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Targeting Interleukin-17 signalling in cigarette smoke-induced lung disease: Mechanistic concepts and therapeutic opportunities

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ABSTRACT

It is widely accepted that compromised lung function in chronic obstructive pulmonary disease (COPD) is, at least in part, a consequence of persistent airway inflammation caused by particles and noxious gases present in cigarette smoke and indoor air pollution from burning biomass fuel. Currently, the World Health Organization estimates that 80 million people have moderate or severe COPD worldwide. While there is a global need for effective medical treatment, current therapeutic interventions have shown limited success in preventing disease pathology and progression. This is, in large part, due to the complexity and heterogeneity of COPD, and an incomplete understanding of the molecular mechanisms governing inflammatory processes in individual patients. This review discusses recent discoveries related to the pro-inflammatory cytokine interleukin (IL)-17A, and its potential role in the pathogenesis of COPD. We propose that an intervention strategy targeting IL-17 signalling offers an exciting opportunity to mitigate inflammatory processes, and prevent the progression of tissue pathologies associated with COPD.

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1. Introduction

1.1. Definition of COPD

Chronic obstructive pulmonary disease (COPD) is a collective term that describes a range of lung disorders characterized by a progressive and largely irreversible airflow limitation (Rabe et al., 2007). Currently the third leading cause of death (Agusti, Sobradillo, & Celli, 2011), COPD exacts a large toll on health care systems and has a substantial impact on global health (Rabe et al., 2007). The diagnosis of COPD is based on lung function, specifically, the ratio between the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC).

Abbreviations: COPD, Chronic obstructive pulmonary disease; ICS, Inhaled corticosteroids; IL, Interleukin; LABA, Long-acting β2 agonist; NTHi, Non-typeable *Haemophilus influenzae*; Th, T helper.

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Between individual patients, however, varying degrees of chronic bronchitis, obstructive bronchiolitis, and emphysema contribute to chronic airflow limitation (Agusti et al., 2011). It is widely accepted that chronic inflammation contributes to airflow limitation, although molecular mechanisms that contribute to different pathologies remain incompletely understood. Moreover, the majority of COPD patients are diagnosed with multiple comorbid conditions (Laforest et al., 2016), although it is unclear how these disorders affect and interact with pulmonary phenotypes. Alarmingly, current pharmacologic interventions for COPD have shown limited efficacy (Barnes, 2009), emphasizing the need for a greater understanding of the mechanisms that contribute to COPD pathogenesis and the development of novel therapeutic interventions.

1.2. Etiology of COPD

Cigarette smoking and exposure to second hand smoke are the main risk factors for the development of COPD (Eisner et al., 2010; Rabe et al., 2007), although emerging evidence suggests that indoor air pollution from burning wood and other biomass contributes to disease burden in the developing world (reviewed in (Eisner et al., 2010)). While cigarette smoking is a key risk factor, only a fraction of all smokers develop airway flow limitation and COPD (Rabe et al., 2007), emphasizing the importance of genetic predisposition and epigenetic mechanisms, in addition to environmental and socioeconomic factors. For instance, factors such as diet, weight and body mass distribution, heart failure, diabetes mellitus, and muscle or hormonal disorders all influence lung function (Ostrowski & Barud, 2006). Moreover, prenatal and early life events that impair lung maturation increase the risk of developing COPD (Rennard & Drummond, 2015). Due to the complexity of COPD, it is of critical importance to develop a better understanding of pathobiological processes that contribute to disease expression in an individual patient, as well as, reliable and reproducible biomarkers identifying distinct disease phenotypes and endotypes. This information is central to guide the management of COPD, and develop novel interventions, as the respiratory field moves into the era of increasingly personalized medicine.

1.3. Acute exacerbation of COPD

COPD is punctuated by episodes of acute disease exacerbation. Clinically, these acute exacerbations (AE) of COPD are defined as a sustained worsening of a patient's condition that necessitates a change in regular medication (Anthonisen et al., 1987; Mackay & Hurst, 2013; Rodriguez-Roisin, 2000). AECOPD is associated with high mortality and exacts a large toll on health care systems (Mackay & Hurst, 2013). Mechanistically, these episodes are characterized by increased inflammation and are thought to contribute to lung function decline and concomitant deterioration of respiratory health. AECOPD are caused predominantly by viral and bacterial infections (Di Stefano et al., 2009; Papi et al., 2006), while a minor contribution is made by air pollution and other environmental factors (Mackay & Hurst, 2013; Rohde et al., 2003; Seemungal et al., 2001).

2. Treatment of COPD

2.1. Current treatment options for COPD

Currently available treatment strategies for COPD are targeted toward symptom relief and disease maintenance. Such treatments include both short acting bronchodilators (SABA) in patients with mild symptoms and few exacerbations, and long-acting bronchodilators (LABA), as maintenance in patients with more advanced disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Rabe et al., 2007) recommend replacing mono therapy with LABA/long-acting muscarinic receptor agonists (LAMA) dual therapy when there is reason to believe that the combination of LABA/LAMA would be of benefit. In addition, mono or dual therapy together with inhaled corticosteroids (ICS) is suggested for patients with an increased risk of acute exacerbation. Lastly, a phenotype characterized by chronic bronchitis with more severe symptoms is treated with an added phosphodiesterase (PDE)-4 inhibitor (Vestbo, Hurd, & Rodriguez-Roisin, 2012; Woodruff, Agusti, Roche, Singh, & Martinez, 2015). Although current treatment strategies are based primarily on maintenance, evidence suggests that the risk of future exacerbations is reduced by 30% by treatment with bronchodilators (Salpeter, Buckley, Ormiston, & Salpeter, 2006). While progress has been made in the management of COPD, there is a clear need for improvement. This holds particularly true for patients with severe symptoms and frequent exacerbations.

2.2. Novel interventions for COPD

The inflammatory mediator profile of COPD has generated substantial interest, as it presents a window of opportunity to reduce harmful inflammation by targeting disease-associated cytokines, chemokines, or growth factors. To date, more than 50 inflammatory mediators and cytokines are implicated in the pathogenesis of COPD, including T helper 1 (Th1), such as interferon (IFN)-γ and tumor necrosis factor (TNF)α, as well as Th17-associated cytokines including interleukin (IL)-1β, IL-6, and IL-17A (Barnes, 2009, 2016; Ivanov & Linden, 2009). In addition, chemokines and growth factors, such as IL-8, C-X-C motif ligand (CXCL)1 and granulocyte colony stimulating factor (G-CSF), have all been implicated in disease pathogenesis (Barnes, 2009; Ivanov & Linden, 2009). While pre-clinical models support the functional involvement of these mediators in pathological processes associated with COPD (Botelho, Bauer, et al., 2011; Botelho, Nikota, et al., 2011; Churg, Sin, & Wright, 2011; Roos, Sethi, et al., 2015), the multitude of immune mediators associated with COPD likely reflects the heterogeneity of disease. Given this complexity, a detailed understanding of the immunological mechanisms and molecular signatures associated with different clinical phenotypes and endotypes is warranted.

3. IL-17 signaling and obstructive airways disease

3.1. Functions of IL-17 family cytokines

After the initial identification of IL-17A (Yao, Fanslow, et al., 1995) and Th17 cells (Yao, Painter, et al., 1995), a large number of studies have suggested a potential role for this cytokine in the pathogenesis of COPD (Chen et al., 2011; Duan, Tang, Zhong, & Huang, 2014; Duan et al., 2016; Harrison et al., 2008; Kang et al., 2012; Podolin et al., 2013; Wang et al., 2012; Zhou et al., 2015). The pro-inflammatory IL-17A belongs to a family of related cytokines, including IL-17B, IL-17C, IL-17D, IL-25 (IL-17E), and IL-17F. Originally identified as key in the coordination of the protection against microorganisms (Ouyang, Kolls, & Zheng, 2008; Weaver, Hatton, Mangan, & Harrington, 2007), subsequent studies have also documented the involvement of IL-17A in several chronic inflammatory disorders and autoimmune processes (Fig. 1) (Hong & Lee, 2010). Of note, IL-17A and IL-25 have been implicated specifically in respiratory diseases. Most studies have associated IL-25 with allergic diseases, while IL-17A may play a more prominent role in cigarette smoke-induced inflammation (Ivanov & Linden, 2009; Kolls & Linden, 2004; Linden, 2006). IL-17F, also expressed by Th17 cells, has been suggested to possess functions similar to IL-17A, although it is still unknown whether IL-17A and IL-17F play redundant roles or if unique functionalities exist. In contrast to the well-characterized activity of IL-17A, the function of the other IL-17 family members remains poorly understood (Ivanov & Linden, 2009).

Several distinct cellular sources of IL-17A are present in the lung and contribute to inflammatory processes. Initially believed to be expressed solely by helper T cells, it is now widely accepted that cytotoxic T cells, γδ T cells, and innate lymphoid cells (ILCs) have the capacity to express and secrete IL-17A (Harrington et al., 2005; Ivanov & Linden, 2007; Park