**CHAPTER 16**

**TITLE**

Application of Mouse Models to the Study of Asthma

**AUTHORS**

Fernando Marqués García, Elena Marcos Vadillo

**AFFILIATION**

Department of Clinical Biochemistry

University Hospital of Salamanca

Paseo de San Vicente, Nº 58

37007, Salamanca, Spain

**SUMMARY**

Phenotypic diversity of asthma complicates its study. Animal models represent a useful tool to elucidate the pathophysiological mechanisms involved in both allergic and non-allergic asthma, as well as to identify potential targets for the development of new treatments. Among all available animal models for the study of asthma, mice offer significant advantages. In this chapter the applications of mouse models to the study of asthma will be reviewed.

**KEY WORDS:**

Animal Models, Asthma, Mouse, Sensitization.

## 1. Introduction

Asthma is a complex and heterogeneous disease characterized by chronic inflammation of the airway, hyperresponsiveness and recurrent symptoms such as sneezing, coughing and breathing difficulty (**1**). This complexity is caused by multiple environmental as well as genetic factors (**1**), which defines different forms of the disease expression as the phenotypes (observable clinics characteristics) and endotypes (different pathogenic mechanisms) (**2**).

Currently, multiple animal models have been developed, not only for the study of asthma but also for other allergic diseases such as atopic dermatitis (**4**), allergic conjuntitivitis (**5**), food allergy and anaplysaxis (**6**) and allergic rinititis (**7**). These mouse models are important to elucidate the pathophysiological mechanisms of asthma, as well as to evaluate both safety and efficacy of treatment therapies (Preclinical Phase) before starting clinical phases in humans. In this chapter, we will focus on the study of mouse models appliedto asthma considering that asthma heterogeneity makes necessary the development of different models.

## 2. Mechanism of Asthma in Mouse

Animal models of asthma have been extensively used to examine mechanisms of asthma disease. Many advances in the understanding of the pathophysiology of asthma would not have been possible without these models (**8**). The different cytokine profiles associated to asthmawere initially described in mice (**9**). Indeed, most of the mechanisms that are discussed today derive from studies conducted in animal models. As an example,the classical Th2 paradigm involving interlukin-4 (IL-4) or interlukin-5 (IL-5) was discovered using animal models (**10**). However, these models only reflected allergic asthma. The identification of interleukin 17 (IL-17) orthe neutrophils participating in severe asthma or steroid resistant asthma, suggested that asthmatic disease was much more complex than what could be described by via Th1/Th2 paradigm. (**11**). These findings needed the development of appropriate mouse models that simulate the characteristics of these forms of asthma. Respiratory viral infections can trigger asthma. Sendai virus (related to the human parainfluenza virus) has been

administered to reach a chronic lung disease associated with airway hyperreactivity (AHR) in mouse (**1**). Asthma is also triggered by pollution. Mouse models have been exposed to ozone (a major component of aerial pollution) to develop AHR (**12**).

For the study of intrinsic asthma the strain A/J mice has been used. These mice spontaneously develop AHR without manipulation (**13**). The intrinsic AHR has been associatedto a chromosomal region containing *Adam33*gene. This association was firstly identified in a mouse model(**14**). The identification of genes associated with asthma in mice before they do in humans revealsthat animal models may be useful for the study of human asthma.

In summary, these models allow us to study specific pathways or genes related to different forms of asthma. This reductionist approach greatly simplifies the study of such a heterogeneous disease facilitating the understanding of mechanisms that would otherwise be difficult to elucidate.

## 3. Asthma Animal Models: Is Mouse the Ideal Model?

A wide variety of animal species have been used for the study of asthma (**21**). From the mouse to the horse, through the rat, dog, sheep, monkey have been used for studies of inflammation and impaired airway (**22-24**). Each has advantages and disadvantages as asthma model (Table 2). Besides the mouse, the species most used for experimentation in asthma are the guinea pig (**25**), sheep (**26**) and monkey (**27**).

Despite the variety of available animal, mouse is the most used model. The widespread use of the mouse for studies of asthma is due to the advantages over other animals. The choice of the mouse as a basic model is mainly based on scientific and economic reasons.

### 3.1 Scientific Reasons

Mouse is the most used model in multiple human diseases. This is due to the extensive knowledge we have obtained fromthe multiple genetic studies previously conducted (**28**) as well as the ease of handling for the generation of transgenic animals (**29**). With regard to allergic diseases, these animals are sensitized with ease, using allergens such as the ovoalbumin (OVA), and House Dust Mite (HDM) (**30**) or molds (**31**).

In addition, the existence of different mouse strains, which do not behave in the same way from the same allergen, is an advantage for identifying the mechanisms (**32**) (**33**) of inflammation and airway hyperresponsiveness.

The rapid expansion of transgenic technology in recent years has allowed the development of mouse models in which the selective expression of a gene is inhibited(Knock-out), or induced (Knock-in) (**34)**. These tools allow us to more clearly understand, the molecular pathways that are involved in the development of asthma (**35**).

### 3.2 Economics Reasons

Besides the scientific reasons previously exposed, there are also economic reasons that favor the use of mice asasthma model. Firstly, there are numerous commercially available mouse-specific probes for studying allergic outcomes, relatively cheapthat allow large studies to be conducted. In addition, mice are small easy handling animals so a high amount of them can be maintained in small areas.

Mice have also a short life cycle. Their gestation period is 21 days that facilitates the rapid procurement of animals for experiments. In this short gestational period they have large litters sum (6-8 mice) providingrapidly a lot of animals. In addition, they reach sexual maturity in a relatively short time (6-8 weeks).

In summary, mouse appears as a good model for conducting a variety of experiments aimed at elucidating the mechanisms involved in asthma.

## 4. Limitations of Animal Models in Asthma

Despite the undoubted advantages of animal models for the study of asthma, they also have limitations that must not be forgotten. These limitations must be always taken into account before choosing the model due to the influence that they may have on the results obtained. The limitations are related to the extrapolation of data to humans, adjuvants used, chronicity of the disease or anatomical differences among others.

### 4.1 Extrapolation of Data to Humans

The question that immediately arises after obtaining data on animal models of disease, including asthma, is how to extrapolate them to the disease in humans. Animal models used in the laboratory do not spontaneously develop a reaction ofasthma;this is the reason why different protocols are performed. This is an artificial experimentally induced asthma in the airway of the animal that has to be compared to the naturally developed asthma in humans.

### 4.2 Adyuvants

In a typical protocol besides the allergen, an adjuvant is usually added (**9**). This molecule modulates the immune response, acting as immune-enhancer ensuring animmune response sufficiently intense. One of adjuvants more used is aluminum hydroxide or Alum(**36**). Other adjuvants, used although to a lesser proportion, are heat-killed *Bordetella pertussis* (**37**) or the complete Freund's Adjuvant (**38**). The main problem of using adjuvants is that they may alter the mechanism of sensitization to the allergen under consideration, and they couldmodifythe immuneresponse(**34**).

To avoid these problems adjuvant-free models (**39**) or models that inoculate previously stimulated immune cells such as T lymphocytes (**40**) have been developed.

### 4.3 Chronicity of Asthma

In asthma, besides the inflammatory process, a remodeling of the airway occurs as a result of the chronicity of the disease.This remodeling involves goblet cell metaplasia and hyperplasia (**41**), mucus hypersecretion (**42**) and thickening of airway smooth muscle (**43**) due to the repeated exposure to the allergen. In addition, animal models initially respond to the intranasal allergen provocation, but if the provocationis prolonged in time the animal may develop tolerance (**44**). To avoid this, the provocation can be done with low doses of allergen maintained over time. With this strategy, mouse models that express the typical characteristics of chronic asthma have been developed (**45**).

### 4.4 Asthma in Early Life

The animals used for the study of asthma are normally adults. However, in human asthma can appear early in life. At that point, there are situations related to the appearance of symptoms such as in utero environment (**46**), viral infection (**47**), exposure to allergens (**48**) smoking and pollution (**49**) or pets (**50**) that should be considered. It is needed to develop models that allow us to study asthma in early life.

### 4.5 Anatomical Differences

It is important to highlight that the anatomical structure of the airway is not equal in rodents than in humans. Firstly, the position, animals arequadrupeds and due to gravity, this position may influence the effort madden by the lungs toinside moving air (**51**). This situation is aggravated by theairflowlimitation of the asthmatic reaction. Another important aspect is the morphology and arrangement of the bronchial tree that affects the penetration of the allergen into the lung. It has been reported an inverse relationship between body size, and relative airway caliberin rodents (**52**). In addition, mice exhibit a

thin smooth muscle layer causing the airway to constrict more easily (**53**), and a high number of goblet cells (**54**).

### 4.6 Size

The size of the animal greatly influences the lung function. For long time, it has been a challenge to design methods to evaluate lung function in small animals. Currently there are 3 types of methods:

- Noninvasive Methods.The most used is the whole body plethysmograph. The animal is placed in a chamber and the respiratory parameters are indirectly analyzed before and after the metacholine administration.
- Invasive Methods.The lung function is directly measured and it is considered the gold standard. The animal is anesthetized and a tracheal tube is introduced to measure lung volumes before and after the metacholine administration.
- Electrical field stimulation (EFS).Although the in vivo response to inhaled methacholine is the most widely used method of assessing the AHR, it was initially limited in the mouse due to the difficulty of delivering an aerosol to the airways. EFS has been described as an alternative method to assess AHR in mouse models.

## 5. Asthma Mouse ModelDesign

Currently, there are a variety of mouse models for the study of asthma. The general outline is based on an initial systemic sensitization followed by an aerial local elicitation. Depending on the hypothesis we want to assess, several aspects must be taken into account, basically, the mouse strain, the type of allergen, the route of administration, and the induction time among others

### 5.1 Mouse Strain

The availability of a high number of different mouse strains is an advantage. Mouse strains can be classified according to the capacity of develop airway inflammation and AHR. There are responder strains, such as A/J and AKR/J with high levels of AHR to methacholine (**55**) or non-responder strains, as the C3H/HeJ or DBA/2, that are resistant to allergen-induced AHR (**56**). However, the most used are the BALB/c and C57B/6strains because their immune response is well characterized. The immune response of BALB/c occurs via Th2 thattypicallyinduces allergic parameters, such as IgE production, AHR and eosinophilic inflammation of the airway; however, C57CL/6 has limitations in developing allergic airway response because the immune response occurs via Th1. This strain is used in many genetically manipulated mice.The different behavior of mouse strains is mainly due to genetic characteristics.

The development of genetic manipulation methods has favored the generation of mice to study the molecular mechanisms involved in asthma. Thus, mice that do not express a particular gene (Knock-out), or conversely that overexpress the gene of interest (knock-in) have been developed. A third modelisthe conditional knock-out mouse in which the expression of the gene of interest can be manipulated to the necessary extent.

### 5.2 Type of Allergen

A variety of allergens have been used in animal models. One of the most used allergen has been ovoalbumin (OVA) in both sensitization and challenge phases. It is cheap, well characterized and can be produced in large quantities (**57**). As already described, the continuous administration of the allergen can trigger tolerance in various mouse strains. At the stage of sensitization,OVA is usually injected with an adjuvant intraperitoneally. The challenge phaseis performed by air without adjuvant. The allergic induction caused by OVA is notthe same to that obtained by other allergens usually present in the environment. The generation of models that pathophysiology more approximate to

human asthma, requires allergens such as pollen, mods, or HDM, naturally present in the environment. These aeroallergens, suspended in the air, reach the airway directly, while OVA normally accessto the body through the digestive tract. The progress of biotechnological techniques is focused in generating isolated epitopes responsible for the asthmatic phenotype to achieve more specific and potent responses than those obtained with the extracts. Other models combine two or more allergens getting stronger inflammatory responses (**58**). Finally, the allergen concentrationvaries depending on the phase of reactionand the type of allergen.

### 5.3 Route of Allergen Administration

The route of allergen administrationdepends on the phase of the experiment. Thus, in the sensitization phase the intraperitoneal via is commonly used, while in the provocation phase the allergen is introduced by air to generate a local response. Nowadays, in the sensitization phase, it is common to replace the intraperitoneal route by the intubation, resembling what happens in human asthma (**59**). There are different strategies in the elicitation phase. The nebulization implies that the concentration of allergen does not penetrate far enough into the airway remaining in the upper respiratory tract. Other possibility is the application of allergen directly in the airway (**60-61**), on the nostrils of the mouse, via intra-tracheal or depositing the allergen into the lungs with the help of a bronchoscopy. The choice of the method to use is determined by the availability of material, as well as the technical skill at the laboratory.

### 5.4 Induction Time

In mice, the inductionof asthma can be achieved in short exposures to the allergen, days or weeks, or in longer periods of months. According to the exposure time there are two different models, acute or short-termand chronic or long-term model. In acute models high concentrations of allergen are used to shorty obtain the asthmatic response. These models are useful to study airway inflammation but do not reflect all changes that occur

in the human asthmatic response. However,in chronic models the exposure to the allergenfor longer periods,produce inflammation and airway remodeling as in human asthma development. As above-mentioned, the main problem of chronic models is tolerance that can be avoided by using low doses of allergen.

## 6. Mouse Models of Asthma

Most mouse strains do not spontaneouslydevelop AHR or allergy airway inflammation for this reason different inducing agents are used. The mouse models of asthma can be grouped according tothe phenotypes of human asthma. The models that have been conventionally developed are those aimed to study allergic asthma in acute or chronic modelsas previously seen. The deeper understanding of asthma has made that other classical asthma phenotypes were identified thus the non-allergic asthma models aroused. In these models,molecules like ozone, cigarette smoke, diessel particles or infectious agents can induce the response as respiratory virus although models of intrinsic asthma such as the strain A/J can be used. In addition to these classic models, genetically modified mice help to better understand the metabolic pathways involved in asthma. Finally, different types of purified blood cells from asthmatic patients can be transferred to nude mice SCID (Severe Combined Inmunodeficiency) simulating human asthmatic reactions in mice. All these models can also be used for the identification of new therapeutic targets for the disease as well as for the development of new drug therapies in asthmatic disease.

Mouse models represent an opportunity to study the mechanisms involved in asthma as well as to findtargets to develop new treatments. The challenge in this field is to develop mouse models that approximate more closely to human asthma, reflecting all the changes that occur in the disease.

## 7. Acknowledgement

This work was supported by a grant of the Junta de Castilla y León GRS1047/A/14.

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Tables

**Table 1. Advantages and Disadvantages of Diferents Asthma Animal Models**

| | Advantages | Disadvantages |
|---|---|---|
| **Mouse** | Short gestacional period<br>Easy manipulation<br>Asthmatic reaccion IgE-mediated<br>Small and Cheap | Not expontaneous AHR<br>Lung anatomical differents<br>Limited airway musculature |
| **Rat** | Asthmatic reaccion IgE-mediated<br>Response Airway late | Inmunological reagments not abundant<br>Need adyuvants for sensibilization |
| **Rabbit** | Asthmatic reaccion IgE-mediated<br>Response Airway late | Difficult manipulation |