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Novel therapeutic strategies for lung disorders associated with airway remodelling and fibrosis

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ABSTRACT

Inflammatory cell infiltration, cytokine release, epithelial damage, airway/lung remodelling and fibrosis are central features of inflammatory lung disorders, which include asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome and idiopathic pulmonary fibrosis. Although the lung has some ability to repair itself from acute injury, in the presence of ongoing pathological stimuli and/or insults that lead to chronic disease, it no longer retains the capacity to heal, resulting in fibrosis, the final common pathway that causes an irreversible loss of lung function. Despite inflammation, genetic predisposition/factors, epithelial–mesenchymal transition and mechanotransduction being able to independently contribute to airway remodelling and fibrosis, current therapies for inflammatory lung diseases are limited by their ability to only target the inflammatory component of the disease without having any marked effects on remodelling (epithelial damage and fibrosis) that can cause lung dysfunction independently of inflammation. Furthermore, as subsets of patients suffering from these diseases are resistant to currently available therapies (such as corticosteroids), novel therapeutic approaches are required to combat all aspects of disease pathology. This review discusses emerging therapeutic approaches, such as trefoil factors, relaxin, histone deacetylase inhibitors and stem cells, amongst others that have been able to target airway inflammation and airway remodelling while improving related lung dysfunction. A better understanding of the mode of action of these therapies and their possible combined effects may lead to the identification of their clinical potential in the setting of lung disease, either as adjunct or alternative therapies to currently available treatments.

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1. Introduction

Inflammatory lung diseases are leading causes of morbidity and mortality worldwide and continue to be some of the most serious threats to health and life in the world. As of 2004, it was estimated that 235 million people had asthma, 64 million people had chronic

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obstructive pulmonary disease (COPD) while millions have other respiratory diseases (World Health Organization (WHO) Global Burden of Disease). Asthma is the most common chronic disorder of children, while COPD is the 4th highest cause of death, accounting for 5% of deaths globally.

1.1. Spectrum of inflammatory lung diseases

Inflammatory lung diseases are characterized by having a high inflammatory cell (e.g. neutrophil) count, and include asthma, COPD, acute respiratory distress syndrome (ARDS) and idiopathic pulmonary fibrosis (IPF). The inflammation associated with these diseases may be present in the airways (trachea, bronchi, bronchioles) and/or in the parenchyma of the lung (alveoli). As such, the impact on the patient's health and lung function may be due to obstruction of the airways typified by increased airflow resistance (obstructive lung disease) or restriction where the lungs are stiffened with a loss of lung compliance and associated loss of gas exchange units (restrictive lung disease). Furthermore inflammatory lung diseases consist of acute and chronic components. Acute disease may result from an acute insult such as an infection or a direct response to environmental stimuli, whereas chronic lung disease is characterized by ongoing and often progressive lung injury that results in tissue remodelling or fibrosis. Acute disease may often occur in the background of chronic disease (e.g. acute exacerbations in the setting of airway remodelling in severe asthma). Furthermore there is much overlap between established disease classifications such as asthma and COPD, which have proven to be very heterogeneous with different subtypes (i.e. atopic vs environmental asthma) and disease phenotypes (Jenkins et al., 2005). Therefore, the rational approach is, rather than focussing on a single disease, to identify and target common and fundamental pathological processes in the diseased lung (Beers & Morrisey, 2011), and of most interest are those occurring at the root of disease pathogenesis. The current review will concentrate on airway remodelling and fibrosis as these processes, in addition to inflammation, play a central role in the genesis and progression of lung diseases but are not adequately or specifically targeted by existing therapies.

1.2. Epithelial damage as a common theme in inflammatory lung diseases

The epithelium can be considered a key part of the innate defence of the lung. It is more than a physical barrier, however, as it is dynamic, and has the ability to repair with a very wide secretory repertoire in addition to a role in mediating crosstalk with mesenchymal cells and cells of the immune system. The significance of the epithelium in lung disease is an increasing focus of investigation (Jenkins et al., 2012; Lambrecht & Hammad, 2012; Nathan et al., 2011; Proud & Leigh, 2011). As such epithelial biology is a hot topic in respiratory science and immunology (Holgate, 2011). The epithelium is composed of several cell types: in the airways including ciliated cells, goblet cells and Clara cells, sitting upon basal cells. In the alveoli, type I and II pneumocytes are the major cell types of the distal lung. The small airways and the broncho-alveolar ducts are the interface between the two vastly different anatomical structures, are of great interest in terms of function and pathology and are composed of more cuboidal cells compared to those that reside within the larger airways (van der Wiel et al., 2013). Epithelial damage, either in the large or small airways or in the alveoli is a common occurrence in lung disease (Jenkins et al., 2012). Epithelial damage may be caused by inhaled toxins, proteolytic enzymes secreted from host immune cells (including eosinophils and neutrophils), or from an inherent vulnerability of the epithelium due to genetic susceptibility to damage, and delayed repair (Holgate, 2011).

1.3. Remodelling and fibrosis

Remodelling refers to the structural changes in the histology of the airway and lung that accompany disease (Sumi & Hamid, 2007). These involve all structural components of the lung — including the epithelium, connective tissue, smooth muscle, and vasculature. The epithelium acts as a barrier to the external environment, and when damaged undergoes alterations in cell phenotype, epithelial thickness and cellular composition (relative numbers of differentiated cells, denudation, hyperplasia and metaplasia). The epithelium is an important cellular promoter of remodelling and fibrosis. The airway smooth muscle may also be remodelled in lung disease. The main pathological changes seen in biopsies from asthma sufferers include airway smooth muscle (ASM) hyperplasia and ASM hypertrophy. Extracellular matrix (ECM) deposition between muscle cells can also contribute to an increased ASM bundle mass (Stewart, 2012). The vasculature of the lung, which largely follows the branching of the airways (Lazarus et al., 2011) to the alveoli is also remodelled, comprising thickening of the vascular wall by collagen and other ECM component deposition, as well as endothelial proliferation equating to angiogenesis and neovascularization (Wilson & Kotsimbos, 2003). The tracheal and large airway cartilage only plays a small role in airway remodelling, but a decreased volume of cartilage has been associated with asthma (Black, 2004).

The major effector cells involved in remodelling and fibrosis are the fibroblasts and myofibroblasts. These cells produce the basement membrane and underlying mesenchymal layers which can be thickened in inflammatory disease due to increased inflammatory cell infiltration, cytokine and growth factor release, fibroblast proliferation and differentiation (into myofibroblasts), as well as myofibroblast-mediated deposition of extracellular matrix (ECM) proteins. Fibrosis represents a failure of the wound healing process (in response to organ injury and inflammation) and results in ongoing ECM synthesis and accumulation, coinciding with a reduction in the degradation of polymeric ECM components such as collagens. Ongoing fibrosis leads to the scarring of the airways/lung, which contributes to a loss of lung function. Although a number of factors contribute to fibrogenesis (reviewed in Sivakumar et al., 2012), the major cytokines that promote and accelerate fibrosis are transforming growth factor (TGF)-β1, its down-stream mediators, connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF), and endothelin-1 (ET-1). TGF-β1 is secreted in the lung mainly by epithelial cells, but also by inflammatory cells (macrophages), and (myo)fibroblasts, and up-regulates collagen production and slows its breakdown (Camoretti-Mercado & Solway, 2005). Its main contribution to fibrosis is to promote fibroblast differentiation to α-smooth muscle actin (α-SMA)-positive myofibroblasts, cells evolved for wound closure with contractile capacity. TGF-β1 binds to its serine/threonine kinase receptors on fibroblasts leading to the phosphorylation of intracellular Smad proteins that promote its signal transduction. In particular, the phosphorylation of Smad2 and Smad3, the formation of complexes between Smad2, Smad3 and Smad4, and the translocation of these complexes to the nucleus result in the expression of pro-fibrotic genes. Smad2 levels have been reported to be increased in bronchial biopsies of asthma patients (Sagara et al., 2002), while Smad3-deficient mice have inhibition of ovalbumin-induced airway remodelling (Le et al., 2007); confirming an increased level of TGF-β1 signalling in asthma.

On the other hand various ECM components can be degraded by zinc-dependent endopeptidases known as matrix metalloproteinases (MMPs). TGF-β1 is able to inhibit MMP production while promoting the production of tissue inhibitors of metalloproteinases (TIMPs) (Edwards et al., 1987). TIMPs are specific for certain MMPs and interact in a 1:1 stoichiometric ratio. The expression of MMPs (and TIMPs) can act as a double-edged sword in lung disease as breakdown of ECM can be not only a powerful means of reversing fibrosis but also a fundamental part of the inflammatory process allowing the egress of inflammatory cells into the lung tissue, while also damaging the alveolar wall (Tang et al., 2006).

2. Genetic components and aetiology of fibrotic lung disorders

The major etiological factors of lung disease are inhaled environmental components and other entities in the lung lumen which interact