflammatory response is self-limiting and in a normal course of events should lead to complete tissue restoration and homeostasis. Specific pathogen-mediated modulation of the host immune response, unrelenting exposure to inflammatory stimuli, and molecular defects in the inflammatory response can redirect the

Abbreviations: AA, arachidonic acid; ATL, aspirin-triggered lipoxin; AT-RvD, aspirin-triggered D-series resolvin; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; I/R, ischemia/reperfusion; LT, leukotriene; LTB_4, leukotriene B_4 (5*S*,12*R*-dihydroxy-eicosa-6*Z*,8*E*,10*E*,14*Z*-tetraenoic acid); LXA_4, lipoxin A_4 (5*S*,6*R*,15*S*-trihydroxy-eicosa-7*E*,9*E*,11*Z*,13*E*-tetraenoic acid); LXB_4, lipoxin B_4 (5*S*,14*R*,15*S*-trihydroxy-eicosa-6*E*,8*Z*,10*E*,12*E*-tetraenoic acid); MaR1, maresin 1; NO, nitric oxide; PD1/NPD1, protectin D1/neuroprotectin D1 (10*R*,17*S*-dihydroxy-docosa-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-hexaenoic acid); PG, prostaglandin; PUFA, poly-unsaturated fatty acid; RvD1, resolvin D1 (7*S*,8*R*,17*R*-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid); RvE1, resolvin E1 (5*S*,12*R*,18*R*-trihydroxy-eicosa-6*Z*,8*E*,10*E*,14*Z*,16*E*-pentaenoic acid)

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physiological resolution of an inflammatory exudate towards the formation of a granuloma, fibrogenesis or scar formation, or towards chronic inflammation with associated tissue damage, structural remodelation and permanent loss of normal tissue function [12–14].

The inflammatory response resembles the execution of a molecular and cellular program which passes check-points that function in assessing the nature of the insult, monitoring the progress of leukocyte accumulation and microbial clearance, and in initiating resolution and tissue repair [4,15–18]. Specific eicosanoids, lipid mediators derived from arachidonic acid (AA), are well established to contribute to the initiation of inflammation and chronic inflammation [19]. These include leukotrienes generated by the fatty acid oxygenase 5-lipoxygenase (5-LO), such as leukotriene B_4 (LTB_4; 5*S*, 12*R*-dihydroxy-eicosa-6*Z*, 8*E*,10*E*,14*Z*-tetraenoic acid), a potent chemoattractant for neutrophils, and the cysteinyl leukotrienes, which are potent mediators of vascular permeability [10,20]. A number of prostaglandins (PG) also play important roles in the early phases of inflammation, such as PGE_2, PGI_2 and $PGF_2\alpha$, as they regulate changes in blood flow which promote leukocyte delivery and plasma exudation to inflamed tissue [21–23].

2. The "front and back" of acute inflammation

Conserved physiological mechanisms limit the extent and duration of the inflammatory response [4,24,25]. These mechanisms can counter-regulate the extent of inflammation (or anti-inflammation), and/or promote the active termination or resolution of inflammation [4,24]. The former encompasses those mechanisms activated to reduce the rate of granulocyte recruitment to the inflammatory focus and limit their state of activation. The latter comprises the active removal of the granulocytic infiltrate, permitting restoration of normal tissue structure and function. The counter-regulation of the inflammatory response is achieved by several physiological mechanisms acting at the systemic level; an increase in circulating levels of glucocorticoids, activation of the acute-phase response, and anti-inflammatory cholinergic efferent neural pathways provide systemically active and protective responses to stress and inflammation [26–28]. Of significance, counter-regulation and resolution of the inflammatory response is also operative at the local tissue level, providing control over tissue-specific regulatory actions required to limit inflammatory injury and restore tissue homeostasis [29]. Recent results establish key roles of specific lipid mediator autacoids derived from poly-unsaturated fatty acids (PUFA) in the endogenous counter-regulation of inflammation and activation of resolution, such as AA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [30]. These lipid mediators, named lipoxins and resolvins, are formed via specific transcellular biosynthetic pathways established at strict temporal intervals during the inflammatory response. Without control of the inflammatory response, tissues would be overwhelmed by persistent inflammatory cell infiltrates, edema, and tissue damage incurred by activated inflammatory leukocytes [31–33]. Thus, active counter-regulation and resolution of inflammation are essential for the conservation of homeostasis and health [34].

Omega-3 fatty acids are dietary poly-unsaturated long-chain fatty acids essential for human health [35–42]. These can also be formed endogenously in men to a limited extent [43]. Phospholipids containing acylated EPA and DHA constitute a significant percentage of the fatty acid composition in specific locations of the body, *e.g.* the central nervous system, the retina, and sperm cells [44,45]. ω-3 PUFAs make an important contribution to structural and functional roles of specific subcellular membrane compartments [46,47]. It is now well documented that dietary ω-3 PUFAs impart protective actions in the cardiovascular and nervous systems, and can counteract a range of inflammatory diseases [30,35–40].

Anti-inflammatory and pro-resolving lipid mediators are derived from both ω-6 AA and ω-3 PUFA, which counteract the extent and regulate the pace of the inflammatory response at several critical cellular events. These include the down-regulation of cell adhesion molecules on both endothelial cells and leukocytes, reduced chemotaxis and transendothelial migration, reduced activation of neutrophils (measured by diminished degranulation and respiratory burst), inhibition of the formation and actions of pro-inflammatory mediators, the stimulation of non-phlogistic phagocytosis of apoptotic neutrophils and macrophages, as well as active egress of inflammatory leukocytes during resolution [48–54]. The transiently established transcellular biosynthetic pathways required for lipoxin and resolvin formation are assembled via heterotypic interactions of inflammatory leukocytes with endothelial cells, epithelial cells, macrophages and platelets that constitute an inflamed tissue. The formation of such lipid-derived cellular interaction products permits gauging the number and activation state of inflammatory leukocytes that participate in the inflammatory response. It is important to appreciate that lipoxins and resolvins act as endogenous receptor agonists at low concentrations (pM to low nM) and at specific G-protein coupled membrane-spanning receptors to actively down-regulate pro-inflammatory events, as well as stimulate the resolution of an inflammatory exudate [55]. In the following sections of this review, we summarize the biosynthesis of these endogenous lipid mediator autacoids, recently identified specific surface receptors, and their cellular actions.

3. Lipoxins and aspirin

Lipoxin A_4 (LXA_4; (5*S*,6*R*,15*S*-trihydroxy-eicosa-7*E*,9*E*,11*Z*,13*E*-tetraenoic acid) is a central anti-inflammatory lipid mediator autacoid which plays an important function in determining the extent of granulocyte (neutrophil and eosinophil) accumulation and activation during inflammation. The formation of LXA_4 is achieved by transcellular biosynthesis via two sequential oxygenation reactions of arachidonic acid (AA; Fig. 2) catalyzed by lipoxygenases present in interacting cell types, with one of the cell types often a neutrophil, eosinophil, or macrophage, and the other an endothelial, epithelial, or parenchymal cell or platelets [56,57]. LXA_4 is a potent endogenous anti-inflammatory lipid mediator that activates the G-protein coupled receptor ALX/FPR2 ($K_d \approx 0.7$ nM; Table 1) to reduce neutrophil chemotaxis, transendothelial migration and degranulation [58,59]. The transcellular formation of LXA_4 likely constitutes a specific signal formed as a result of the physical proximity of inflammatory cells with cells in the inflammatory focus, and activates subsequent tissue responses which limit further inflammatory cell infiltration. LXA_4 also exerts potent immuno-modulatory actions, promotes apoptosis of leukocytes *in vivo* by over-riding pro-survival signals, promotes migration of monocytes/macrophages to inflamed tissue, and stimulates the non-phlogistic phagocytosis of apoptotic leukocytes and lymphocytes by macrophages (efferocytosis) [50,60–63]. Taken together, LXA_4 reduces inflammatory leukocyte accumulation and also promotes the active removal of inflammatory exudate cells and debris.

A unique feature of the non-steroidal anti-inflammatory drug aspirin (acetyl-salicylic acid) is its action on the second described isoform of cyclooxygenase (COX-2), a fatty acid oxygenase which catalyzes the stereospecific double oxygenation of AA to form prostaglandin H_2, the central precursor for the formation of PGs. By acetylation of a conserved serine residue in the COX-2 active site, aspirin changes the enzymatic activity to allow the incorporation of one oxygen molecule to form 15*R*-hydroperoxy-eicosatetraenoic acid (15*R*-HpETE; 15*R*-hydroperoxy-5*Z*5*Z*,8*Z*,11*Z*,13*E*-tetraenoic acid) [64]. This product contains oxygen in the R configuration at carbon 15 and hence is epimeric and stereospecific compared to the oxygenation product formed during the second oxygenation step in PG biosynthesis. 15*R*-HpETE as well as 15*R*-HETE can be used as substrates by 5-LO to form 15-epi-LXA_4 (5*S*,6*R*,15*R*-trihydroxy-eicosa-7*E*,9*E*,11*Z*,13*E*-tetraenoic acid) [65] (Fig. 2). This aspirin-triggered biosynthetic route can function efficiently between a COX-