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From production to intracellular signalling, the molecules controlling inflammatory cell migration present a significant opportunity for the therapy of common chronic respiratory diseases.

Leukocyte navigation mechanisms as targets in airway diseases

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Respiratory diseases, including asthma and chronic obstructive pulmonary disease, are among the most significant diseases in terms of their disabling effects and healthcare burden. A characteristic feature of almost all respiratory diseases is the accumulation and activation of inflammatory leukocytes in the lung or airway. Recent advances in the understanding of the molecules and intracellular signalling events controlling these processes are now translating to new therapeutic entities. In this article, the process of leukocyte accumulation is summarized, together with the preclinical and clinical evidence supporting the utility of the individual components of this process as targets for disease therapy.

Activation and accumulation of different leukocyte populations are defining features of inflammatory disease. To begin addressing the possibility of targeting leukocyte movement within chronic lung diseases, we will outline the main characteristics of each disease of interest, followed by the differences most common animal models possess in comparison with human pathology. Table 1 summarizes the key features of chronic inflammatory lung diseases.

Heterogeneity of airway disease and animal models

Asthma

Asthma is one of the most common chronic diseases in the world. It is estimated that ~300 million people currently have asthma and that it accounts for ~1 in every 250 deaths worldwide. Furthermore, it is estimated that there could be an additional 100 million people with asthma by 2025 [1]. Bronchial asthma is characterized by airway eosinophilia, goblet cell hyperplasia with mucus hypersecretion and airway hyperresponsiveness (AHR) to inhaled allergens and to non-specific stimuli [2]. In individuals with an allergic predisposition, T cells exposed to allergen on the surface of antigen-presenting cells (mainly dendritic cells) mature preferentially towards the T-helper (Th) 2 subtype. By producing different chemical mediators, these cells influence the activity of mast cells, granulocytes, B cells and local cells (epithelial, fibroblasts and airway smooth muscle cells), causing the pathophysiological characteristics found in asthma [2] (Figure 1).

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TABLE 1

Main characteristics of chronic inflammatory lung diseases

Disease	Major cell types involved	Defining characteristics	Associated risks and causes
Asthma	T cells (Th2>Th1) Eosinophils Mast cells Airway epithelial cells	Airflow limitation is usually reversible Airway hyperresponsiveness Episodes of coughing, wheezing and dyspnea Onset early in life	Allergy, rhinitis or eczema Family history of asthma
Chronic obstructive pulmonary disease	T cells Neutrophils Macrophages Airway epithelial cells	Airflow limitation is progressive and irreversible Atypical responses to noxious particles Main syndromes: chronic bronchitis and emphysema. Onset in midlife	Long smoking history
Idiopathic pulmonary fibrosis	Neutrophils Fibrocytes Fibroblasts	Chronic fibrosing interstitial pneumonia Limited to the lung Dyspnea with worsening of pulmonary function Pulmonary dysfunction is progressive and irreversible Onset late in life	Unknown

The study of respiratory diseases *in vitro* is limited by the fact that probing a certain molecular or cellular response in isolation does not represent well the situation in the lung of the whole animal. By contrast, *in vivo* modelling is able to capture some of the complicated genetic, biochemical and environmental interactions that combine in a disease state. However, no one model portrays all the human characteristics of the disease; each model focuses on certain characteristics more than others [3].

In the majority of current asthma models, mice are intraperitoneally injected with a sensitizing agent [like ovalbumin (OVA), cockroach antigen or *Aspergillus* conidia]. Upon subsequent exposure to the sensitizing agent in an aerosolized form, animals develop AHR and eosinophil recruitment into their airways, which mimics, to a certain extent, human asthma [3]. However, other aspects of these models are very different compared with human disease. For example, in mice, there is an absence of acute bronchoconstriction [3], a dramatic variation of eosinophil influx in different strains of mice [4] and a prominent role for serotonin, which is nonexistent in human asthma [5]. The chronic inflammation of airway walls, and their remodelling processes by fibrosis

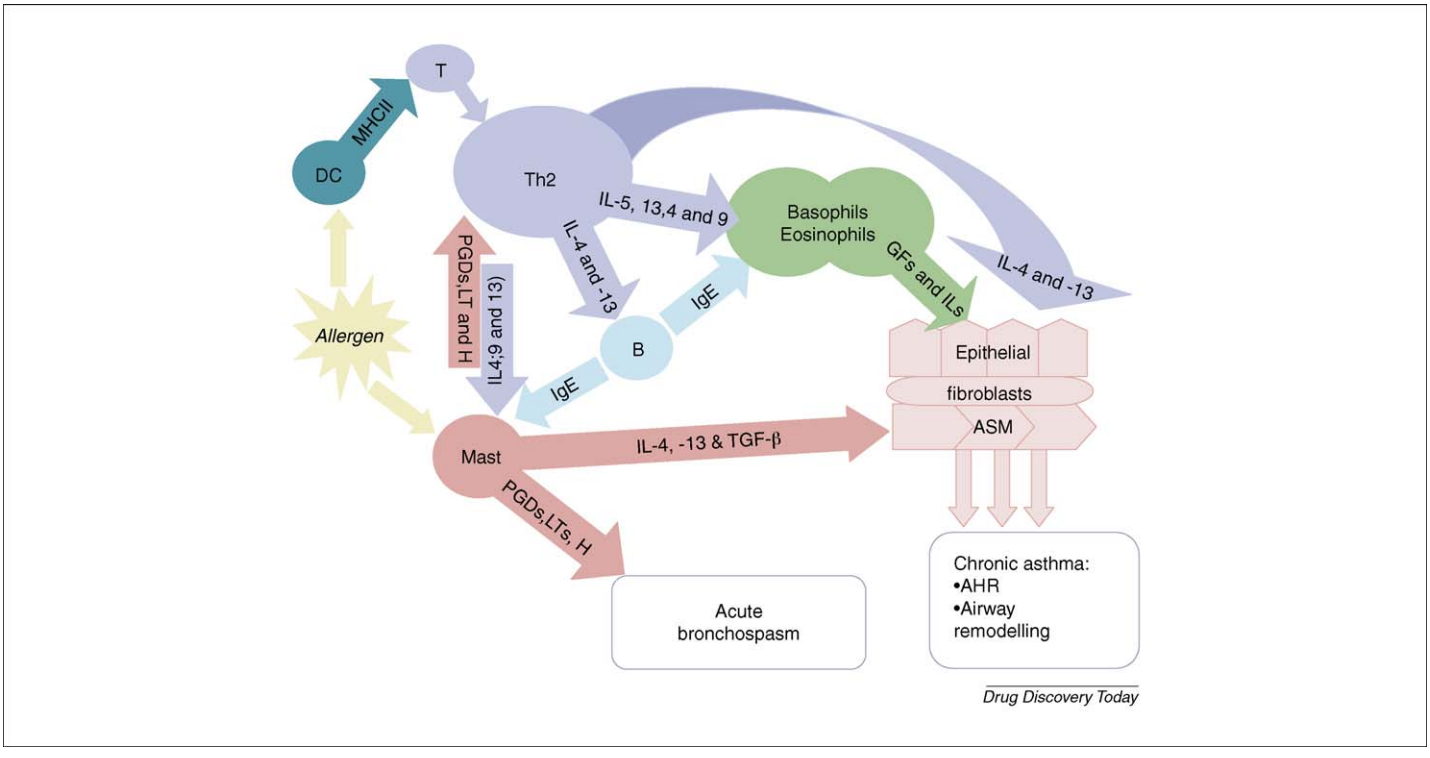

FIGURE 1

The role of T cells in asthma. After allergen exposure, mast cells (Mast) release prostaglandins (PGDs), leukotrienes (LTs) and histamine (H), causing the acute bronchospasm of the airway. For the chronic manifestations, the chemical mediators produced by mast cells in conjunction with T cell interaction with allergen-exposed dendritic cells (DC) preferentially induce T cells into a Th2 subtype. These T cells secrete interleukins (IL-5, IL-4, IL-13 and IL-9), which induce B lymphocyte immunoglobulin (Ig) E synthesis; eosinophil and basophil survival and recruitment; and mast cell maturation and activation. These cells respond by secreting growth factors (GFs) like transforming growth factor-β (TGF-β), and more interleukins. This myriad of immune mediators directly induces lung cells (epithelial cells, fibroblasts and airway smooth muscle (ASM) cells into the asthmatic phenotype, culminating in airway remodelling and hyperresponsiveness (AHR).