Progress in Lipid Research 50 (2011) 75–88

Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

# Resolvins: Natural agonists for resolution of pulmonary inflammation

Mohib Uddin, Bruce D. Levy *

*Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Institutes of Medicine, Room 855, 77 Avenue Louis Pasteur, Boston, MA 02115, USA*

ARTICLE INFO

*Article history:*
Received 14 September 2010

*Keywords:*
Catabasis
Lipid mediators
Lung
Neutrophils
Omega-3
Polyunsaturated fatty acids

ABSTRACT

Inappropriate or excessive pulmonary inflammation can contribute to chronic lung diseases. In health, the resolution of inflammation is an active process that terminates inflammatory responses. The recent identification of endogenous lipid-derived mediators of resolution has provided a window to explore the pathobiology of inflammatory disease and structural templates for the design of novel pro-resolving therapeutics. Resolvins (resolution-phase interaction products) are a family of pro-resolving mediators that are enzymatically generated from essential omega-3 polyunsaturated fatty acids. Two molecular series of resolvins have been characterised, namely E- and D-series resolvins which possess distinct structural, biochemical and pharmacological properties. Acting as agonists at specific receptors (CMKLR1, BLT1, ALX/FPR2 and GPR32), resolvins can signal for potent counter-regulatory effects on leukocyte functions, including preventing uncontrolled neutrophil swarming, decreasing the generation of cytokines, chemokines and reactive oxygen species and promoting clearance of apoptotic neutrophils from inflamed tissues. Hence, resolvins provide mechanisms for cytoprotection of host tissues to the potentially detrimental effects of unresolved inflammation. This review highlights recent experimental findings in resolvin research, and the impact of these stereospecific molecules on the resolution of pulmonary inflammation and tissue catabasis.



**Contents**



*Abbreviations:* AA, arachidonic acid; ALI, acid lung injury; ALX/FPR2, lipoxin $A_4$ receptor/formyl peptide receptor 2; ARDS, acute respiratory distress syndrome; ATL, aspirin-triggered lipoxin; AT-RvD1, aspirin-triggered-resolvin D1 (7*S*, 8*R*, 17*R*-trihydroxy-docosa-4*Z*, 9E, 11E, 13*Z*, 15E, 19*Z*-hexaenoic acid); AT-RvD2, aspirin-triggered-resolvin D2 (7*S*, 16*R*, 17*R*-trihydroxy-docosa-4*Z*, 8E, 10*Z*, 12E, 14E, 19*Z*-hexaenoic acid); AT-RvD3, aspirin-triggered-resolvin D3 (4*S*, 11*R*, 17*R*-trihydroxy-docosa-5, 7E, 9E, 13*Z*, 15E, 19*Z*-hexaenoic acid); AT-RvD4, aspirin-triggered-resolvin D4 (4*S*, 5*R*, 17*R*-trihydroxy-docosa-6E, 8E, 10*Z*, 13*Z*, 15E, 19*Z*-hexaenoic acid); BALF, bronchoalveolar lavage fluid; BLT1, $LTB_4$ receptor; BPI, bactericidal/permeability-increasing protein; CDK, cyclin-dependent kinases; CHO, chinese hamster ovary; CMKLR1, chemokine receptor-like 1; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; DHA, docosahexaenoic acid; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; fMLP, *N*-formyl-methionyl-leucyl-phenylalanine; GCs, Glucocorticoids; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GPCR, G protein-coupled receptor; HUVEC, human umbilical vein endothelial cells; LC-UV-MS/MS, liquid chromatography-ultraviolet spectrometry-tandem mass spectrometry; LOX, lipoxygenase; $LTB_4$, leukotriene $B_4$ (5*S*, 12*R*-dihydroxy-eicosa-6*Z*, 8E, 10E, 14*Z*-tetraenoic acid) $LXA_4$, lipoxin $A_4$ (5*S*, 6*R*, 15*S*-trihydroxy-eicosa-7E, 9E, 11*Z*, 13E-tetraenoic acid); M1, classically activated macrophages; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; $\omega-3$, omega-3; $\omega-6$, omega-6; PD1, protectin D1 (10*R*, 17*S*-dihydroxy-docosa-4*Z*, 7*Z*, 11E, 13E, 15*Z*, 19*Z*-hexaenoic acid); PDGF, platelet-derived growth factor; PI3-K, phosphatidylinositol 3′-kinase; PUFA, polyunsaturated fatty acid; rM, resolution-phase macrophages; RvD1, resolvin D1 (7*S*, 8*R*, 17*S*-trihydroxy-4*Z*, 9E, 11E, 13*Z*, 15E, 19*Z*-docosahexaenoic acid); RvD2, resolvin D2 (7*S*,16*R*,17*S*-trihydroxy-docosa-4*Z*,8E,10*Z*,12E,14E,19*Z*-hexaenoic acid); RvD3, resolvin D3 (4*S*, 11, 17*S*-trihydroxy-5E, 7E, 9E, 13*Z*, 15E, 19*Z*-docosahexaenoic acid); RvD4, resolvin D4 (4*S*, 5, 17*S*-trihydroxy-6E, 8E, 10*Z*, 13*Z*, 15E, 19*Z*-docosahexaenoic acid); RvE1, resolvin E1 (5*S*,12*R*,18*R*-trihydroxy-6*Z*,8E,10E,14*Z*,16E-eicosapentaenoic acid); RvE2, resolvin E2 (5*S*,18*R*-dihydroxy-8*Z*,11*Z*,14*Z*,16*E*-eicosapentaenoic acid; TGF-β, transforming growth factor -beta; TNF-α, tumor necrosis factor-alpha; VSMCs, vascular smooth muscle cells.

* Corresponding author.
*E-mail address:* blevy@partners.org (B.D. Levy).

0163-7827/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.plipres.2010.09.002

## 1. Introduction

Acute inflammation is an essential host response to danger signals, including potential infection, noxious stimulus or tissue injury [1]. However, non-resolving inflammation is linked to many chronic inflammatory diseases, including asthma, rheumatoid arthritis, inflammatory bowel disease, and psoriasis (reviewed in [2]). In association with clinical symptoms in these chronic inflammatory diseases are elevated levels of pro-inflammatory mediators [3]. The overall magnitude and duration of inflammation depends on competing physiological processes, namely pro-phlogistic mechanisms that amplify inflammation and endogenous braking programs that control the resolution of inflammation (reviewed in [4]). In health, progression through the resolution phase of inflammation is primarily driven by the orderly phagocytic clearance of apoptotic granulocytes and debris by macrophages [5,6]. It is now established that resolution of inflammation is an active coordinated process that is spatiotemporally controlled by endogenously generated autacoids at sites of inflammation [4,7,8]. The enzymatic transformation of polyunsaturated fatty acids (PUFAs) during inflammation leads to the generation of specific endogenous mediators that act as potent agonists for resolution by exhibiting anti-inflammatory, pro-resolving, anti-fibrotic, anti-angiogenic and anti-infective actions (reviewed in [4]). The discovery that PUFAs are indispensable for health and dietary deficiencies can lead to clinical symptoms of diseases was first established in the late 1920s [9]. Such pioneering work suggested a specific relationship between the immunoregulatory role of PUFAs and the pathogenesis of major human diseases. As such, the identification of PUFA-derived mediators generated locally during the resolution of inflammation has led to a rapidly advancing understanding of the cellular and molecular mechanisms that are fundamental to resolution. Here, we review recent insights into the resolution of airway inflammation, and in particular, highlight anti-inflammatory and pro-resolving roles for resolvins in inflammation and pulmonary diseases.

## 2. Resolution of acute inflammation

Resolution is now appreciated to be an active process that terminates acute inflammation. At present, we know that efficient restoration of inflamed tissues to their basal state requires that inflammatory cells are effectively cleared and further neutrophil recruitment is abrogated. During this process, tissue neutrophils undergo apoptosis and are recognised and subsequently engulfed by phagocytic macrophages in a non-inflammatory manner [5,6]. Clearance of apoptotic neutrophils leads to the production of additional mediators that suppress the progression of inflammation and promote repair of damaged tissues [10–12]. Dysregulation of this process leads to unresolved inflammation, which underlies the pathology of several chronic inflammatory disease processes [4,13,14]. Hence, resolution of inflammation requires a cellular flexibility in the affected tissues in order to re-establish a homeostatic state after a limited period of inflammation. This sequence of events is also referred to as 'catabasis' – the reversion from a pathological state to one that is non-inflammatory in restoring tissue homeostasis [1,7].

### 2.1. Emerging cellular and molecular concepts of resolution

Inflammation resolution is a dynamic program that is partially dependent on the equilibrium of leukocyte ingress and egress at inflamed sites (reviewed in [15]). Several cellular and molecular mechanisms can limit the acute inflammatory response, including lipid mediator class switching [16]. During acute inflammation, early phase prostaglandin (PG) $E_2$ and $PGD_2$ can decrease neutrophil leukotriene (LT) generation and increase expression of 15-lipoxygenase (15-LOX) to switch LOX-derived AA metabolism to the biosynthesis of lipoxins [16], which are stop signals for neutrophil transmigration and activation, as well as go signals for macrophage clearance of apoptotic neutrophils. Combined, these actions actively promote resolution by clearing inflammatory cells from the previously inflamed tissue.

Distinct macrophage subsets, termed resolution-phase macrophages (rM) and fibroblastic macrophages, can play an active role in promoting the resolution of acute inflammation via phagocytic clearance of leukocytes [17,18]. Neutrophil clearance from mucosal tissues can also proceed by transmigration from the apical epithelial surface into the lumen via an epithelial CD55-mediated process [19] (reviewed in [20]). Mucosal epithelium can also express anti-microbial peptides and lipoxins can enhance host defense at mucosal surfaces by inducing epithelial bactericidal/permeability-increasing