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Bronchoprotective mechanisms for specialized pro-resolving mediators in the resolution of lung inflammation

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ABSTRACT

Bronchi are exposed daily to irritants, microbes and allergens as well as extremes of temperature and acid. The airway mucosal epithelium plays a pivotal role as a sentinel, releasing alarmins when danger is encountered. To maintain homeostasis, an elaborate counter-regulatory network of signals and cellular effector mechanisms are needed. Specialized pro-resolving mediators (SPMs) are chemical mediators that enact resolution programs in response to injury, infection or allergy. SPMs are enzymatically derived from essential polyunsaturated fatty acids with potent cell-type specific immunoresolvent properties. SPMs signal by engaging cell-based receptors to turn off acute inflammatory responses and restore tissue homeostasis. Several common lung diseases involving the airways, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), are characterized by unresolved bronchial inflammation. In preclinical murine models of lung disease, SPMs carry potent bronchoprotective actions. Here, we review cellular and molecular effects for SPM-initiated catabasis in the lung and their human translation.

1. Introduction

Inflammation is the body's response to injury or infection and manifests clinically as fever and in the lung as cough, sputum production, dyspnea and edema. Biologically, the initiation of acute inflammation results from a highly coordinated network of cellular and molecular events. Pro-inflammatory cytokines and chemokines and eicosanoids including leukotrienes and prostaglandins create a beacon of chemoattractants that results in leukocyte trafficking to sites of lung infection or injury. Endothelial and epithelial barriers become compromised by the inflammatory response creating tissue edema and purulent exudate (expectorated as sputum). Recruited granulocytes and lymphocytes then augment innate tissue-resident leukocytes and macrophages to contain and rid the body of the insult or invading pathogen. Initiating acute inflammation is vital for host protection and survival with many examples of immunosuppression increasing susceptibility to excess morbidity and mortality from infection. Equally important to health is the timely resolution of acute lung inflammation.

To counter the complexity and amplitude of pro-phlogistic mechanisms there exists endogenous resolution programs that are spatio-temporally regulated in the lung. Resolution is an active process designed to restore host tissues to a baseline non-inflamed state, a process termed catabasis. Inflammation resolution is orchestrated by several classes of mediators, including peptides, gases and lipids. Of particular relevance to this review is a superfamily of lipid mediators that are enzymatically-derived from dietary essential polyunsaturated fatty acids (PUFA). These specialized pro-resolving mediators (SPMs) include the arachidonic acid-derived lipoxins and the omega-3 fatty acid-derived resolvins, protectins, and maresins (reviewed in Serhan, 2014). Each of the SPMs are stereoselective with structure activity relationships consistent with agonist properties at cognate receptors. During acute inflammation, lipid mediator class switching occurs as PUFA metabolism switches from pro-inflammatory mediators (*e.g.*, prostaglandins, leukotrienes) to pro-resolving mediators (*i.e.*,

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SPMs) (Levy et al., 2001). SPMs have cell-type specific and potent immunoresolvent actions to quench pro-inflammatory cytokine production by airway epithelial cells, increase epithelial production of anti-microbial peptides, halt leukocyte trafficking, and promote clearance of the inflammatory leukocytes through natural killer cell-mediated leukocyte apoptosis and macrophage phagocytosis of apoptotic leukocytes (Levy and Serhan, 2014). Thus, in health, SPMs promote the timely resolution of inflammation.

Chronic inflammation results from a failure of the body's resolution pathways to adequately turn off acute inflammatory responses and switch on mechanisms to restore homeostasis. Chronic unresolved inflammation underlies the pathophysiology of several common human lung diseases including asthma, chronic obstructive pulmonary syndrome (COPD), and cystic fibrosis (CF). Active research in humans and pre-clinical animal models of these diseases has uncovered a deficiency of SPMs and their tissue protective pro-resolving actions. Here, we review SPMs molecular, cellular, and biochemical bronchoprotective actions in response to acute inflammation of injury, infection and allergy with human translation in health and, when defective, in airway diseases.

2. SPM bronchial epithelial actions

The airway mucosa is a first line of host defense against inhaled irritants, allergens, and pathogens. The epithelium provides a physical barrier against inhaled pathogens and toxins and initiates host immune responses through production of alarmins, inflammatory chemokines and cytokines that signal to cellular members of the innate and adaptive immune system. Epithelial cells are targets for regulation by SPMs that act to attenuate pro-inflammatory responses and promote epithelial restitution. In this section, we review SPM receptor expression on bronchial mucosal epithelial cells and SPM effects on the epithelium to resolve injury and promote host defense.

2.1. SPM receptor expression in the human airway

The pro-resolving and anti-inflammatory bioactions of SPMs stem from their signaling as agonists at specific receptors. To date, the molecular identify of five SPM receptors have been elucidated (Fig. 1).

2.1.1. ALX/FPR2

The lipoxin A_4/formyl peptide receptor 2 (ALX/FPR2) is a high affinity receptor for lipoxin A_4 (LXA_4) and a number of additional SPMs including 15-epi-LXA_4, resolvin D1 (RvD1) and aspirin-triggered-resolvin D1 (AT-RvD1) (Chiang et al., 2006; Fiore et al., 1994; Krishnamoorthy et al., 2010, 2012; Perretti et al., 2002). LXA_4 binding to ALX/FPR2 is stereoselective, specific, and reversible with a Kd of ~0.5 nM (Fiore et al., 1992, 1994). ALX/FPR2 receptors can also engage and transmit signals from non-lipid ligands including annexin A1 (Chiang et al., 2006) and cathelicidin/LL-37 (Wan et al., 2011). Ligand recognition sites for lipids and peptides differ on ALX/FPR2 receptors and the ligands can trigger distinct downstream events that dramatically change the signaling properties of the receptor (Cooray et al., 2013). For example, 15-epi-LXA_4 is an allosteric inhibitor of serum amyloid A at ALX/FPR2 receptors and decreases cytokine production from airway epithelial cells (Bozinovski et al., 2012).

ALX/FPR2 is expressed on human and mouse airway epithelial cells as well as other cells directly related to inflammation at mucosal epithelial borders, including neutrophils, eosinophils, mast cells, monocytes, macrophages, lymphocytes, dendritic cells, innate lymphoid cells (ILCs), and natural killer (NK) cells (Barnig et al., 2013; Bonnans et al., 2006; Chiang et al., 2006; Fiore et al., 1994; Hua et al., 2014; Maddox et al., 1997; Miyazaki et al., 2014). ALX/FPR2 cellular expression is regulated locally by cytokines, transcription factors, and epigenetic mechanisms. LXA_4 itself binds to the ALX/FPR2 promoter and increases ALX/FPR2 expression in a positive feedback loop (Simiele et al., 2012). ALX/FPR2 expression is altered in several diseases of chronic inflammation. In severe asthma, ALX/FRP2 expression on granulocytes is decreased (Planaguma et al., 2008). In COPD lungs, epithelial ALX/FPR2 expression is increased in proximity to extrahepatic, submucosal serum amyloid A. Plasma pro-inflammatory ALX/FPR2 ligand serum amyloid A is produced in approximately 2-log order higher amounts than pro-resolving LXA_4, creating an imbalance towards a more pro-inflammatory state in COPD despite increased ALX/FPR2 expression (Bozinovski et al., 2012).

2.1.2. ERV

The E-series resolvin (ERV) receptor (also known as chemokine receptor-like 1 (CMKLR1) and chemerin receptor 23 (ChemR23)) is a high affinity receptor for resolvin E1 (RvE1) and likely resolvin E2 (RvE2) (Oh et al., 2012). Like ALX/FPR2, ERV can also engage non-lipid ligands, in particular chemerin, a chemoattractant peptide (Wittamer et al., 2003). ERV is expressed in the lung on airway epithelial cells and leukocytes, in particular those of the innate immune system, including neutrophils, monocytes, macrophages, dendritic cells, ILCs, and NK cells (Barnig et al., 2013; Campbell et al., 2007; Cash et al., 2008, 2013; Du and Leung, 2009; Herova et al., 2015; Parolini et al., 2007; Samson et al., 1998). ERV expression, in particular on NK cells, is highly regulated by cytokine expression in early phases of inflammation (Parolini et al., 2007). ERV signaling pathways may play an important role in protection against viral pathogens, as ERV knockout mice are particularly susceptible to viral respiratory pathogens with compromised viral clearance, increased lung leukocyte infiltration, compromised lung function, and increased mortality (Bondue et al., 2011).

2.1.3. BLT1

The leukotriene B_4 receptor 1 (BLT1) is expressed on inflammatory leukocytes including neutrophils, eosinophils, monocytes, macrophages, mast cells, dendritic cells, and lymphocytes (Yokomizo et al., 1997). Both RvE1 and RvE2 engage the BLT1 receptor as antagonists, competing with leukotriene B4 (LTB_4) to counterregulate neutrophil chemotaxis, calcium mobilization, and NF-κB activation (Arita et al., 2007). RvE1 blocks LTB_4 binding at BLT1 to promote apoptosis of neutrophils and macrophage efferocytosis (El Kebir et al., 2012).

2.1.4. DRV1 and DRV2

The RvD1 receptor (DRV1; formerly GPR32) engages a number of activating lipid ligands including RvD1, AT-RvD1, RvD3, AT-RvD3, and RvD5 (Chiang et al., 2012; Dalli et al., 2013; Krishnamoorthy et al., 2010, 2012; Sun et al., 2007). DRV1 is expressed on human neutrophils, lymphocytes, macrophages, monocytes, and vascular tissues (Krishnamoorthy et al., 2010). Of note, RvD1 binds and engages DRV1 during periods of homeostasis whereas RvD1 interacts and signals through ALX/FPR2 during periods of resolving inflammation highlighting that SPMs can engage different receptors on different cell types in different physiologic states to exert spatiotemporally distinct effects.

The RvD2 receptor (DRV2; formerly GPR18) engages RvD2 to promote tissue resolution in a self-limited murine model of acute inflammation by promoting macrophage efferocytosis, enhancing phagocytosis of bacteria, and preventing neutrophil transmigration (Chiang et al., 2015). DRV2 is expressed on mouse and human neutrophils, monocytes, and macrophages (Chiang et al., 2015).

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