Allergology International 65 (2016) S2–S5

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Eosinophil polyunsaturated fatty acid metabolism and its potential control of inflammation and allergy

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ARTICLE INFO

Article history:
Received 20 May 2016
Accepted 23 May 2016
Available online 29 June 2016

Keywords:
Eosinophil
Lipid mediator
Lipidomics
Lipoxygenase
n-3 fatty acid

Abbreviations:
PUFA, polyunsaturated fatty acid; LC-MS/MS, liquid chromatography tandem mass spectrometry; COX, cyclooxygenase; LOX, lipoxygenase; CYP, cytochrome P450; HETE, hydroxy-eicosatetraenoic acid; EET, epoxy-eicosatrienoic acid; LT, leukotriene; PG, prostaglandin; LX, lipoxin; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DLN, draining lymph node; PMN, polymorphonuclear leukocyte; PAF, platelet activating factor

ABSTRACT

Polyunsaturated fatty acids (PUFAs) exhibit a range of biological effects, many of which are mediated through the formation and actions of their bioactive metabolites. It is well appreciated that dietary PUFA balance affects inflammation and/or allergic diseases, and recent advances in liquid chromatography tandem mass spectrometry (LC-MS/MS)-based mediator lipidomics have revealed a potential link between PUFA metabolism and biological phenotypes. This review presents insights into the emerging roles of eosinophil PUFA metabolism in controlling inflammatory responses and its potential involvement in allergy control.

PUFA metabolism and regulation of inflammation

PUFA metabolism is recognized as an important factor in immune regulation and disease control. In particular, the metabolic balance between n-6 and n-3 PUFAs is widely held to be important in human health and diseases. PUFA-derived bioactive metabolites are formed *in vivo* by enzymatic oxidation through the action of cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 monooxygenases (CYP). From n-6 PUFAs, e.g., arachidonic acid, the COX pathway leads to the formation of prostaglandins (PG) and thromboxanes, the LOX pathway leads to leukotrienes (LT) and lipoxins (LX), and the CYP pathway leads to hydroxy-eicosatetraenoic acids (HETE) and epoxy-eicosatrienoic acids (EET).[1,2] In general, COX-derived PGs and 5-LOX-derived LTs are involved in the initiation of inflammatory responses, whereas 12/15-LOX-derived LXs counter-regulate the inflammatory processes and may be involved in the resolution of inflammation. The CYP pathway generates EETs, which may have roles in regulation of inflammation and vascular tone.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are n-3 PUFAs, and dietary supplementation with such compounds is widely held to have beneficial effects in many inflammatory disorders.[3] Consistently, elevation of tissue n-3 PUFA levels in fatty acid n-3 desaturase (*fat-1*) transgenic mice is protective in many disease models.[4,5] EPA and DHA are good substrates for LOX and CYP, and thus can be efficiently converted into bioactive

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2016.05.010

metabolites such as E-series resolvins, D-series resolvins, protectins and maresins.[6] The n-3 PUFAs are thought to play anti-inflammatory and tissue protective roles via several mechanisms; by competing with the arachidonate cascade to attenuate the formation and action of pro-inflammatory eicosanoids (e.g., PGs and LTs), or by being converted to potent anti-inflammatory and/or pro-resolving mediators such as resolvins and protectins (Fig. 1). Thus, to elucidate the molecular mechanisms underlying the importance of PUFA balance and to gain a comprehensive understanding of their physiological and/or pathophysiological roles, it is important to know when, where and how much of these PUFA metabolites are formed in inflammatory sites. To this end, we developed a LC-MS/MS-based mediator lipidomics system that can detect and quantify more than 500 PUFA metabolites simultaneously.[1]

Eosinophils control inflammatory responses via lipid signals

Acute inflammation is an important host defense mechanism, and its proper resolution is required to maintain homeostasis.[7] The resolution of inflammation involves active cellular and molecular programs that enable inflamed tissues to return to their homeostatic state. The mechanisms by which acute inflammation is resolved are of interest to both basic scientists and clinicians, and research in recent years has uncovered novel endogenous mechanisms that involve 12/15-LOX-expressing eosinophils in controlling resolution of inflammation.[8]

LC-MS/MS-based mediator lipidomics revealed temporal changes in PUFA metabolites during the course of acute inflammation and resolution. The highest levels of COX- and 5-LOX-derived mediators such as PGE_2 and LTB_4 were observed during the initiation phase, and the formation of 12/15-LOX-derived mediators such as LXA_4 and protectin D1 was increased during the resolution phase of acute peritonitis.[8,9] In the resolution phase, eosinophils were the major cell type expressing 12/15-LOX. The *in vivo* depletion of eosinophils significantly reduced 12/15-LOX products in resolving exudates and caused a resolution defect characterized by impaired lymphatic drainage to draining lymph nodes (DLNs), along with increased polymorphonuclear leukocyte (PMN) numbers in inflamed sites. Furthermore, the resolution deficit caused by eosinophil depletion was rescued by adoptive transfer of eosinophils, but eosinophils deficient in 12/15-LOX were unable to rescue the resolution phenotype. These results indicated that eosinophils are recruited to the inflamed site, where they locally produce pro-resolving mediators via a 12/15-LOX-initiated biosynthetic route and play roles in promoting resolution of acute inflammation (Fig. 2).[8]

Macrophages play important roles in the resolution of inflammation by efficient clearance of apoptotic cells and/or tissue debris from inflamed sites, and thereby facilitate the return of the tissue to a state of homeostasis. 12/15-LOX-expressing eosinophils promote resolution of acute peritonitis by regulating gene expression patterns in macrophages. Microarray analysis revealed that eosinophils significantly increased the expression of macrophage CXCL13 by a 12/15-LOX-dependent mechanism.[10] CXCL13 was expressed in a subset of macrophages present in the resolution phase, and mice treated with anti-CXCL13 antibody displayed a resolution deficit, with reduced lymphatic drainage to DLNs. It is well established that CXCL13 is a functional chemokine in the early development of peripheral lymph nodes.[11] Since lymphatic drainage is involved in promoting inflammatory cell clearance from the periphery, we questioned whether 12/15-LOX-expressing eosinophils actively contribute to this process. Analysis of the cellular composition of the inflamed DLNs revealed that eosinophils were present, and that their depletion or 12/15-LOX deficiency resulted in reduced numbers of every immune cell component examined, including lymphocytes, macrophages, PMNs and dendritic cells. Adoptive transfer of eosinophils, or administration of recombinant CXCL13, restored the inflamed DLN expansion with increased cell numbers. These results demonstrated that 12/15-LOX-expressing eosinophils control inflamed DLN hypertrophy through the CXCL13 pathway in mice (Fig. 2). It is possible that eosinophils actively promote DLN remodeling and expansion that could in turn drive lymphatic drainage and efficient clearance of inflammatory exudates from peripheral tissues.[10]

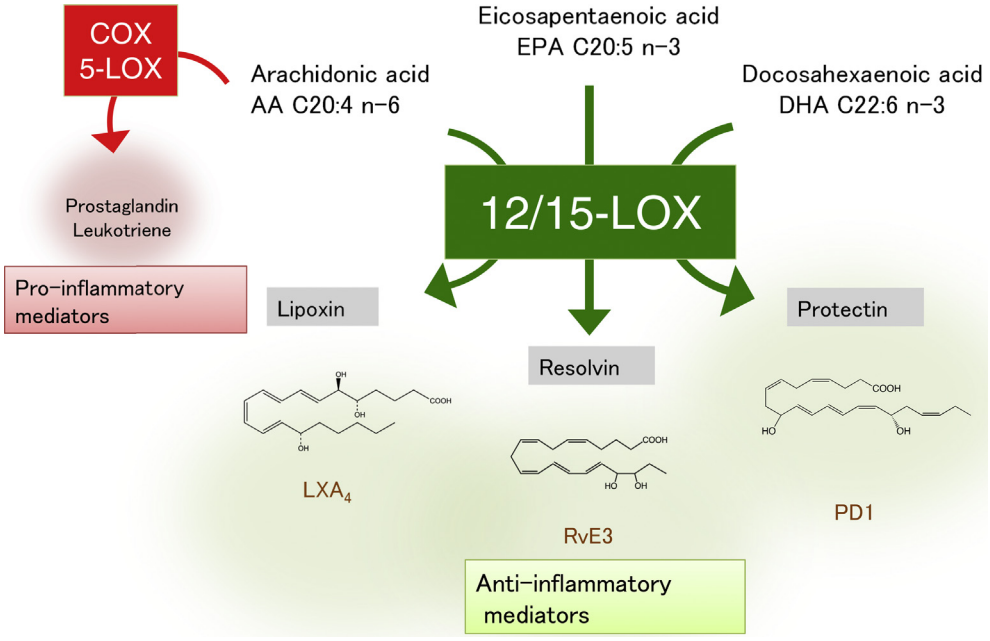

Fig. 1. Lipid mediators that regulate inflammatory responses. In addition to arachidonic acid-derived mediators such as COX-derived PGs and 5-LOX-derived LTs, 12/15-LOX-derived mediators such as LXs and n-3 PUFA-derived resolvins and protectins are also produced. These mediators play important roles in regulating inflammatory responses.