

# Animal Models for Human Asthma: The Perspective of a Clinician

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**Abstract:** The asthma animal model is still the only system that is available for modelling *in vivo* processes of human disease since for obvious ethical reasons these experiments are not possible in humans. However, there is a marked discrepancy between numerous successful studies in animals and very few rather disappointing clinical trials in patients. The current available models are usually uniform models of an acute asthmatic attack in adult animals, which do not spontaneously develop asthma. Major anatomical differences exist between human and animal airways and comparable lung function measurements are very difficult or impossible. The main reason why simplistic animal models may be inadequate lies probably in the diversity that exists within the different phenotypes of human asthma. Whereas progress is made to develop chronic asthma models with signs of airway remodelling, severe asthma and the role of small airways is still poorly reflected in current animal models.

**Key Words:** Animal model, asthma, severe asthma, small airways, airway remodelling.

## INTRODUCTION

Studies to determine critical pathways in the pathophysiology of asthma and to discover new ways of pharmacological intervention, should be ideally conducted on human asthmatics. However, for obvious ethical reasons these experiments are not possible in humans. Therefore, biological models are required which mimic specific aspects of the underlying cellular and molecular mechanism. Whereas several basic mechanism can be investigated in *in vitro* systems the only system that is available for modelling *in vivo* processes of human disease is still the animal model.

Several reviews including this edition of the journal have summarized the necessity and advantages of different asthma animal models in recent years [1-13]. Animal models of asthma have been particularly helpful for mechanistic studies in which specific mediators, e.g. the Th2 cytokines, have been identified as key player in the allergic airway inflammation. Furthermore, animal models are necessary for discovery and development of new drug candidates to demonstrate the proof-of-principle *in vivo* and to estimate the toxicity of new therapeutic interventions in the complex immune and respiratory system.

## HUMAN ASTHMA AND LIMITATION OF ANIMAL MODELS

Human asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role [14]. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early

morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Although this definition is accepted worldwide [14], it is well recognized that asthma is a complex and heterogeneous disease, in which the genetic background, the age of the patients, environmental factors (including trigger factors and infections) are important determinants of the severity and variability of the disease. Several subsets of asthma, e.g. viral induced, allergic, non-allergic, intrinsic, extrinsic, occupational, persistent, seasonal, exercise induced, nocturnal and steroid resistant asthma have been distinguished. Therefore, asthma is rather a disease complex without a single and established pathophysiological mechanism.

The current available animal models are usually uniform models of an acute asthmatic attack in adult animals. Most animal models do not naturally and spontaneously develop asthma. Therefore, an allergic asthmatic reaction has to be artificially induced by active immunization, using adjuvants like aluminum hydroxide or Bordetella pertussis. Major anatomical differences exist between human and animal airways and comparable lung function measurements are very difficult or impossible in animal models compared to human.

The aim of this review is to summarize several aspects of clinical asthma, which are not yet sufficiently addressed in available asthma models.

## NEW THERAPEUTIC INTERVENTIONS IN ANIMALS HAVE NOT PREDICTED THE EFFECTIVENESS IN HUMAN ASTHMA

Animal research has discovered a wide range of potential new cellular and molecular targets which have been successfully tested in asthma animal models [summarized by 15]. These include more general approaches like allergens (epitopes, TCR activation status), chemokines (Th2-related

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chemokine receptors), complement (C3a and C5a receptor antagonists), proteases (tryptase, MMP inhibitors), Th1 response (CpG Oligo/adjuvant, T-bet), Th2 response (GATA-3, FOG-1, CD28, CTLA-4), viruses (RSV vaccine, anti-RSV Ab/mAb) and more specific targets like adenosine (adenosine receptor inhibitors), CLCA3/Gob-5 (anti-sense CLCA3 oligonucleotide), IFN- $\alpha$ /IFN- $\gamma$  (recombinant IFN- $\alpha$  and IFN- $\gamma$ ), IgE/IgE receptors (anti-IgE mAb, Fc $\epsilon$ RI, and Fc $\epsilon$ RII), IL-2 (anti-IL-2R mAb), IL-4 (anti-IL-4 mAb, soluble IL-4R), IL-5 (anti-IL-5 mAb), IL-9 (anti-IL-9 mAb), IL-12 (recombinant IL-12), IL-13 (soluble IL-13R, IL-4/13 trap), LTD<sub>4</sub> (5-LO inhibitor, LTR antagonist), PDE-4 (specific enzyme inhibitor), PGD<sub>2</sub> (CRTH2 receptor antagonist), TNF- $\alpha$  (anti-TNF mAb), VLA-4 (anti-VLA-4 mAb). However, the outcome of most of the clinical programs was either negative, with minor effects, with side-effects, uncertain or is still pending.

For example, animal models have clearly demonstrated that eosinophils and the Th2-cytokines IL-5 and IL-4 are pivotal in the asthmatic inflammation. Therefore, it was a major drawback in asthma research when clinical trials with specific antibodies against IL-5 and soluble IL-4, which neutralizes IL-4, were unsuccessful in clinical trials [16, 17]. Furthermore, IL-12, which was successfully used in animal models to abolish Th2-responses, also failed in asthma trials because of marked toxicity [18].

On the other hand, the intervention with anti-IgE is the only example of the new biological drugs which is effective in humans to suppress early and late phase responses to inhaled allergen [19] and which has been implemented in clinical guidelines [14]. Although anti-IgE had been successfully used in animal models as well the majority of researches at that time was not convinced that this would be a promising therapy for asthma.

This discrepancy between numerous successful studies in asthma animal models and very few rather disappointing clinical trials in patients points to the limitation of animal models in a complex disease like asthma [20]. Therefore, from a clinical point of view asthma models have severe limitations in predicting the efficacy and non-toxicity of new drug candidates for human asthma. So far bronchodilators and non-specific anti-inflammatory steroids are still golden standards for asthma therapy. From the new approaches only anti-leukotrienes and anti-IgE have reached the status of guideline recommendation, however either with limited effect and for specific indications only.

### THE IMPORTANCE OF SEVERE ASTHMA

Although only 10% of the patients are suffering from severe to very severe asthma the proportion of cost for this subpopulation reaches 55% of the total cost for asthma. [21]. Therefore, in particular for severe asthma there are unmet needs to improve the pathophysiological knowledge and therapeutical options. Severe asthma is associated with female gender, obesity, and smoking [22]. Atopy is less frequent in severe asthma, but occupational sensitizers are common inducers of new-onset severe asthma. Viruses contribute to severe exacerbations and can persist in the airways for long periods. Furthermore, patients with adult-onset nonatopic asthma and positive IgG antibodies to C pneumo-

niae had a 4-fold greater estimated decline in lung function, which suggest that C pneumoniae infection might promote the development of persistent airflow limitation in patients with nonatopic adult-onset asthma. [23, 24]. Inflammatory cells are in the airways of the majority of patients with severe asthma and persist despite steroid therapy. The classical T(H)2 immune process alone is inadequate to explain severe asthma. In severe asthma an eosinophilic but also a non-eosinophilic, neutrophilic inflammation has been described in humans [25, 26]. Therefore, therapies which target the neutrophilic inflammation might be more effective in severe asthma [27]. Epithelial cell and smooth muscle abnormalities are found, contributing to airway narrowing. Large and small airway wall thickening is observed, but parenchymal abnormalities may influence airway limitation. Higher numbers of fibroblasts, an increase in collagen type III deposition, larger mucous gland and airway smooth muscle areas, augmented smooth muscle cell size, and myosin light-chain kinase expression distinguished patients with severe persistent asthma from patients with milder disease [28].

These characteristic features of severe asthma easily explain why a classical allergic, eosinophilic, Th-2-driven asthma animal model is unable to mimic a non-allergic disease, where infectious agents and a neutrophilic inflammation play a major role.

### THE ROLE OF THE SMALL AIRWAYS IN ASTHMA

Physiological and pathological evidence suggests that the small airways and lung parenchyma participate in asthma pathogenesis, and may explain many of the clinical observations noted [29]. With the help of transbronchial biopsy in addition to endobronchial biopsies it has been recognized that airway inflammation and remodelling in asthma occurs in the central airways and also in the small airways and in the lung parenchyma [30]. Small airways and the lung parenchyma can produce many Th2 cytokines, chemokines, and mediators involved in initiation and perpetuation of the inflammatory process [31]. Distal inflammation has been described as more severe than large airway inflammation, and strong evidence of remodelling in the lung periphery is emerging. Furthermore, the distal lung has been recognized as a predominant site of airflow obstruction in asthmatics. Lung function of the small airways can be assessed by spirometry (MEF), CO-diffusion, frequency dependence of compliance and single breath nitrogen test. Furthermore, nitric oxide and 8-isoprostane in exhaled air have been shown to be associated with small airways function in asthma [32]. This suggests that these markers reflect small airway inflammation and favours a role for them as disease markers that is complementary to spirometry in the monitoring of patients with asthma. Advances in imaging technology allows to measure the contribution of small and large airways in asthma pathogenesis using computer tomography [33], hyperpolarized helium MRI [34, 35] and positron emission tomography [36]. The approach using PET was specifically utilized to identify the relative importance of small and large airways in the simultaneous deterioration of mechanical function and ventilation in asthma. The results show that matching both the degree of mechanical impairment and the size and location of the PET ventilation defects requires either constriction of airways <2.4 mm alone, or a simultane-

ous constriction of small and large airways, but not just large airways alone.

These emerging studies demonstrate that the role of small airways seems to be critical in asthma pathophysiology. However, in animal models rather large airways compared to small airways have been investigated. However, also in animal models the role of small airways has been recognized [37] and new lung function [38] and imaging technologies [39] are developed which are able to assess the contribution of small airways in future asthma research.

## CHRONIC INFLAMMATION AND AIRWAY RE-MODELLING

Studies in murine experimental models have contributed to understanding the mechanisms of allergic inflammation underlying asthma. However, models involving short-term high-level exposure of sensitized animals to antigen have significant limitations for investigating the pathogenesis of the lesions of chronic asthma which is characterized by airway remodelling. Airway remodelling refers to the structural changes that occur in the airway wall [40]. These include persistence of inflammatory cells, epithelial hyperplasia and metaplasia, goblet cell and mucus gland hyperplasia subepithelial fibrosis and increased matrix deposition, muscle cell hyperplasia and angiogenesis. These structural changes result in thickening of the airway wall, mucus secretion, cough, escalation of symptoms, increased bronchial responsiveness, persistent airflow limitation, severe bronchospasm during exacerbations and reduced elasticity-dynamic collapse. Currently, there are no effective treatments that halt or reverse the changes of airway remodelling and its effects on lung function. Glucocorticoids have been unable to eliminate

the progression of remodelling changes and there is limited evidence of a beneficial effect from other available therapies. The search for novel therapies that can directly target individual components of the remodelling process is a clear medical need [41].

Most animal models used so far are models of an acute allergic airway inflammation and they lack the chronic inflammatory markers and long-term airway hyperresponsiveness. Modelling chronic asthma is problematic, because long-term antigenic challenge often triggers widespread pulmonary parenchymal inflammation or leads to eventual downregulation of inflammation and airway hyperreactivity. Therefore, only recently chronic animal models have been developed [42] and studies are emerging which demonstrate efficacy of new compounds in these chronic models [43, 44]. The features of these models include long-term effects on hyperresponsiveness and structural changes. In some cases, lung parenchymal and vascular inflammation/remodelling are also noted, which are not seen in human asthma (45). However, one of the most characteristic features of chronic human asthma, large increases in airway smooth muscle, does not occur. Since human airway smooth muscle cells are actively involved in cytokine production they may contribute to airway inflammation in asthma through the production and release of e.g. eotaxin [46].

The term "remodelling" in the mouse studies often describes the subepithelial deposition of matrix proteins. In human asthma, airway remodelling extends beyond this to include the full thickness of the airway wall and the region of alveolar attachments. Furthermore, in most cases, remodelling elements of murine models are responsive to corticosteroids, yet the response in humans has been much less [47].

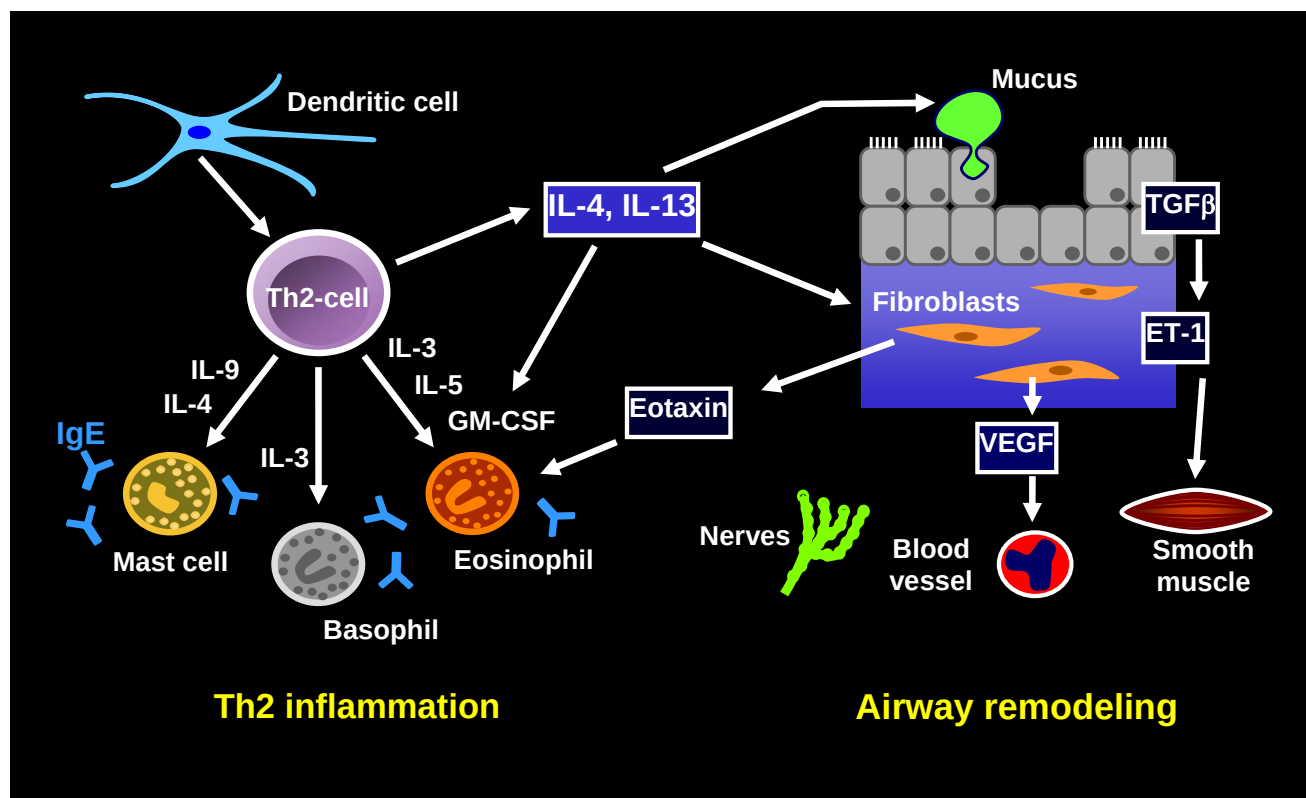


Fig. (1). Components of airway pathology in asthma: Th2-inflammation and airway remodelling.

## EPIDEMIOLOGY AND PRIMARY INTERVENTION STUDIES IN ASTHMA

Epidemiological studies have shown that environmental factors influence the prevalence of asthma: For example, exposure of young children to older children at home or to other children at day care protects against the development of asthma and frequent wheezing later in childhood [48, 49]. The exposure of children during the first year of life against microbial products reduces the risk of the development of allergic diseases [50, 51]. On the other hand air pollution is a risk factor for asthma exacerbation [52, 53]. The role of food intake as a risk factor for asthma is under investigation and has yet to be determined.

If animal models are predictive for human asthma primary intervention studies in animal models should resemble these epidemiological results. In this respect several studies have shown indeed that animals can be protected from developing asthma by using immune stimulatory strategies which induce Th1 responses or regulatory T cells [54, 55]. These strategies from observational human studies which are incorporated into animal models might become promising models for future asthma research in order to detect crucial elements in the pathogenesis of asthma which might be more successfully treated than several non-successful attempts in the past.

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