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Review

Animal Models of Chronic Obstructive Pulmonary Disease☆

Sandra Pérez-Rial, Álvaro Girón-Martínez, Germán Peces-Barba*

Laboratorio de Neumología, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz-CIBERES-UAM, Madrid, Spain

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ABSTRACT

Animal models of disease have always been welcomed by the scientific community because they provide an approach to the investigation of certain aspects of the disease in question.

Animal models of COPD cannot reproduce the heterogeneity of the disease and usually only manage to represent the disease in its milder stages. Moreover, airflow obstruction, the variable that determines patient diagnosis, not always taken into account in the models. For this reason, models have focused on the development of emphysema, easily detectable by lung morphometry, and have disregarded other components of the disease, such as airway injury or associated vascular changes.

Continuous, long-term exposure to cigarette smoke is considered the main risk factor for this disease, justifying the fact that the cigarette smoke exposure model is the most widely used. Some variations on this basic model, related to exposure time, the association of other inducers or inhibitors, exacerbations or the use of transgenic animals to facilitate the identification of pathogenic pathways have been developed. Some variations or heterogeneity of this disease, then, can be reproduced and models can be designed for resolving researchers' questions on disease identification or treatment responses.

Modelos animales de enfermedad pulmonar obstructiva crónica

Palabras clave:
Enfermedad pulmonar obstructiva crónica
Modelo animal
Tabaco
Enfisema
Transgénico
Exacerbación
Autoinmune
Ensayos terapéuticos

RESUMEN

El desarrollo de modelos animales de una enfermedad ha sido siempre bien acogido por la comunidad científica porque permite realizar una aproximación a la investigación de determinados aspectos de la misma.

Los modelos animales de la EPOC no pueden llegar a reproducir la heterogeneidad de esta enfermedad y generalmente solo llegan a representar los estadios más leves de la misma. Además, la obstrucción al flujo aéreo, variable que determina el diagnóstico en un paciente, no siempre se tiene en cuenta en los modelos. Por este motivo, los modelos se han centrado en el desarrollo de enfisema, fácilmente detectable por morfometría pulmonar, sin prestar atención a otros componentes de la enfermedad, como la lesión de las vías aéreas o las alteraciones vasculares asociadas.

La exposición continua y prolongada al humo de tabaco se considera el principal factor de riesgo de esta enfermedad, lo que justifica que sea el modelo de exposición al humo de tabaco el más ampliamente utilizado. Sobre esta base de modelo podemos encontrar algunas variantes relacionadas con el tiempo de exposición, la asociación de otros inductores o inhibidores, las exacerbaciones o el uso de animales transgénicos que facilitan la identificación de las vías patogénicas. Es posible, por tanto, reproducir algunas variantes o heterogeneidades de esta enfermedad y diseñar uno u otro modelo que sea capaz de responder a una u otra pregunta de investigación, dirigida bien a una identificación patogénica y/o bien a una respuesta terapéutica.

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* Corresponding author.
E-mail address: gpeces@fjd.es (G. Peces-Barba).

Introduction

Chronic obstructive pulmonary disease (COPD) has a huge global impact, and clinicians must make use of all the tools available to tackle the many aspects of this disease. The development of animal models can help address problems such as under-diagnosis, frail exacerbator patients, and existing uncertainties about the development of one or other clinical form of the disease or its natural history (in which cases with minor and accelerated disease progression are mixed). Similarly, all new therapeutic trials are generally based on an earlier study in an animal model.

Smoking is the leading cause of COPD, but its ability to generate a permanent inflammatory response depends on the patient's susceptibility. For this reason, animal models of COPD developed by exposure to cigarette smoke are primarily chosen to study the pathogenic mechanisms of the disease and of susceptibility to development and progression. In these cases, the use of transgenic animals, in which a particular metabolic pathway is inhibited or activated, helps researchers understand the pathogenic pathways that exist in each case. Likewise, new approaches to the classification of COPD proposed by both the GOLD initiative[1] and Spanish COPD guidelines (GesEPOC)[2] place greater emphasis on exacerbations due to their effect on the severity of symptoms, progression of the obstruction, and mortality. For this reason, interest has grown in the study of exacerbations in models of COPD, and the results may help to improve knowledge of the mechanisms underlying the condition in the exacerbator patient.

When evaluating the results of studies in animal models of any disease, the limitation of having to extrapolate a conclusion as to what is potentially present in a patient must always be taken into consideration. However, they are an essential part of clinical research when used as "preclinical models", an increasingly widespread term that encompasses the notion of translation into clinical practice that must form the basis of any study design.

Models of Cigarette Smoke-Induced COPD

Models of cigarette smoke-induced COPD are those that best reflect the inflammatory and pathogenic mechanisms of the disease and, consequently, those that are potentially better suited to testing new therapies. Exposure to cigarette smoke has been applied in numerous animal species, such as dogs, guinea pigs, rabbits, rats, and mice. Of these, guinea pigs and mice have proven to be most susceptible to the development of COPD through prolonged exposure.[3] There are two general procedures for administering cigarette smoke: the so-called "*nose only*" method, where the smoke is channeled directly into the animal's nose, and "*whole body*" administration (Fig. 1), where the animal is placed in a chamber filled with a controlled concentration of smoke to ensure complete exposure to stable, non-toxic carboxyhemoglobin levels.[4,5] Conceptually different, both methods have been widely used, and have shown similar findings as regards the presence of inflammatory cell populations, cytokine levels, changes in lung remodeling, and therapeutic response[6] (Fig. 2).

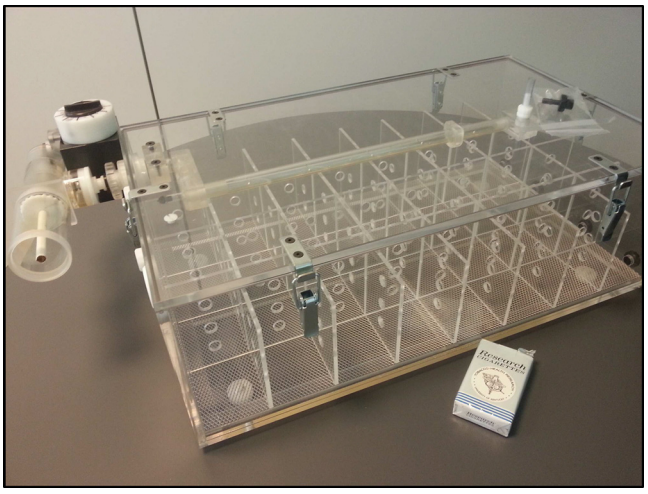

Fig. 1. Whole body tobacco exposure system.

In approximately 90% of patients, COPD is caused by smoking an average of at least 10 pack-years, and they develop a disease that can take different clinical forms, with different levels of progression and severity.[7] Animal models of COPD, guinea pig or murine are usually established over a 6-month exposure period,[8] although major inflammatory and morphometric changes can already be detected after the second month.[9] They do not usually reach the stage equivalent to severe COPD in a patient, but they can develop many of the characteristics typical of this disease, such as chronic inflammation with increased neutrophil and macrophage counts, presence of CD4 and CD8T lymphocytes, mucus hypersecretion, changes in lung function, emphysema, and vascular and airway remodeling.[10]

The murine model of cigarette smoke exposure is the most widely used, due to its low cost and easy management, well-mapped genome, the availability of many transgenic variants, a wide range of specific antibodies for laboratory use, and a large number of strains with differing susceptibilities to cigarette smoke. Strain-dependent susceptibility for developing COPD is well identified in the murine model,[11–14] and the pulmonary morphometric pattern of COPD can be generated when mice are exposed to cigarette smoke for at least 3 to 6 months, with typical inflammatory cells, inflammatory mediators and functional changes characteristic of the disease.[15]

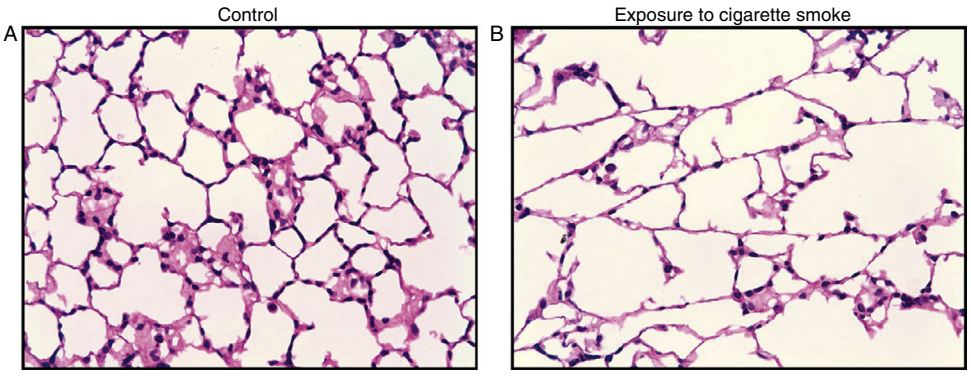

Fig. 2. Histological sections (H&E) of the lungs of mice exposed to ambient air (A) and mice exposed to tobacco smoke for 6 months (B), showing emphysema.