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Epigenetic targets for novel therapies of lung diseases

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ABSTRACT

In spite of substantial advances in defining the immunobiology and function of structural cells in lung diseases there is still insufficient knowledge to develop fundamentally new classes of drugs to treat many lung diseases. For example, there is a compelling need for new therapeutic approaches to address severe persistent asthma that is insensitive to inhaled corticosteroids. Although the prevalence of steroid-resistant asthma is 5–10%, severe asthmatics require a disproportionate level of health care spending and constitute a majority of fatal asthma episodes. None of the established drug therapies including long-acting beta agonists or inhaled corticosteroids reverse established airway remodeling. Obstructive airways remodeling in patients with chronic obstructive pulmonary disease (COPD), restrictive remodeling in idiopathic pulmonary fibrosis (IPF) and occlusive vascular remodeling in pulmonary hypertension are similarly unresponsive to current drug therapy. Therefore, drugs are needed to achieve long-acting suppression and reversal of pathological airway and vascular remodeling. Novel drug classes are emerging from advances in epigenetics. Novel mechanisms are emerging by which cells adapt to environmental cues, which include changes in DNA methylation, histone modifications and regulation of transcription and translation by noncoding RNAs. In this review we will summarize current epigenetic approaches being applied to preclinical drug development addressing important therapeutic challenges in lung diseases. These challenges are being addressed by advances in lung delivery of oligonucleotides and small molecules that modify the histone code, DNA methylation patterns and miRNA function.

Contents

Abbreviations: ACD/MPV, alveolar capillary dysplasia and misalignment of pulmonary veins; BMPR2, bone morphogenetic protein receptor 2; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; DNMT, DNA methyltransferase; EMT, epithelial–mesenchymal transition; eRNA, enhancer RNA; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, house dust mite; HIF1α, hypoxia inducible factor-1α; HOTAIR, HOX antisense intergenic RNA; IL-β, interleukin-1β; IFN-γ, interferon-γ; IPF, idiopathic pulmonary fibrosis; lncRNA, long noncoding RNA; lincRNA, long intergenic noncoding RNA; LNA, locked nucleic acid; MALAT-1, metastasis associated lung adenocarcinoma transcript 1; miRNA, microRNA; Nrf2, NF-E2-related factor 2; OVA, ovalbumin; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVT-1, Pvt1 non-protein coding RNA; SIRT1, Sirtuin-1; SNPs, single nucleotide polymorphisms; SAHA, suberoylanilide hydroxamic acid; TGF-β1, transforming growth factor β1; TNF-α, tumor necrosis factor-α; UNA, unlocked nucleic acid.

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1. Introduction

Epigenetic regulation of gene expression and protein abundance is carried out by a set of highly conserved processes that contribute to normal development and adaptation to changes in cellular and organ homeostasis. Any disease that alters the cellular milieu to the point of triggering adaptive changes in phenotype will likely involve one or more epigenetic mechanisms. Transcription is regulated by DNA methylation, often at CpG islands in promoters of protein-coding genes, and by posttranslational modification of histones. Noncoding RNAs also modify transcription, mRNA processing and mRNA stability to modulate protein abundance. Because DNA methylation, the histone code and microRNA-mediated gene silencing are highly conserved processes many clinically diverse conditions should respond to drugs that modify these epigenetic regulatory systems. It is also clear that epigenetic modifications can be cell and tissue specific, which suggests that epigenetic therapies might be designed to be directed to particular diseases. It is also very important to note that changes in epigenetic modifications of DNA and histones and changes in miRNA expression may be a consequence of a disease as well as cause the disease. Substantial effort is now being spent defining the timing and the necessity of epigenetic adaptations in lung diseases. Many of those studies have identified potential new drug targets which are summarized in this review. The working hypothesis is that antagonizing causative epigenetic features of disease or antagonizing adaptive epigenetic responses might favor a return to more normal structure and function of the lung. There are two processes of particular interest in this regard — lung inflammation and subsequent lung remodeling. Lung inflammation is often well controlled by corticosteroid therapy, but in severe asthmatics may require additional approaches including novel antibody-based therapies targeting IgE, thymic stromal lymphopoietin or interleukin-5. For more information on these important developments in asthma therapy the reader is referred to recent advances in antibody-based antiinflammatory therapies (Bel et al., 2014; Gauvreau et al., 2014; Humbert et al., 2014; Ortega et al., 2014). In this review we will cite studies of epigenetic modifiers in lung disease as well as other diseases when they provide proof of key principles, but the focus will be on novel therapy of pulmonary hypertension, restrictive lung diseases and obstructive lung diseases. The reader should consult other recent reviews for a general appreciation of advances in epigenetic therapy in other organ systems (Natarajan, 2011; Dhanak & Jackson, 2014; Haldar & McKinsey, 2014; Tao et al., 2014).

In all cases the appeal of targeting epigenetic mechanisms is that they are reversible biochemical processes amenable to manipulation with small molecule drugs, and in some cases small oligonucleotides. This contrasts with mutations in genomic and mitochondrial DNA most of which are uncorrectable in a clinical setting. Identifying the best epigenetic targets and developing the best therapeutic strategies topics of great interest and high significance for developing novel drugs for lung diseases. In addition to targeting inflammation we suggest that targeting tissue remodeling will be a fruitful strategy. Tissue remodeling is a common feature of pulmonary vascular disorders as well as obstructive and restrictive diseases of the airways. The key aspects of pathology of each disease will be described along with some emerging epigenetic targets. Recent progress in preclinical studies of small molecule and oligonucleotide modifiers will be summarized with the goal of focusing attention on promising therapeutic approaches that may add to the current standards of care.

2. Tissue remodeling in lung diseases

2.1. Pulmonary hypertension

Patients with pulmonary hypertension (PH) suffer from abnormally high pulmonary artery blood pressure that leads to right ventricular dysfunction. In severe pulmonary arterial hypertension (Group I PH, PAH), the normally thin-walled, highly compliant pulmonary arteries become thickened, stiffer and hypercontractile (Humbert et al., 2004; Chan & Loscalzo, 2008; Rabinovitch, 2008). Peripheral pulmonary arteries become occluded by neointimal and plexiform lesions which are hypothesized to contribute to disease severity (Yi et al., 2000; Pietra et al., 2004; Tuder et al., 2007). Pathological vascular remodeling is due to increased proliferation and decreased apoptosis of endothelial cells, smooth muscle cells and adventitial fibroblasts. The resulting wall hypertrophy may also be due to disrupted autophagy, enhanced progenitor cell migration and differentiation as well as immune cell migration and differentiation. The biochemical processes that regulate these diverse processes are the subject of intense study, and are targets of numerous drugs in preclinical development (Morrell et al., 2013; Tuder et al., 2013). In addition to small molecule inhibitors of cell signaling pathways, microRNAs (miRNA) have become intensely studied molecular targets for novel anti-remodeling therapy (White et al., 2012). There is also emerging evidence for altered DNA methylation (Archer et al., 2010) and histone posttranslational modifications (Xu et al., 2010) in pulmonary hypertension, both of which are targets for new drug development (Saco et al., 2014).

2.2. Obstructive lung diseases – asthma and chronic obstructive pulmonary disease

Remodeling of the airways occurs in asthma and COPD resulting in obstruction of airflow. The pathophysiology of the two diseases is quite different, but there are some common features relevant to identifying novel targets for anti-remodeling drug therapy. Asthma is a multifactorial syndrome triggered by allergens, infections, aspirin, exercise or cold air that results in symptoms of obstruction. The wheezing, and shortness of breath are frequently, but not always, reversible with bronchodilators. Treatment with inhaled corticosteroids usually controls allergic inflammation and prevents asthma episodes. Acute therapy with beta agonists relaxes airway smooth muscle and relieves the symptoms in most subjects. However, in a significant minority of asthmatics (5–10%) airway obstruction is not reversible (Sullivan et al., 2007; Chipps et al., 2012). In severe cases steroid resistance and lack of response to beta agonists can result in potentially fatal attacks (Wenzel, 2005). The lack of adequate treatment of severe asthma makes a compelling case for developing new therapies. Recent progress in novel anti-inflammatory therapy is described elsewhere (Bel et al., 2014; Gauvreau et al., 2014; Humbert et al., 2014; Ortega et al., 2014). The goal of our prospective analysis is to describe potential targets for anti-remodeling therapy.

Aside from bronchial thermoplasty there are no clinically proven therapies to reverse airway obstruction in severe asthmatics, whether they are steroid-resistant or not. What is needed is an effective way to prevent or reverse airway smooth muscle hyperplasia and hypertrophy, mucosal metaplasia, submucosal and parenchymal fibrosis and persistent inflammation. This is a challenging task because multiple cell types contribute to airway and vascular remodeling and no single agent is likely to reverse all features of pathological remodeling. Thus, it is imperative that we identify drug targets that affect those cells most responsive to treatment.

Therapy of COPD overlaps with asthma therapy in that corticosteroids are used for their anti-inflammatory effects and beta agonists for bronchodilation. A key difference between asthma and COPD is that obstruction is not fully reversible in COPD. Patients with COPD often present with emphysema, bronchitis or both. Smoking is a common insult that elicits mucosal hyperplasia and excess mucous production as well as smooth muscle hypertrophy in the small airways. In both asthma and COPD inflammation is a proximal event leading to symptoms, but there are key differences in the immune cell infiltrates; eosinophilia in many asthmatics versus neutrophils in COPD. Another key difference is destruction of elastin in the lung parenchyma in COPD by neutrophil elastases coincident with increased collagen deposition. This suggests

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