RESEARCH COLLECTION ON

ALLERGIC DISEASES

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Chapters from books edited by: **Marek Kowalski** and **Celso Pereira**

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Preface

This book is a collection of selected and relevant previously published research, concerning the developments within the Allergic Diseases field of study. The collection includes scholarly contributions by various authors and edited by a group of experts pertinent to Immunology, Allergology and Rheumatology. Each contribution comes as a separate chapter complete in itself but directly related to the book's topics and objectives. The target audience comprises scholars and specialists in the field.

ALLERGIC RHINITIS

Edited by **Marek L. Kowalski**

From Mouse to Man: Translational Value of Animal Models of Allergic Rhinitis

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1. Introduction

Allergic rhinitis (AR) is the most prevalent atopic disease in the world, affecting 10-20% of the population or up to 600 million people (Asher et al. 2006; Meltzer and Bukstein 2011). Data from multi-year international studies show that the incidence of upper airway allergy is greater than that for asthma, and since 1994 the prevalence of AR has increased more rapidly than allergic asthma (Asher et al. 2006; Weinmayr et al. 2008). The common clinical definition of AR is nasal obstruction, sneezing, rhinorrhea, and pruritus associated with known or suspected allergens. Comorbidity with asthma is common, with 50% to 100% of allergic asthma patients in the United States and Europe reporting AR symptoms (Gaugris et al. 2006). Furthermore, as much as 30% of individuals with AR have lower airway symptoms, such as bronchial hyperreactivity, and AR has emerged as a risk factor for eventually developing asthma (Ciprandi and Cirillo 2006; Ponikau et al. 2003). Because of the frequency of AR coexisting with allergic asthma, a role for common pathophysiologic linkages between asthma and AR has been a focus of discussion among clinical scientists. Comparison of the nasal and bronchial mucosa from allergic airways reveal similar inflammatory and epithelial cell alterations in both tissues, suggesting that common mechanisms of pathogenesis may contribute to each condition (Chanez et al. 1999). Given the clinical and pathologic commonalities of AR and asthma, recent efforts of physicians worldwide has led to Allergic Rhinitis and its Impact on Asthma (ARIA), a collaborative development of diagnostic and therapeutic strategies to treat AR as an asthma risk (Bousquet et al. 2001). A central tenet of ARIA is that AR and asthma represent a "united airway disease" and should be viewed as an interrelated disease with common etiology, features and treatments (Compalati et al. 2010; Marple 2010).

However the inherent differences in the anatomic, morphologic, and functional aspects of nasal versus pulmonary airways result in unique inflammatory and allergic responses in each site. For example, airway obstruction in upper and lower airways occurs by very different mechanisms. Smooth muscle contraction narrows conducting airways in lung, whereas acute vasodilation of vascular tissue limits airflow through nasal airways. Mucus overproduction and hypersecretion may also contribute to airway occlusion and obstruction in both nasal and bronchial airways. Excess mucus such as during rhinorrhea might be more easily cleared from the nose, but mucus plugging in pulmonary airways is a prominent feature associated with mortality in *status asthmaticus*. While the "one-airway" concept may be an attractive paradigm to describe relationships in allergic airways in support of the ARIA framework, differences in clinical opinions for treatment remain (Chipps et al. 2010).

Basic research directed at the study of each condition separately, as well as in tandem, is needed to fully understand the pathophysiology of allergic airways disease. AR is a unique pathophysiological entity that is part of a spectrum of atopic disease including eczema and asthma. The use of relevant animal models of allergic airways disease is necessary to provide the supportive data that defines the extent and nature of AR:asthma relationships. In the last decade, research efforts that focused on animal models of AR have begun to provide a scientific framework with which to understand the role of upper airways in allergic airways disease.

2. Insights from animal models of allergic asthma

Extensive work in susceptible rodent strains using ovalbumin as the test allergen, or environmentally-relevant allergens (e.g., house dust mite, cockroach), has helped describe both the acute and chronic immune and inflammatory responses in pulmonary airways.
The strengths and limitations of laboratory animal models has been debated (Shapiro 2006; Wenzel and Holgate 2006). Studies using mice, especially transgenics and knockout strains, have been important for understanding of the role of cytokines, adhesion molecules, and cell receptors in allergic inflammatory responses. Asthma is a chronic disease of inflammation that is marked by extensive airway remodeling. By comparison, most rodent models of asthma are relatively acute, with regular exposure to allergen challenges over a few days or weeks. As such, the reproduction of the human asthma pathophysiology is not perfect. While airway hyperreactivity, eosinophilic and lymphocytic infiltration, and mucus overproduction can be induced in experimental asthma, other features such as smooth muscle cell proliferation, myofibroblast activation, subepithelial fibrosis, and epithelial proliferation and shedding are often absent in allergic rodent models.
Given the limitations of acute rodent models, efforts to develop chronic asthma models that use frequent exposures to lower allergen concentrations can better portray exposure histories of allergic subjects to seasonal and episodic exacerbations. Specifically, airway remodeling in these mice include key features of human asthma, such as intraepithelial eosinophils, collagen deposition, epithelial hyperplasia and metaplasia, smooth muscle hyperplasia and hypertrophy, and increases in myofibroblasts (Lloyd and Robinson 2007; Nials and Uddin 2008; Yu et al. 2006).
Regardless of the rodent model (mouse, rat or guinea pig), the method to induce allergic responses in lower airways is similar across species and allergens. Primary sensitization to the allergen is accomplished by using either systemic (e.g., intraperitoneal, subcutaneous or dermal) or airway (aerosol inhalation, or instillation in the nose, pharynx, or trachea) routes of exposure, and given as a single or multiple administrations. An adjuvant, usually alum (potassium aluminium sulfate), may also be used. Sensitized animals are then challenged with a secondary exposure by either dermal, inhalation, or airway instillation, and with varying volumes and allergen concentrations or several days or weeks. Several groups have conducted comparisons of the different protocols and determined strengths and limitations of several approaches. (Farraj et al. 2006; Pauluhn and Mohr 2005; Samarasinghe et al. 2011; Southam et al. 2002; Ulrich et al. 2008).

3. Animal models of allergic rhinitis

Preclinical research on allergic airways disease has focused predominately on the lower airways and asthma. By comparison, animal models of AR are relatively underdeveloped and understudied. Until recently, AR models have relied on short-term protocols and