Editorial

Do Experimental COPD Models Make Sense?☆

Modelos experimentales de EPOC. ¿Tienen sentido?

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The use of animal models of a disease usually progresses in parallel with research carried out on that disease, and generally follows 2 main lines: anticipating the value of a particular gene or biological marker and subsequently transferring this to the patient; or using animal models as a platform for an in-depth analysis of the pathways involved in a marker that was first detected in patients.

In COPD, most commonly used model is the murine model of exposure to tobacco smoke.

This model admittedly has some limitations, such as the absence of ciliated cells and goblet cells characteristic of the human bronchial epithelium in the murine bronchial epithelium, and its inability to model disease progression after stopping smoking. Nevertheless, it is a very versatile technique that offers multiple combinations. For example, pathological production of mucus can be achieved by combining the endobronchial administration of bacterial lipopolysaccharides (LPS) with exposure to tobacco smoke.[1] Other aspects of its versatility are the availability of a wide catalog of mutational variants, relatively easy access to specific antibodies, and lower costs than in other species. In short, experimental intervention in the regulation of molecular pathways is more accessible.

Many of the characteristics of COPD can be reproduced in animal models, including pulmonary emphysema and remodeling of the airways and pulmonary vessels.[2] Exacerbation models can also be reproduced by inducing viral or bacterial infections[3] or by administering toxins such as LPS.[4] Models can even be used to study associated systemic involvement, for example, in the muscles and skeleton.[5] The conventional patterns of exposure to tobacco smoke can only achieve mild-moderate disease intensities, but greater severity can be induced with the associated use of other toxic agents, such as intratracheal cadmium chloride or elastase[6] or with the use of especially sensitive mutants.[7] This versatility enables the design of targeted experiments to answer specific research questions. When a new hypothesis is being explored, animal models are the researcher's first choice due to their advantages over cell-based assays or tests performed directly in humans. However, the animal model must be carefully selected, depending on the disease characteristic to be examined or treated. The induced onset and progression of COPD are highly influenced by a complex interaction between the immune system and the mechanical properties of the lung tissue that cause chronic inflammation and tissue remodeling. Therefore, a model designed, let us say, for the study of a pathogenic metabolic pathway that participates in the onset of the disease will not be suitable for a therapeutic trial examining the advanced stages.

The use of models of chronic exposure to cigarette smoke increased after it was established that morphological and physiological manifestations of emphysema could be found, first in guinea pigs[8] and later in mice.[9] This exposure increases lung inflammation, protease activity, oxidative stress, and apoptosis, and in selected strains leads to the development of moderate emphysema and mild grades of small airway remodeling, with deterioration of lung function, vascular remodeling, and pulmonary hypertension.[2,10] Practically all possible features of COPD in patients can be found in the models.

Lung development and maturation differ among the different animal species, as does lung anatomy. Even within a given species, there is a marked variation between the different strains, with widely varying susceptibility and response to the injury-inducing agents. This means that individual susceptibilities to developing the disease among smokers can be investigated, although a finding in an animal model of COPD cannot always be transferred to patients. Many studies are looking for common genes and pathways that might help explain the differences in susceptibility or resistance to the development of COPD.[11] In the referenced study, different mouse strains, both susceptible and resistant to emphysema (transgenic and wild strains), were exposed to cigarette smoke for a period of 6 months during which gene expression in the entire lung was analyzed, and the results were compared with gene expression studies in the lungs of non-smokers and former smokers, with or without COPD. More differences than similarities were found when all pulmonary gene expression profiles were compared, both within the same mouse species, and when the results were compared with the expression profiles of patients with COPD. These findings show that responses in gene expression to cigarette smoke

are largely species- and model-dependent, but certain shared pathways can provide significant understanding of the biology that underlies individual susceptibility to exposure to cigarette smoke. Understanding these differences is important if therapeutic targets in COPD are to be translated from mouse studies to humans.

In addition to serving as a basis for research into metabolic targets, COPD models can also assist in the study of phenotypic variants of the disease, which are emerging as new platforms for study. For example, the combined administration of ovalbumin and tobacco smoke can induce mixed COPD/asthma, permitting analysis of the metabolic interactions characteristic of this presentation.[12]

Thanks to the use of the models, new therapeutic targets can be identified, and a multitude of experimental tests can be performed that would otherwise be impossible. We have evidence of regenerative therapy using mesenchymal cells,[13] growth factors,[14] and other commercial compounds.[15] Virtually all new treatments need a preclinical phase of animal experimentation before they can be applied to patients.

In short, experimental models continue to provide quality information on complex, interconnected immune pathways and continue to be essential for unraveling the role of those myriad genes whose action remains to be clarified, and, incidentally, for verifying the similarities of gene functions between humans and mice, the sword of Damocles of animal research.

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