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Animal models of asthma: Innovative methods of lung research and new pharmacological targets

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Abstract

Allergic diseases like bronchial asthma are increasing in societies with western lifestyle. In the last years substantial progress was made in the understanding of the underlying mechanisms and explanations like the hygiene hypothesis were developed. However the exact mechanisms of the physiological and immunological events in the lung leading to bronchial asthma are still not fully understood. Therefore, animal models of asthma have been established and improved to study the complex cellular interactions in vivo. Since mice became the most frequently used animal species the methods for detecting lung physiology, e.g. lung function measurements were adapted to the small size of the murine lung. Laser-dissection and precision cut lung slices have become common techniques to get a view into distinct lung compartments and cells. In addition genomic and proteomic approaches are now used widely. On the other hand a major conclusion of the workshop stated that more than one species is necessary in research and for pharmacological screening in asthma and COPD. The resulting new understanding in the mechanisms of asthma pathogenesis has lead to a rapid identification of novel pharmaceutical targets for treatment of the disease.
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Animal models of asthma are widely used to investigate the immunological and physiological pathogenesis of the disease (Pauluhn and Mohr, 2005; Hellings and Ceuppens, 2004; Taube et al., 2004). Progress in the last 10 yr demonstrated that the mouse is a suitable model for some aspects of the disease. The current "chronic" asthma models using repetitive allergen aerosol provocation mimic important features of human disease. They show an allergen dependent sensitization with IgE production, a Th-2 dependent allergic inflammation characterized by eosinophilic influx into the airway mucosa, airway remodeling, airway hyperreactivity and allergen specific early phase response. However other features of asthma like an allergen independent chronification or acute "asthma attacks" were not registered in mice. To characterize the pathophysiological mechanisms in detail it became important to adapt the diagnostic methodology of lung research to the smaller size of the mouse (Epstein et al., 2006).

In the past most of the research was performed either directly in man with all its ethical problems or larger

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animals like monkey, dog, rat or guinea pig were used. But due to the scientific revolution in molecular biology that leads to a wide range of transgenic and knock-out animals and the generation of specific tools like monoclonal antibodies and or RNA-probes the mouse became more and more important for biomedical research. Especially for determination of physiological parameters, e.g. lung function measurements for determination of broncho-constriction the small size is a real problem. For example, the tidal volume is approx. 0.2 ml in the mouse compared to 500 ml in human and the resistance is 1000-fold higher in the mouse then in the human airway. Therefore techniques that allow precise and valid lung function testing in mice were developed in the recent years. For the needs of immunological and pharmaceutical laboratories easy to use methods like whole body plethysmography were developed and parameters like penh were created (Lomask, 2006). This approach was not commonly accepted by physiologists who argued that penH has no direct physiological meaning. Due to the easy handling and the possibility to measure high numbers of animals this methodology is now performed by many laboratories for screening purposes. Other methods for lung function measurements are much more expensive and require a team of experts and highly sophisticated technology is needed. In this issue the orotracheally intubated mouse is described as a possibility to measure "gold standard parameters" like resistance and compliance repetitively. In addition, aerosol can be applied using a dose control system and therefore airway hyperreactivty or early phase response can be measured very accurately (Hoymann et al., 2006).

To investigate the cellular interaction in the murine lung several methods has been adapted. Flow cytometric analysis of, e.g. BAL is due the low volumes and cell numbers that can be obtained very difficult to perform. In this issue, the optimization of these analyses for the mouse is described by H. Garn from Marburg (Garn, 2006). An other possibility to gain information from cells in situ is the laser dissection microscopy (Fink et al., 2006). After dissection, gene expression or protein content can be determined on nearly single cell level. In order to find new pharmaceutical targets gene profiling has become a widely used method. E. Hamelmann describes his experience on basis of his work in the German NGFN network (Dittrich et al., 2006).

Since drugs like corticosteroids and $\beta 2$ agonists are extremely potent drugs in asthma therapy the question of a real medical need and the realistic chance to find better drugs emerged. Since asthma is a disease with the involvement of multiple mediators and pathways I. Szelenyi stated the need of "dirty" drugs with multiple modes of action (Amon et al., 2006).

Examples of new potential targets for asthma therapy are peptide transporters as demonstrated by D. Groneberg (Groneberg et al., 2006) or neurotrophin antagonists as shown by C. Nassenstein (Nassenstein et al., 2006).

In this issue of Experimental and Toxicoligical Pathology new experimental possibilities in animal models of asthma are highlighted and some examples for the consequences for drug finding and testing are given. Therefore this issue should stimulate the critical discussion about the use of animal models to find new drugs for asthma therapy.

References

Amon A, Pahl A, Szelenyi I. Is asthma research in dead end? Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Dittrich AM, Quarcoo D, Krokowski M, Ahrens B, Hamelmann E. Gene expression profiling as novel tool in experimental asthma research. Exp Toxic Pathol 2006; 57(Suppl. 2) xx–xx.

Epstein MM. Are mouse models of allergic asthma useful for testing novel therapeutics? Exp Toxic Pathol 2006; 57(Suppl. 2) xx–xx.

Fink L, Kwapiszewska G, Wilhelm J, Bohle RM. Laser-microdissection for cell type- and compartment-specific analyses on genomic and proteomic level. Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Garn H. Specific aspects of flow cytometric analysis of cells from the lung. Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Groneberg DA, Paul H, Welte T. Novel strategies of aerosolic pharmacotherapy. Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Hellings PW, Ceuppens JL. Mouse models of global airway allergy: what have we learned and what should we do next? Allergy 2004;59:914–9.

Hoymann HG. New Developments in Lung Function Measurements in Rodents. Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Lomask M. Further Exploration of the Penh Parameter. Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Nassenstein C, Möhring UH, Luttmann W, Virchow JC, Braun A. Differential expression of the neurotrophin receptors p75NTR, TrkA, TrkB and TrkC in human peripheral blood mononuclear cells. Exp Toxic Pathol 2006;57(Suppl. 2) xx–xx.

Pauluhn J, Mohr U. Experimental approaches to evaluate respiratory allergy in animal models. Exp Toxicol Pathol 2005;56:203–34.

Taube C, Dakhama A, Gelfand EW. Insights into the pathogenesis of asthma utilizing murine models. Int Arch Allergy Immunol 2004;135:173–86.