Biochimica et Biophysica Acta 1851 (2015) 397–413

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome☆

Charles N. Serhan *, Jesmond Dalli, Romain A. Colas, Jeremy W. Winkler, Nan Chiang

Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 2 May 2014
Received in revised form 6 August 2014
Accepted 9 August 2014
Available online 17 August 2014

Keywords:
Resolvin
Leukocyte
LC–MS–MS-based targeted lipid mediator metabolomics
Lipid mediator
Eicosanoid

ABSTRACT

Acute inflammatory responses are protective, yet without timely resolution can lead to chronic inflammation and organ fibrosis. A systems approach to investigate self-limited (self-resolving) inflammatory exudates in mice and structural elucidation uncovered novel resolution phase mediators *in vivo* that stimulate endogenous resolution mechanisms in inflammation. Resolving inflammatory exudates and human leukocytes utilize DHA and other n−3 EFA to produce three structurally distinct families of potent di- and trihydroxy-containing products, with several stereospecific potent mediators in each family. Given their potent and stereoselective picogram actions, specific members of these new families of mediators from the DHA metabolome were named D-series resolvins (Resolvin D1 to Resolvin D6), protectins (including protectin D1–neuroprotectin D1), and maresins (MaR1 and MaR2). In this review, we focus on a) biosynthesis of protectins and maresins as anti-inflammatory–pro-resolving mediators; b) their complete stereochemical assignments and actions *in vivo* in disease models. Each pathway involves the biosynthesis of epoxide-containing intermediates produced from hydroperoxy-containing precursors from human leukocytes and within exudates. Also, aspirin triggers an endogenous DHA metabolome that biosynthesizes potent products in inflammatory exudates and human leukocytes, namely aspirin-triggered Neuroprotectin D1/Protectin D1 [AT-(NPD1/PD1)]. Identification and structural elucidation of these new families of bioactive mediators in resolution has opened the possibility of diverse patho-physiologic actions in several processes including infection, inflammatory pain, tissue regeneration, neuroprotection-neurodegenerative disorders, wound healing, and others. This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".

1. Introduction

Docosahexaenoic acid (DHA) is a highly conserved structure, an essential fatty acid in humans, and has physical properties that evolved to impact cellular membrane and neural function [1–4]. Recent results from this laboratory indicate that DHA is also a precursor to potent local autacoids. These include the D-series resolvins, protectins and maresins that are produced in self-resolving inflammatory exudates in mice [reviewed in ref. 5]. Neutrophils (PMN) are first to arrive at the site of inflammation during the acute inflammatory response and play an important protective role in innate immunity and host defense. However, excessive accumulation of PMN within tissues can lead to tissue damage, amplification of the inflammatory response, injury from within and prolongation of the signs of inflammation [6]. The control of neutrophil infiltration is of wide interest, as new anti-inflammatory agents are needed to control excess neutrophil responses within tissues that can give rise to chronic inflammatory diseases [7]. Along these lines, evidence was sought for the endogenous mechanism(s) controlling PMN infiltration and natural tissue resolution, since protective PMN (i.e. acute inflammatory responses) are programmed to be self-limited and tightly controlled [8–10]. Lipid mediators such as prostaglandins and leukotrienes play pivotal roles in the initiation of acute inflammation [11], whereas resolvins and protectins promote and stimulate active resolution [8,9,12]. In excess, prostaglandins and leukotrienes are generally pro-inflammatory [11] and involved in the classic initiation phase of the acute inflammatory response in humans.

Studies in this laboratory uncovered potent new families of n−3 essential fatty acid (EFA)-derived mediators generated during resolution that are antiinflammatory, neuroprotective, and activate novel resolution pathways [9,10,13,14]. Resolution of acute inflammation is a central component of host defense and the return of tissue to homeostasis [15]. It is now well recognized that inflammation plays a key role in many prevalent human diseases including cardiovascular diseases, atherosclerosis, Alzheimer's disease, and cancer [16–18]. Although much is known about the molecular basis of initiating signals and proinflammatory chemical mediators in inflammation [19], it has only recently

☆ This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".

* Corresponding author at: Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, HIM 829, Boston, MA 02115, USA. Tel.: +1 617 525 5001; fax: +1 617 525 5017.
E-mail address: cnserhan@zeus.bwh.harvard.edu (C.N. Serhan).

http://dx.doi.org/10.1016/j.bbalip.2014.08.006
1388-1981/

become apparent that endogenous stop signals are critical at early checkpoints within the temporal events of inflammation [20–22]. In this context, lipid mediators are of considerable interest. The arachidonic acid-derived prostaglandins and leukotrienes are potent pro-inflammatory mediators [23], whereas the lipoxins, biosynthesized from arachidonic acid, are potent anti-inflammatory and proresolving molecules (for reviews see [24, 25, 26]). During the course of inflammation, arachidonate-derived eicosanoids switch from prostaglandins and leukotrienes within inflammatory exudates to lipoxins that in turn stop the recruitment of neutrophils to the site. This switch in eicosanoid profiles and biosynthesis is driven, in part, by cyclooxygenase-derived prostaglandin E_2 and prostaglandin D_2, which instruct the transcriptional regulation of enzymes involved in lipoxin biosynthesis [22]. Hence, the appearance of lipoxins within inflammatory exudates is concomitant with self-limited, or also described in the literature as spontaneous, resolution of inflammation [22], and these chemical mediators are non-phlogistic stimulators of monocyte recruitment and macrophage phagocytosis of apoptotic PMN [27,28].

Further studies on the endogenous mechanisms of anti-inflammation using a murine model of self-limited resolution demonstrated, for the first time, that resolution is an active biochemical process that involves the generation of specific new families of mediators [for recent reviews, see refs. [29,30]. During self-limited resolution, cell–cell interactions and transcellular biosynthesis lead to the production of these new families of potent bioactive lipid mediators from ω−3 essential fatty acid precursors and were termed resolvins (resolution phase interaction products derived from DHA, EPA and n−3 DPA) and protectins (docosatrienes derived from DHA) [9,10,13,31,32]. These novel di- and trihydroxy-containing products from n−3 essential fatty acids are biosynthesized by previously unrecognized enzymatic pathways that include resolvins, protectins and maresins. Specific members of each family display potent anti-inflammatory, immunoregulatory and pro-resolving actions *in vitro* and *in vivo* in murine models of inflammatory diseases [9,10,13] (see Fig. 1).

The omega-3 polyunsaturated fatty acids were assigned, in 1929, essential roles because their exclusion from the diet gave rise to a new form of deficiency disease [33]. Many more recent reports document the importance of fish oil (omega-3) fatty acids EPA and DHA in human diseases associated with uncontrolled tissue inflammation. In particular, omega-3 DHA and EPA are protective in inflammatory bowel disease and colitis [34], cardiovascular disease [35–38], and Alzheimer's disease [39]. However, the cellular and molecular mechanisms responsible for these now well-documented beneficial actions of omega-3 fatty acids remain an important challenge and public health concern, given the widespread use of n−3 supplements and the many diseases characterized by excessive inflammation. DHA is enriched in neural tissues, where it appears to play functional, not just structural roles [4,40]. Along these lines, results from earlier studies indicated that DHA was enzymatically converted to products coined docosanoids, whose structures were unknown at the time, that might be linked to retinal protection [41] and potentially neuronal function [42]. The complete structures of those molecules and functions were not established.

Human whole blood, isolated leukocytes, and glial cells each enzymatically convert DHA to 17*S*-hydroxy-containing docosatrienes (dihydroxy products) and 17*S*-series resolvins [9,13]. The new 10,17*S*-docosatriene series displayed potent anti-inflammatory actions that included reducing or limiting further PMN numbers in exudates *in vivo* (the cessation process in resolution of inflammation [15]), and down regulating production of proinflammatory lipid mediators and cytokines by glial cells *in vitro* [13]. During the resolution phase of peritonitis, unesterified DHA levels increase and 10,17*S*-docosatriene is generated within the resolving exudates, where it appears to promote catabasis (the return from disease, cf. refs. [8,43]), namely the return to homeostasis, by shortening the resolution interval [9,43]. This novel DHA-derived 10,17*S*-docosatriene was next also found to be produced *in vivo* during strokes in murine tissues, studies in collaboration with Nicolas Bazan and colleagues, and limited the entry of leukocytes into the area of neural damage in the brain, thus reducing the magnitude of tissue injury [44]. Also, in collaboration with Bazan and colleagues, we found that this 10,17*S*-docosatriene is neuroprotective in retinal pigmented cells and introduced the term neuroprotectin D1 for this potent DHA product [14], a member of the protectin family of mediators [9,31] that accumulates in the ipsilateral hemisphere of the brain following focal ischemia [45].

NPD1 is formed from DHA in cornea in a lipoxygenase-dependent fashion to protect from thermal injury as well as promote wound healing [46]. Importantly, neuroprotectin D1, resolvin D1, and resolvin D5 are produced by trout brain cells from endogenous DHA, suggesting that the structures of these DHA-derived local mediators are highly conserved from fish to humans [47]. Together, these results underscored the need to establish the complete stereochemistry of endogenous biologically active 10,17*S*-docosatriene, namely the configuration of the conjugated double-bond system and chirality of the carbon-10 position alcohol in the potent bioactive molecule. In recognition of its wide scope of formation and actions, protectin D1 (PD1) is used to denote the structure of this chemical mediator and the prefix *neuro* before *protectin D1* notes its neural system origins (i.e. retina, brain) and addresses functional role [46–50].

The chemical signals and mediators produced by macrophages are of wide interest, because macrophages play key roles in innate host responses and local inflammation [51,52], as well as in neovascularization, resolution of inflammation, and wound healing [51,53,54]. Along these

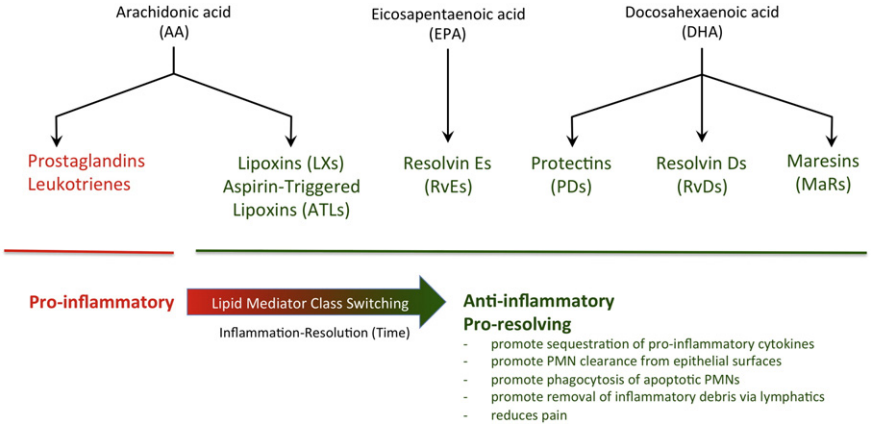

Fig. 1. Specialized pro-resolving lipid mediator families biosynthesized from their parent polyunsaturated fatty acids. Resolving exudates utilize essential fatty acids such as DHA to form several structurally distinct groups of specialized pro-resolving mediators that promote clearance and resolution.