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Pharmacology & Therapeutics 107 (2005) 343 – 357

Pharmacology & Therapeutics

www.elsevier.com/locate/pharmthera

Associate editor: D. Spina

What targets have knockouts revealed in asthma?

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Abstract

There have been numerous studies of mice rendered genetically deficient of various genes in the context of allergic inflammatory airway disease. These studies have provided invaluable information about basic immune processes, but have also been considered to be useful in predicting novel pharmacological targets. In this review, the effect of a wide range of individual knockouts (KO) on the development of asthma-like pathologies in mice is compiled and considered. How the results of these studies compare with effects of agents that interfere with the function of each gene product, where known, is also described. Finally, a personal view of the utility of these studies in drug development is presented.
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Keywords: Asthma; Eosinophilia; Remodelling; Hyperresponsiveness; Knockouts; Mice

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doi:10.1016/j.pharmthera.2005.03.007

1. Introduction

Asthma is a complex syndrome encompassing several pathophysiological signs that are variably present in patients. These include reversible airflow limitation (bronchoconstriction), wheeze, and cough. The airways of asthmatics are also usually inflamed, showing signs of oedema and inflammatory cell infiltration, principally by eosinophillic granulocytes, mast cells, and lymphocytes. It is a generally held view that chronic inflammation of the airways leads to structural changes that are loosely grouped together as airway wall remodelling (Cohn et al., 2004). These changes include structural changes that lead to thickening of the airway wall (myocyte and fibroblast proliferation), enlargement of mucous glands, as well as proliferation of mucous-producing cells within the epithelium. Finally, asthmatics demonstrate heightened bronchomotor responsiveness to a variety of stimuli. How these features of the disease interrelate is not fully established because the history of the disease is generally unknown prior to formal diagnosis (Cohn et al., 2004). The current paradigm–increasingly questioned–is that mild inflammation causes mere bronchoconstriction, whereas chronic, severe inflammation results in remodelling and hyperresponsiveness (Bousquet et al., 2000).

Many, but not all, patients are demonstrably allergic to one or more common environmental allergens, although paradoxically many similarly atopic individuals do not have any of the symptoms of asthma (Pearce et al., 1999). The principal immunoglobulin responsible for such allergic responsiveness is IgE. However, there is also a group of patients (10–50% of all asthmatics) for whom no allergic basis for symptoms is apparent. Such nonatopic asthmatics tend to develop symptoms later in life and the cause of their disease is uncertain (Humbert et al., 1999; Renauld, 2001). The patterns of symptoms and responsiveness to therapeutics suggest that there are many more phenotypes of asthma than this simple atopic/nonatopic dichotomy (Bush, 2004).

2. The pharmacological challenge

The 2 major classes of drugs used to manage the symptoms of asthma are β_2-adrenoceptor agonists and glucocorticosteroids (Barnes, 2004). Both are generally inhaled, although in severe asthma, high dose oral glucocorticosteroids may be required. Asthma, therefore, is a disease where few to no useful mediator antagonist drugs are available, and current agonist-based treatment mimics the body's own protective responses. β_2-Agonists are used simply as bronchodilators, and improvements in their pharmacological properties over the last few decades have been limited to improved β_2-selectivity and increased duration of action. Glucocorticosteriods are used additionally in those patients who rely frequently (>3 times per week) on β_2-agonist therapy and who are thought to have more profound airway inflammation. Improvements in this class of drug over the last 30 years have been increased efficacy and first-pass metabolism to limit the site of action to the lung.

Current therapeutics for the treatment of asthma have several limitations (Barnes, 2004). First, none are curative, but merely treat or prevent symptoms. Second, a small group of patients do not respond well to current drugs. These patients represent the majority of emergency hospital admissions for asthma exacerbations. Third, apart from high-dose glucocorticosteroids, drugs are generally not orally administered and patient compliance is frequently a concern. This final consideration is important because glucocorticosteroids are used prophylactically. Orally available drugs might also act on other allergic diseases associated with asthma, such as rhinitis and dermatitis. Finally, side effects are a concern, particularly when high doses of glucocorticosteroids are required. Side effects of current drugs include tremors and effects on the heart (β_2-agonists) as well as oral/throat thrush and disorders of bone metabolism (glucocorticosteroids).

A potential drug for asthma, therefore, will fit into one of 2 basic categories:

(a) Market share. A drug that can compete with an existing therapeutic and effectively replace it in the clinic, if only in certain patients. Recently, an attempt was made to obtain market share using orally dosed drugs that interfere with leukotriene synthesis or signalling in asthma (Horwitz et al., 1998). It was hoped that this novel class of therapeutic agent could effectively replace glucocorticosteroids in some patients, whereas, in fact, glucocorticosteroids have generally proved more effective. Nonetheless, leukotriene antagonists have proved effective in some asthma phenotypes, such as asprin-induced asthma (Dahlen et al., 2002). Thus, while the size of the market share has not turned out to be as large as originally envisaged, this class of drugs is an example of a successful attempt. The increasing evidence that asthmatics fall into several phenotypes suggests that identifying and targeting disease subsets might be a successful therapeutic strategy and allow market space for drugs of this kind.

(b) Market dominance. A drug, preferably a once-a-day pill, which effectively and safely reverses the symptoms of asthma in its many guises. It might be an antiinflammatory bronchodilator or it might have highly specific immunomodulatory effects sufficient to prevent the disease occurring without seriously compromising the immune system. Such a "magic bullet" might not actually be feasible, but is still the dream of pharmacologists (Fernandes & Goldie, 2003).

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