Animal models of pulmonary fibrosis: how far from effective reality?

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IDIOPATHIC PULMONARY FIBROSIS (IPF) is a chronic and progressive lung disease, associated with high mortality rates and unresponsive to currently available treatments. Animal models are critical to identify and validate new therapeutic drug targets, a concept that is nicely highlighted by the review by Drs. Bethany Moore and Cory Hogaboam (7) in this issue of AJP-Lung. Dr. Lorraine Ware (9), in an Editorial also in this issue, points out the cautions and necessities of animal models for human diseases, and these are very prevalent in models of pulmonary fibrosis. In the review, the authors point out that the bleomycin model appears the most clinically relevant. While this is true for bleomycin-induced human pulmonary fibrosis, it has not provided relevance for the idiopathic form of disease (1). We (6) recently published a “meta-analysis” on the value of the bleomycin model for the development of useful therapies, which suggests that the clinical relevance of this model is questionable. These models have provided excellent indications of important molecules and cells involved in the fibrogenic process, yet have failed to provide convincing correlative preclinical data for any new effective therapeutic intervention for human disease.

This lack of effective correlation may be related to a number of reasons. Although we believe that some drug targets identified through animal studies, such as the transforming growth factor-β pathway of ligand activation, receptor binding, and intracellular signaling, are correct ones for human disease, it has recently been pointed out that we know far less about the pathogenesis of human IPF than of experimental fibrosis in mice and rats (3, 4). The other possible explanation of failed drug development in this area may be related to the fact that the assessment of drug efficacy in animals is vastly different from assessment of disease in human patients, and thus there are substantially different therapeutic goals. Basic scientists aim to prevent or completely dissolve scar tissue as a proof of principle, notably in a species that is known to have the ability to regenerate alveolar structure. In contrast, the progressively declining clinical course of patients with IPF, and lack of knowledge regarding the natural history of the disease, would make it a success if even the progression could be halted. Indeed, researchers in pharmaceutical drug development are increasingly aware that “we have relied a bit too much on animal models and fooled ourselves into thinking they tell us exactly what happens” (2), which should lead to a more skeptical look at the models, and recognize a need to find better ways to translate findings in animals to better management of human disease.

Moore and Hogaboam (7) point out the advantages and disadvantages of the various models. This makes clear that there is no single model that has the correct temporal, spatial, and dynamic development aspects that reflect the human condition. The duration of the models alone shows the lack of correlation to the human disease, a slow smoldering and progressive disease that may take 10–20 years to present, whereas the animal models hover around 21–28 days, a practical constraint, but perhaps also a serious limitation. A second and equally limiting aspect of the rodent models is in the methods of assessment of the fibrotic changes. Animal models are best assessed by pathology and biochemical measurements of matrix deposition. Human disease progression is measured best by lung function assessments and possibly CT scans, while pathology assessments are minimal. For measures of efficacy in an animal model to more directly translate to the human disease, we need to develop new rodent assessment approaches that reflect the human reality, such as microimaging and animal-specific lung function assessments.

Although mouse models have attraction for many reasons, the rat is still one of the most robust species to elicit consistent fibrotic responses, and rats have shown many of the morphological hallmarks of human IPF, including fibroblastic foci and honeycombing features (5, 8). Even this species suffers from the age consideration, given that rodents are usually used within weeks or a few months of birth, and the human disease does not develop until into middle age. As pointed out in the review, models are useful to discover possible new pathways of pathogenesis or resolution and need to be used appropriately. The human pulmonary disease is usually encountered at the chronic progressive stage. To use a model such as bleomycin in a clinically relevant manner, interventions should be initiated after the acute inflammatory stage has subsided and the fibrogenic phase is well underway, 10–15 days after the initiation. Given these caveats, the models described by Moore and Hogaboam (7) can provide important insights and possible new targets for therapeutic intervention in this devastating disease.

REFERENCES