Modeling human lung disease in animals

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“All animals are equal but some animals are more equal than others.”
Animal Farm
George Orwell (1903–1950)

MODELING OF HUMAN DISEASE in animals forms the basis of much of biomedical research. Animal models have been used to explore normal physiology, the pathophysiology of human disorders, and to test the safety and efficacy of new therapies in preclinical studies. In the field of lung research, much of our understanding of lung physiology under normal and pathological conditions derives from classic studies in dogs and sheep, including studies of normal pulmonary function by Julius Comroe (6), studies of the distribution of ventilation and perfusion by James West (25), studies of the pulmonary vasculature and alveolar surface tension by Solbert Permutt (10, 18), and studies of the mechanisms of formation of pulmonary edema by Norman Staub (23, 24) and the resolution of pulmonary edema by Michael Matthay (15).

In lung-related biomedical research, animal models have been developed for most of the common human lung disorders including pneumonia, acute lung injury, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pulmonary hypertension. Although these models have been invaluable in improving the mechanistic understanding and testing potential treatment modalities for human lung disorders, all animal models have inherent limitations. For investigators, readers of the literature, and scientific reviewers of grants and manuscripts, an understanding of the pros and cons of animal models of human lung disease is critical. The need for every investigator to have a basic familiarity with animal models is illustrated by the fact that in the past six months, the majority (102 of 159) of the original articles published in The American Journal of Physiology–Lung Cellular and Molecular Physiology included animal models or experiments using primary cells or tissues derived from animals.

Some of the limitations of animal models of human lung disease are due to the differences between laboratory animals and humans. The normal anatomy and physiology of the lung differs among species. For example, the alveolar and airway architecture is fundamentally different between mice and humans (21). Mice have 6–8 generations of branching airways compared with 20 or more in humans. In mice, terminal bronchioles empty into alveolar ducts and alveoli (2), whereas in humans, respiratory bronchioles empty into alveolar ducts and alveoli. Pleural anatomy also differs substantially between species. The visceral pleura in humans is thin, whereas the visceral pleura in the dog, cat, monkey, and rabbit is thin (1). As another example, the normal rates of alveolar epithelial fluid transport differ markedly across species (4, 5, 7–9, 11–14, 16, 20, 22), as does the responsiveness of alveolar epithelial fluid transport to β-agonist stimulation (Fig. 1). These and other fundamental differences in anatomy and physiology complicate the interpretation of findings from animal models. Furthermore, certain species may not be suitable for modeling some aspects of human disease. For example, the distal lung epithelium of the rabbit, unlike most other species that have been studied (Fig. 1), is not responsive to β-agonist-induced stimulation of alveolar epithelial fluid transport (22), making this species a poor choice for studies of alveolar epithelial fluid transport in acute pulmonary edema. Also, while the DeltaF508 mutation of the cystic fibrosis transmembrane conductance regulator is the most common genetic cause of human cystic fibrosis, mice with the DeltaF508 mutation do not have any respiratory abnormalities (19).

Other important differences between animals and humans relate to living conditions and inbreeding. Most laboratory animals are kept in highly controlled environments with limited exposure to environmental pathogens that may affect innate responses to pathological processes. While inbreeding has the advantage of producing genetically identical offspring leading to highly reproducible experimental findings, it also may produce strain-specific phenotypes that are not relevant outside of that strain.

Beyond the limitations that are inherent to animal studies in general, one of the fundamental problems with animal models of human lung disease is that they do not adequately reproduce the underlying pathophysiology of human disease. For example, although acute lung injury can be modeled in dozens of ways in rodents, only acid aspiration and sepsis models such as cecal ligation and puncture mimic to any significant extent human etiologies of acute lung injury. Even in these models, the similarity between rodent acute lung injury and human acute lung injury is modest because the inability to provide...
prolonged intensive care to critically ill rodents limits the severity of injury that can be induced without death of the animal from shock or hypoxemia. The problem is even worse in lung conditions in which the underlying triggers are not known. For example, of the available models of pulmonary hypertension, there are currently none that adequately reproduce clinical disease (3).

Although fraught with limitations, there are still many advantages of animal studies. As any clinical investigator is well aware, the pace of human studies is slow, the majority of human tissues is not routinely accessible for research purposes, and there is a very limited opportunity for interventional studies. By contrast, large numbers of animals (especially rodents) can be bred and studied in short time periods, interventional studies are straightforward, and established and emerging tools for targeted manipulation of levels of gene expression facilitate insight into the function of mediators in both health and disease.

In this issue of AJP-Lung, we begin a series of reviews on Animal Models of Human Lung Disease with an invited review by Drs. Moore and Hogaboam on animal models of pulmonary fibrosis (17). The goal of this series of reviews is to familiarize the reader with the commonly used animal models of human lung diseases, including pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary hypertension, acute lung injury, and pneumonia. The strengths and limitations of various models will be discussed as will the degree to which individual models mimic human disease. It is our hope that these reviews will serve as a resource for lung investigators at all levels, both those engaged in animal research and those seeking to understand the literature. We encourage Letters to the Editor with questions or comments on these reviews.

REFERENCES


