

EDITORIAL

Clinical and Experimental Allergy

Using the mouse to model asthma: the cup is half full and then some

This editorial discusses the findings of the paper in this issue by G.R. Zosky et al (ref 14), pp ...

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Before 1989 most workers in the asthma field used a variety of animal species to investigate asthma pathogenesis. In a National Institutes of Health workshop report of 1989 it was pointed out that all animal models have virtues and shortcomings, but it was also pointed out that 'Because the mechanisms underlying airways hyperresponsiveness cannot be exhaustively investigated in human subjects because of limitations in experimental techniques, there is considerable interest in the development of models that can *simulate* the physiologic patterns of patients with hyperresponsive airways' [1]. At present a considerable part of what we know about the cellular, molecular, pathologic or physiologic aspects of lung function has been largely derived from animal experiments. Mice are currently all the rage in modelling all forms of human disease because the toolbox that we have to work with is so rich [2]. Currently, scientists have embraced the mouse almost to the exclusion of other species, so it seems likely that the mouse is here to stay for well into the foreseeable future. With this in mind, let us take a careful look at both the virtues and shortcomings of using mice as an experimental system to understand and determine the mechanisms causing the syndrome of asthma, and let us also try to answer the question – is the glass half full or is it half empty?

The glass is at the very least half full with regard to the usefulness of mice in explaining the causes or preventions of pulmonary pathology and airways dysfunction, in particular airways hyperresponsiveness (AHR) in response to antigen sensitization and challenge. The mouse was adopted as a model for a variety of reasons. First, when we originally developed the ovalbumin (OVA) model we chose the mouse because it had recently been shown (ca. 1989–1990) that asthma was predominately an aller-

gic phenomenon [3]. This made the mouse a logical choice because its immune system was being extensively explored by immunologists, and a vast array of reagents were readily available for this species [4, 5]. Indeed, if you pick up any catalogue for antibodies, cytokines, molecular probes or ELISA kits, there are literally orders of magnitude more items available for the mouse than any other laboratory animal. Second, the advent of techniques for altering the genome such as knockouts or transgenics made the mouse an obvious choice. These two factors together have subsequently turned the movement for using mice in unravelling the pathogenesis of allergic airways disease into a stampede.

The real payoff for using mice to explore asthma pathogenesis has been two outcomes. First, mouse systems have led to a real appreciation of the profound complexities of the immuno-inflammatory response to antigen challenge [5]. As such our understanding of the cell and molecular signals that occur at the initiation of the inflammatory response is becoming clearer and more complete. Second, there is no question that since the wide adoption of the mouse the identification of potential targets for therapeutic intervention has literally exploded. Just consider the number of targets associated with the T-helper type-2 cytokines such as anti-IL-4, IL-5 and IL-13 strategies, but there are many other examples. Based solely on these two outcomes alone, the mouse systems have, to date, outperformed any other species in the study of asthma pathogenesis [5–7].

Unfortunately, for some the glass is half empty because the mouse as a model system does have many significant limitations. This has resulted in a number of negative reviews that provide the reader with a long list of shortcomings that range from the trivial to the significant [8–11]. It will be decades before we will totally determine whether or not the mouse leads to significant changes in diagnosis and treatment of human patients with asthma. However, even if there is only one clinically significant outcome, the effort will have been worthwhile. A recent

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and potentially relevant example is chitinase. This is an enzyme that breaks down chitin, a primitive structural polysaccharide, but chitinase is also implicated in infections and inflammation. Using a mouse asthma system, workers at Yale showed that anti-chitinase ameliorated asthma-like outcomes [12]. In a recent paper in the *New England Journal of Medicine*, it has been shown that chitinase can be associated with asthma and asthma severity in humans [13]. Whether this finding will lead to a significant change in the treatment or diagnosis of asthma is unclear, but what is clear is that this association would never have even been looked for in humans without using the lessons learned from the mouse.

In the current issue of the journal, Zosky et al. [14] present a provocative set of data derived from carefully examining the mechanical response of the sensitized mouse lung to inhaled antigen to determine both the early asthma response (EAR) that occurs within minutes of antigen challenge and the late asthmatic response (LAR) that occurs 4–8 h after antigen challenge. In some species, such as the guinea-pig, rabbit or more pertinently man, EAR and LAR responses can be quite substantial [1]. However, as shown by Zosky et al. [14], the EAR and LAR responses either do not occur or are very small in magnitude in the mouse. As the authors correctly point out, these findings are consistent with data from our studies [15] and those of others [16]. The authors conclude that the mouse/OVA system is 'useful for studying mechanisms relating to increased responsiveness to bronchoconstricting agents but is limited as a model for acute allergen-induced responses'. Given the careful and skilful application of state-of-the-art techniques by these experienced investigators, this is a seemingly reasonable conclusion.

Is this apparent limitation of using the mouse to explore asthma pathogenesis really a surprise? I would submit it is not because of the non-typical anatomy of the airways of the mouse. To describe the airways of the mouse as huge is an understatement (Fig. 1), but they are huge relative to the rest of the lung for a very good reason. The normal mouse breathes with a 0.2 mL tidal volume but at 350–450 breaths/min [17, 18]. This high minute ventilation is apparently in support of a high metabolic rate so that large-diameter airways reduce airflow resistance and the work of breathing. In addition, the diameter of the airways is particularly large in the more central airways [19, 20]. Calculations of airflow resistance as a function of airway generation (Fig. 2) show that the central airways of mice are likely to contribute much less and the small airways more to total resistance compared with humans [21]. In addition, mouse airways have relatively little smooth muscle and constrict to a very limited repertoire of smooth muscle agonists [22]. Taken together it might be no surprise then that the EAR and LAR responses of the mouse to inhaled antigen are small or non-existent.



Fig. 1. This is a longitudinal (AP) section of a micro-computed tomography scan of a BALB/c mouse taken with techniques as previously described [23]. Note the size of the airways as compared with the ribs as a point of reference.

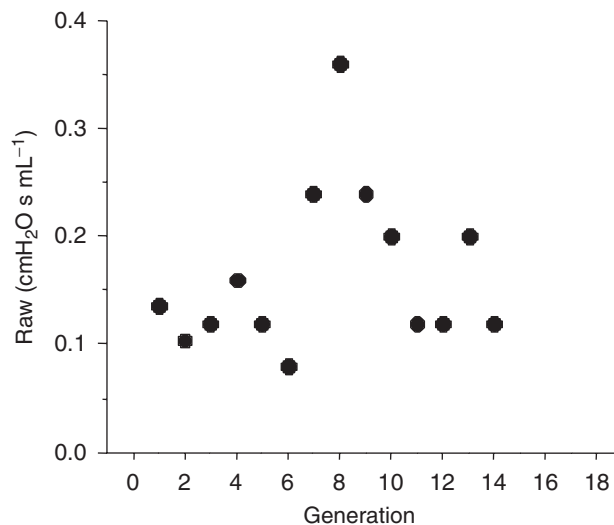


Fig. 2. Calculated airflow resistance of the airways of mouse lungs as a function of airway generation. The relationship was generated using the measurements of the mouse airway diameter [24] and the laminar flow equation (C. G. Irvin and J. H. T. Bates, unpublished observations). Note that there is little difference in airflow resistance as a function of airway generation. On the other hand, in the human lung the central airways (first 4–6 generations) have high resistance, whereas the small airways (<2.0 mm) have little contribution to total airflow resistance [19].

The big question is whether the mouse ever shows a marked bronchoconstricting response in any situation? Here the answer is yes; in fact, the mouse airways can respond in such an exuberant fashion that it compromises

life. We have recently shown that if eosinophils are targeted to and activated by eotaxin in the central airways, there is a significant change in baseline resistance and the animals have such severe bronchospasm that they die when challenged with low doses of inhaled methacholine [23]. In another study we have shown that in mice immunized and challenged with OVA, just as reported here by Zosky et al., the additional breaching of the epithelium with cationic proteins (that mimic the effects of eosinophil major basic protein) is also lethal [24]. These findings suggest that the large-diameter mouse airway is no real protection from severe airway narrowing. Taken together, one must conclude that either the mouse lacks a key mechanism to transduce antigen challenge to bronchoconstriction, or the epithelium of the mouse mounts a robust defence that prevents significant bronchospasm. It is only when it is compromised by insults such as cationic proteins that marked bronchoconstriction occurs.

There are some who will pounce on the results of Zosky et al. and claim that the mouse is useless for understanding asthma pathogenesis. But they will have failed to see that these modest responses to antigen may indicate the presence of profound protective mechanisms [24]. Moreover, these mechanisms may hold important clues to improving the defence of the airways of human asthmatics and potentially prevent fatal responses to inhaled antigens. In this regard I agree completely with Zosky et al. that finding a difference between mouse and human asthmatics is an advantage that needs to be exploited and not dismissed. I think we can safely conclude that the cup is not just half full, it is overflowing!

Acknowledgement

This editorial discusses the findings of the paper in this issue by Zosky et al. [14].

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