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Towards targeting resolution pathways of airway inflammation in asthma

Cindy Barnig [a,b,*], Nelly Frossard [c], Bruce D. Levy [d]

[a] Department of Chest Disease, Strasbourg University Hospital, 1, place de l'Hôpital, 67091 Strasbourg, France
[b] EA 3072, University of Strasbourg, France
[c] UMR 7200 CNRS/Université de Strasbourg, Laboratoire d'Innovation Thérapeutique and LabEx MEDALIS, Faculté de Pharmacie, Strasbourg, France
[d] Pulmonary and Critical Care Medicine, Department of Internal Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

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ABSTRACT

Asthma is a chronic disorder characterized by persistent inflammation of the airways with mucosal infiltration of eosinophils, T lymphocytes, and mast cells, and release of proinflammatory cytokines and lipid mediators. The natural resolution of airway inflammation is now recognized as an active host response, with highly coordinated cellular events under the control of endogenous pro-resolving mediators that enable the restoration of tissue homeostasis. Lead members of proresolving mediators are enzymatically derived from essential polyunsaturated fatty acids, including arachidonic acid-derived lipoxins, eicosapentaenoic acid-derived E-series resolvins, and docosahexaenoic acid-derived D-series resolvins, protectins, and maresins. Functionally, these specialized pro-resolving mediators can limit further leukocyte recruitment, induce granulocyte apoptosis, and enhance efferocytosis by macrophages. They can also switch macrophages from classical to alternatively activated cells, promote the return of non-apoptotic cells to lymphatics and blood vessels, and help initiate tissue repair and healing. In this review, we highlight cellular and molecular mechanisms for successful resolution of inflammation, and describe the main specialized pro-resolving mediators that drive these processes. Furthermore, we report recent data suggesting that the pathobiology of severe asthma may result in part from impaired resolution of airway inflammation, including defects in the biosynthesis of these specialized pro-resolving mediators. Finally, we discuss resolution-based therapeutic perspectives.

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Contents

Abbreviations: AA, Arachidonic acid; ALX/FPR2, Lipoxin A_4/formyl peptide receptor 2; AnxA1, Annexin A1; ASA, Acetylsalicylic acid; AT, Aspirin-triggered; BHR, Bronchial hyperreactivity; COX, Cyclooxygenase; DHA, Docosahexaenoic acid; Eos, Eosinophils; EPA, Eicosapentaenoic acid; HEPE, Hydroxyeicosapentaenoic acid; HETE, Hydroperoxyeicosatetraenoic acid; IL, Interleukin; IFN, Interferon; ILC2, Type 2 innate lymphoid cells; LOX, Lipoxygenase; LT, Leukotrienes; LTA_4, Leukotriene A_4; LXA_4, Lipoxin A_4; LXB_4, Lipoxin B_4; Ly, Lymphocyte; MaR1, Maresin 1; NK cells, Natural killer cells; PGD_2, Prostaglandin D_2; PD1, Protectin D_1; PGE_2, Prostaglandin E_2; PLA2, Secretory phospholipase A_2; PMN, Polymorphonuclear cell; PUFA, Polyunsaturated fatty acids; RvD1, Resolvin D_1; RvE1, Resolvin E_1; SPMs, Specialized pro-resolving lipid mediators; Th2, T helper type-2; Th17, T helper type-17.

* Corresponding author.
E-mail address: cindy.barnig@chru-strasbourg.fr (C. Barnig).

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1. Introduction

Inflammation is a response initiated by the host that has developed throughout evolution in response to tissue insult or injury (Medzhitov, 2008). It is initiated within minutes of recognition of a danger signal with the ultimate purpose to restore tissue integrity and homeostasis.

The acute inflammatory response is a highly coordinated sequence of events involving a large number of molecular, cellular and physiological interplays (Nathan, 2002). Early events are controlled by several families of chemokines, cytokines and pro-inflammatory mediators (including lipid mediators such as prostaglandins and leukotrienes) produced by resident cells in the injured tissue. They act in a coordinated fashion to drive the initiation of the inflammatory reaction with edema from leakage-permeability changes followed by a rapid influx of granulocytes (e.g. neutrophils) from blood to the inflammatory site, and by a self-amplifying network of pro-inflammatory pathways, which perpetuate leukocyte recruitment and activation (Larsen & Henson, 1983). In otherwise healthy tissues, the inflammatory response is programmed to stay within limits, both spatial and temporal, resolving and returning the injured tissues to the pre-inflamed state. If the process of resolution fails, inflammation is perpetuated, resulting into chronicity with tissue injury, remodelling and subsequent fibrosis and loss of tissue function (Serhan, 2017). Persistent and non-resolving inflammation has emerged as a critical process in the pathogenesis of numerous chronic diseases, including asthma where chronic airway inflammation is central to the pathogenesis of the disease (Holgate, 2012).

Until the beginning of this century, acute inflammation was thought to resolve passively, involving a decreased expression of cytokines, the dilution of chemokine gradients over time, and the natural catabolism of pro-inflammatory mediators; together explaining why leukocytes stop migrating from blood into tissues. However, investigations in the past decade have identified critical molecular and cellular processes that are specifically engaged in the inflammatory response to actively promote resolution, leading to a new paradigm in our understanding of the host mechanisms for cessation of the inflammatory response (Serhan, 2017). Elucidating these mechanisms of resolution of the inflammatory process is therefore of great interest, since it can provide new windows to understand disease pathogenesis and design rationale therapeutic approaches to augment host resolution mechanisms (Fig. 1).

In this review, we discuss the recent discoveries in resolution pathways involved in asthmatic inflammation with a focus on the role of specialized pro-resolving mediators (SPMs) derived from polyunsaturated fatty acids (PUFAs) and their potential therapeutic applications.

2. Airway inflammation in asthma

Asthma is a very common inflammatory disorder of the conducting airways affecting 300 million people worldwide due to bronchial hyperreactivity (BHR), subsequent airway smooth muscle contraction, airway remodelling with edema, subepithelial fibrosis and mucus hypersecretion leading to airflow limitation and breathing difficulties (Busse & Lemanske, 2001; Lambrecht & Hammad, 2015).

Besides episodes of acute inflammation in response to various stimuli, such as allergen inhalation, exposure to micro-environmental pollutants or viral infection, an underlying chronic airway inflammation is often found, even in patients with infrequent or recent-onset asthma symptoms (Bousquet, Jeffery, Busse, Johnson, & Vignola, 2000). The airway inflammation in chronic asthma is mediated in many cases through ongoing type 2 responses with infiltration of activated mast cells, dendritic cells (DCs) and T helper type-2 (Th2) cells into the bronchial mucosa, that release pro-inflammatory mediators (e.g. interleukin (IL)-5, IL-13, prostaglandins, leukotrienes, …) and cause eosinophil (Eos) infiltration (Lloyd & Hessel, 2010), a hallmark of asthmatic inflammation (Fig. 2).

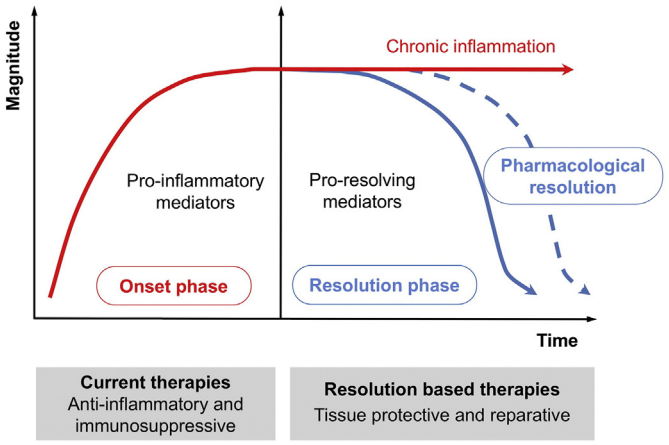

Fig. 1. Dynamics of the inflammatory response. The acute inflammatory response is a highly coordinated sequence of events characterized i) by an onset phase coordinated by several families of chemokines, cytokines and pro-inflammatory mediators that is followed ii) in health by an active resolution phase brought about by the engagement of specific cellular mechanisms under the control of several pro-resolving mediators to promote resolution of the tissue inflammation as well as healing and repair. A failure in proresolving pathways can extend in time the actions of proinflammatory mechanisms resulting in prolonged or chronic inflammation. Current therapeutic agents are predominantly anti-inflammatory in their action with mixed success and most of them are also immunosuppressive. As discussed in this review, elucidating the mechanisms of resolution of the inflammatory process is of relevance, since it can give rise to new therapeutic approaches by exploiting the intrinsic tissue repair systems.

In addition, a role of type 2 innate lymphoid cells (ILC2) was recently reported (Barnig et al., 2013; Lambrecht & Hammad, 2015). Indeed, ILC2 play crucial roles in the initiation and propagation of type 2 inflammatory responses in allergic asthma models. They are directly activated by epithelial cell-derived cytokines (e.g. IL-25, IL-33, thymic stromal lymphopoietin) and mast-cell derived prostaglandin D_2 (PGD_2) and can independent of adaptive immunity induce bronchial hyperreactivity through the production of IL-13 and airway eosinophilia through the production of IL-5 (Barlow et al., 2012; Chang et al., 2011; Kim et al., 2012). During the allergic asthmatic inflammatory response in murine asthma models, ILC2 can also be activated by vasoactive intestinal peptide released by nodose ganglion neurons through the activation of nociceptive transient receptor potential (TRP) channels (Talbot et al., 2015), as complex interplays between nociceptors and immune cells in the asthmatic inflammatory response (Baker et al., 2016; Grace, Baxter, Dubuis, Birrell, & Belvisi, 2014).

Asthma exacerbations are notable for a neutrophil (PMN)-enriched inflammatory response, which in some cases can also be the principal cellular infiltrate in chronic asthma (Duvall et al., 2017; Li et al., 2015; Peters et al., 2014; Simpson et al., 2016). In this neutrophil-predominant disease, Th17 cells are mainly involved, *via* IL-17 production promoting neutrophil recruitment (Cosmi, Liotta, Maggi, Romagnani, & Annunziato, 2011).

Activated structural cells (e.g. airway epithelial and smooth muscle cells) together with inflammatory cells perpetuate the chronic inflammation by the secretion of a vast array of pro-inflammatory mediators, including eicosanoids, cytokines, chemokines, growth factors which contribute to the symptoms and BHR observed in asthma patients (Djukanovic et al., 1990; O'Byrne & Postma, 1999).

Along with airway inflammation, disruption of the respiratory epithelial tight junctions responsible for impaired epithelial barrier function is observed (Holgate, 2007; Xiao et al., 2011). Other structural changes are characteristic of the airways of asthma patients, termed 'airway remodelling'. These changes include sub-epithelial fibrosis, thickening of airway smooth muscle, increased number of airway wall blood vessels, increased number of goblet cells in the airway epithelium, and increased size of sub-mucosal glands. Some of these changes have been related to the severity of the disease and may result in irreversible

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