Mice Are Not a Good Model of Human Airway Disease

Spurred by dramatic developments in reductive biology, mouse models of asthma are now in extensive use. Who wouldn’t wish that a small, easily bred animal, in which you can do so much knocking in and out of genes and where so much immunology has already been put on the map (1), were a good model? However, as discussed in the following passages, reports of molecular and cellular mechanisms in allergic mice disregard or are unaware of the lack of asthma-like pathophysiology. Not surprisingly then, there is coincidence between the popularity of mouse models of bronchial asthma and the wishful thinking that mice are a good solution. The wishful thinking that mice are a good model of human airway disease is particularly problematic. In mice, lung accumulation of eosinophils is the prime outcome parameter. Yet the distribution of eosinophils, particularly in airway epithelium, differs between mouse and human asthma (4, 10). Because plasma exudation and eosinophil degranulation may correlate with disease severity, it appears logical to consider a mouse model exhibiting degranulated eosinophils in degranulated eosinophils (9). Meanwhile, it would be nice to see a model of eosinophilic airway inflammation and airway hyperresponsiveness in mast cell deficient mice. J Exp Med 1997;186:449–454.

Efficacy must be established in previously sensitized/challenged hosts.

Humans remain the best model of human disease. As a surrogate, murine models have and will continue to play a prominent and important role in the evolution of our thinking. To quote Yogi Berra, “You can observe a lot just by watchin’!”

Erwin W. Gelfand, M.D.
National Jewish Medical and Research Center
Denver, Colorado

References


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in vivo and as widely discussed based on in vitro and purely molecular data, simple epithelial restitution processes potentially contribute to disease by evoking many inflammatory and remodeling sequelae (12, 13). It is unfortunate, therefore, that evidence for epithelial injury repair in allergic mice is meager to nonexistent (4). The epithelium of mouse tracheobronchial airways is further aberrant by a dominant presence of Clara cells; it appears that transformation of Clara cells may explain the goblet cell metaplasia occurring in mouse models (4, 5). This latter feature is of interest in its own right. However, goblet cell metaplasia may also be treacherously interpreted as evidence of epithelial injury repair processes in allergic mice (14).

Mouse is not man and hyperresponsiveness is not hyperresponsiveness. Without knowing the involved mechanisms and accepting that it is not pathognomonic, we consider airway hyperresponsiveness a hallmark of bronchial asthma. But airway hyperresponsiveness is also used to describe an unexplained, exaggerated response of mouse lungs. How likely is it that this black box phenomenon in mice has any important mechanistic resemblance to asthmatic hyperresponsiveness where the pathology is so different from what you may see in mice? Lacking other phenomena hyperresponsiveness, nevertheless, is accepted proof of asthma-like physiology in mouse models (1, 4, 10).

So where do mouse models fit in? Their lack of similarities with human airway disease does not preclude utility in studies of development of allergy and tolerance (15). However, also considering late pathogenic and curative mechanisms, mouse experiments no doubt will continue to flourish. What one then can wish for is that critical tests of emerging murine concepts will also flourish, or at least that experimental shortcomings are spelled out as in a recent discussion of airway remodeling in mice (16). The author also hopes that the present debate as well as previous warnings of “the mouse trap” (4) will stimulate research into possible improvements of mouse models (17). Unfortunately, the hard work of really critical research is seldom undertaken, simply because it is not rewarded by the kind of appraisals of scientific work and journals that have evolved (2, 18). It is so much easier, and “successful,” to grab the novel technological and molecular advances that always emerge (2, 18). It is so much easier, and “successful,” to grab the novel technological and molecular advances that always emerge (2, 18). It is so much easier, and “successful,” to grab the novel technological and molecular advances that always emerge (2, 18). It is so much easier, and “successful,” to grab the novel technological and molecular advances that always emerge (2, 18).

No model can be properly validated unless we have sufficient undisputable knowledge about the human disease itself. Ann Woolcock ran a series of meetings aiming at brutal honesty regarding what we really know about “asthma: the important questions” (19); whether endothelium, epithelium, smooth muscle, eosinophils, or other cells, actual facts about roles and processes in asthma are rare. So we need to learn much more about the disease itself. Perhaps this cannot be accomplished unless the balance is shifted significantly toward patient-oriented research, where in vivo discoveries independent of mouse and in vitro paradigms are allowed, even encouraged (2, 20). Incidentally, the strategy of making such “surprise” discoveries in disease-relevant complex biosystems has produced the major asthma drug classes of today (2). The author concludes that progress in respiratory research has been slowed down by the false inference that a “furred, four-legged hypothesis generator” (16), the allergic mouse, provides a good model of human airway disease.

CARL G. A. PERSSON, M.D.
Department of Clinical Pharmacology
Lund University Hospital
Lund, Sweden

References


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REBUTTAL FROM DR. GELFAND

Pretentious, misdirected, problematic data, lack of awareness of asthma-like pathophysiology, and misguided efforts of hundreds of committed researchers characterize the “wishful thinking” that Dr. Persson has labeled the large amount of work performed in murine models. He advocates for more in vivo models of asthma, although these models are as readily available as patients are, but these studies are necessarily restricted. Asthma is not as simple as plasma exudation or epithelial injury and shedding, which have not necessarily been well-correlated with altered airway function. Asthma is a long-standing chronic syndrome, reflected in the heterogeneity from patient to patient and even the same patient at different time points.
Examination of a patient with asthma is not only limited but simply a snapshot in time, potentially resulting in overinterpretation and misleading information. If there was “undisputable knowledge about the human disease,” we would not need models. In the absence of such critical information, models and testable hypotheses are developed. Although the end results in mice and humans may show obvious or subtle differences, it is the means to get there that are critical—here is where studies in the mouse have provided not only essential information but have guided investigations of human asthma. To be specific, evidence, albeit limited, for mouse eosinophil degranulation has been presented (1, 2) but not accepted by Persson and colleagues (3). In humans, evidence for degranulation in vivo is also limited. Differences described between human and mouse eosinophils have been defined in in vitro systems primarily. Why then does Persson demand, for example, that valid extrapolation to asthma patients requires eosinophil degranulation in the mouse? This argument presupposes that all eosinophil effector factors are dependent on degranulation. Are all eosinophil effector factors dependent on degranulation in vivo? This argument presupposes that all eosinophil effector factors are dependent on degranulation. The value of a small animal model, independent even of the multiple genetic and immunologic tools and markers that mice provide, lies in its use in exploring biologic plausibility for asthma pathogenesis and therapeutic manipulations. To conclude that progress in human asthma research has been slowed by the work in mice is only an admission of comfort with old problems rather than attempting to find new solutions.

References

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REBUTTAL FROM DR. PERSSON

Dr. Gelfand provides an impressive but incomplete list of agents that are effective in mouse models but are not effective in asthma. The immediate conclusion then is that mice, although of use in studies of immune regulation etc., are not a good model of human airway disease. It is noteworthy that Gelfand acknowledges finally that he has been erring with regard to mouse eosinophil degranulation (1). May the future hold more concessions of this nature. One cannot be fooled by the gallant turns in Gelfand’s fandango-like performance as he attempts to defend the fantasy that asthma occurs in mice. A mischievous person (pun intended) is clearly hidden there.

Gelfand now proposes that heterogeneity in mouse systems “is equal to heterogeneity of human disease.” This kind of proposal may exemplify that if you use selected information at the molecular level you can claim almost anything. The term “heterogeneity” can also refer to diverging observations. But heterogeneity, just the same as hyperresponsiveness, is merely a label likely reflecting very different things in mouse models and in human asthma.

I appreciate Gelfand’s attempts to distinguish between the pharmacology of primary and secondary allergen challenges (2), and I agree that research on drug efficacy must focus on complex “downstream” conditions. Unfortunately, there is a severe imbalance between studies of “prophylactic” effects of drugs (administration before an allergen challenge) and studies of “curative” effects of drugs (administration when inflammation is already established). The latter is clinically relevant, but it is rarely studied in vivo—even in mice. Considering the broad “prophylactic” and narrow “curative” pharmacology of many drugs and drug candidates (2, 3), a shift in focus toward reversal of established airway inflammation would reduce the cornucopia of inflated promises of novel antiasthma drugs. This too, however, is an area where mouse models, lacking significant asthma-like pathology and pathophysiology, are insufficient.

Hopefully, the era of wishful thinking—everything is fine with current mouse models—is gone. Instead, let continuous criticism be a stimulus to the development of meaningful disease-like animal models using combined animal–human approaches. “Disease-like” primarily involves the major pathophysiologic processes, and then molecular medicine comes into the picture. Without getting the pathophysiology right, molecular “links” between model and disease may be of little value.

References

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