Meeting report

First Siena International Conference on Animal Models of Chronic Obstructive Pulmonary Disease, Certosa di Pontignano, University of Siena, Italy, September 30–October 2, 2001

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Abstract

The meeting proved of great interest to those developing an animal model of chronic obstructive pulmonary disease (COPD). COPD is caused by cigarette smoking, evidenced by deterioration in lung function. Lung function is only rarely assessed in animal models. A cigarette smoke driven pathology should provide the best *in vivo* model for COPD. However, as lesions produced this way take 8–12 months to develop other strategies have to be employed. Emphysematous lesions were also achieved by treatment with elastase, lipopolysaccharide, ozone and other inducers. Several studies described treatments that have shown activity in these models. Transgenic models were discussed, as was the importance of species and strain selection.

Keywords: animal models, COPD, cigarette smoke, elastase, lung function

Introduction

The meeting was attended by approximately 80 people and was designed to bring together an international group of academic investigators and industrial scientists in a forum that would foster discussion and exchange of ideas. The purpose of the meeting was to assess current animal models of emphysema and COPD, and to promote the use of new technologies. The immediate goal was to accelerate the translation of information gained from the development of animal models to improvements in patient care. Specifically, the formal presentations and informal discussions held during the conference addressed aetiological factors in COPD, and emphasized transgenic technologies and naturally occurring genetic variants. The objectives of the programme were to consolidate our present understanding of lung and airway inflammation, and its involvement in the pathogenesis of COPD caused by cigarette smoking, ageing and genetic predisposition; and to promote further imaginative investigations.

Lung physiology and lung function

Dr A. Ten Have-Opbroek (Leiden University, Leiden, The Netherlands) presented an overview of lung development, stating that animal models may contribute to our insight into the pathogenesis of human COPD because there are major similarities in lung development and lung structure between mammals. Many attendees presented data at the meeting on the pathogenesis of emphysema/COPD, whereas little was presented regarding function of the lungs. The use of pathology to establish the presence of disease allied to an assessment of lung mechanics may provide a more meaningful assessment in the animal model of choice.

COPD=chronic obstructive pulmonary disease.

Dr M. Rubio (Fundacion de Jimenez Diaz, Madrid, Spain) presented work in the rat. Intratracheal instillation of cadmium chloride was used to induce lung fibrosis, and instillation of elastase was used to generate an emphysematous pathology. Forty-five days after instillation lung function was assessed and significant changes were demonstrated with both treatments, effects that could be reversed by oral administration of the antioxidant *N*-acetylcysteine. This clearly demonstrates that emphysema-induced changes in lung function can be demonstrated in the rat, and informal discussions at the meeting revealed that work is underway to develop equipment to allow similar measurements in the mouse. This will be a significant step forward in the assessment of these models, not least because many groups are using the mouse as their animal of choice. As mentioned below, Dr. P. Belloni (Roche Bioscience, Palo Alto, California, USA) also measured changes in lung function after elastase treatment in the rat.

Smoking models

Dr J. Wright (University of British Columbia, Vancouver, British Columbia, Canada) provided an overview of cigarette-smoke-induced models, highlighting the time needed to produce lesions (up to 12 months in some species) and the importance of the choice of animal and strain. Of people who smoke 15–20% develop COPD, and the lesions produced in these models are similar to those observed in humans.

Dr C. Hobbs (Lovelace Respiratory Research Institute, Albuquerque, New Mexico, USA) outlined a study in which the responses to chronic exposure to cigarette smoke in the rat and mouse were compared. That work revealed a greater inflammatory and emphysematous response in the B6C3F1 mouse than in the F344 rat. These changes were seen in the mouse after 7 and 13 months of exposure to cigarette smoke for 6 h/day, 5 days/week, and were progressive.

A poster from Dr M. Fitzgerald (Bayer, Stoke Poges, UK) described the effect of BAY 15-7496, a potent inhibitor of matrix metalloproteinases, on cigarette smoke exposure in mice. Short-term exposure to cigarette smoke for 4 or 20 min elicited an acute inflammatory response. Interestingly, an analysis of the cells involved showed only macrophage and epithelial cells, with no neutrophil influx evident. After long-term exposure to cigarette smoke (6 days/week for 14 or 26 weeks), a significant degree of emphysema developed. Treatment with BAY 15-7496 (10 mg/kg twice a day) throughout exposure to cigarette smoke almost completely abolished the emphysematous response, thus supporting a role for matrix metalloproteinases in the development of cigarette-smoke-induced emphysema.

Dr J. Hogg (McDonald Research Laboratory, Vancouver, Canada) presented data demonstrating that latent adenovirus infection enhances the emphysematous destruction of lung in guinea pigs after exposure to cigarette smoke. An interesting observation was that both exposure to cigarette smoke and adenovirus infection increased levels of neutrophils and alveolar macrophages, whereas only the former increased $CD4^+$ lymphocytes and only the latter increased $CD8^+$ lymphocytes. Also of interest was that, contrary to other studies [1], retinoic acid had no effect on the inflammatory response or the emphysematous changes observed in that study. However, Dr P. Belloni (Roche Bioscience) presented data suggesting that retinoids selective for the retinoic acid receptor-γ or retinoic acid analogues (e.g. all-trans retinoic acid) are necessary to promote alveolar repair by inducing anabolic pathways similar to those activated in late-stage lung development. By measuring lung function in an elastase-induced model of emphysema in the rat Dr Belloni demonstrated an increase in lung resistance and capacity after elastase treatment. This increase was partly reversed by retinoid treatment, but reversals of elastase-induced changes in forced expiratory volume/forced vital capacity or forced expiratory $flow_{25-75}$ were not seen.

Dr Tralau-Stewart (GlaxoSmithKline, Stevenage, UK) described work in a 3-day model of cigarette smoke exposure in mice in which cigarette-smoke-induced neutrophilia was inhibited by pretreatment with the p38 kinase inhibitor SB 239063.

Other models

Smoking accounts for 85–90% of cases of COPD in humans and, although a cigarette-smoke-driven model would be desirable, Dr Tralau-Stewart (GSK) also discussed a variety of other animal models and outlined the approaches necessary to develop drugs for the treatment of COPD. Mechanistic models that mimic certain aspects of the disease are widely used in drug development to identify and optimize candidate compounds. Models that employ ozone, lipopolysaccharide, sulphur dioxide, nitrogen dioxide and diesel particles have all been used to produce aspects of COPD such as cough, inflammation and mucus hypersecretion. Elastase has been used in a variety of species. Dr Tralau-Stewart and coworkers have demonstrated inhibition in an ozone-induced model of COPD with the p38 kinase inhibitor SB 239063; inhibition of neutrophilia in an lipopolysaccharide-driven model with GW 311616, an elastase inhibitor; and, in a multidose lipopolysaccharide model, they demonstrated efficacy of the steroid, fluticasone. Dr Tralau-Stewart stressed the need to look for improved methodologies and protocols, and end-points other than pathology with biomarkers and lung function being the desired goal.

Transgenic models

Several authors presented work with different transgenic mice. Dr P. Martorana (Siena University, Siena, Italy)

described the development of spontaneous emphysema in the pallid mouse, an animal that has reduced elastase inhibitory capacity. Development of emphysema is slow, taking 8–12 months, but can be accelerated by treatment with formyl-methionyl-leucyl phenylalanine or exposure to cigarette smoke. Dr Suga (Gunma University, Japan) described work with the Klotho mouse, which develops airspace enlargement early in life. However, there was some discussion as to whether this was due to alveolar destruction or a lack of septation with development. The same argument could be levelled at transgenic mice expressing transforming growth factor-α, a model described by Dr W. Hardie (Children's Hospital Medical Center, Cincinnati, OH, USA). However, in this model Dr Hardie and coworkers confirmed the importance of the gene by conditional expression in adulthood, which resulted in the development of significant alveolar emphysema.

Strain variations

Dr B. Bartalesi (Siena University, Siena, Italy) described a study employing several strains of mice in which neutrophil influx into the airways was induced by formyl-methionyl-leucyl phenylalanine instillation. This influx resulted in the development of significant emphysema in pallid mice and C57Bl/6J mice; both of these strains have a lower serum elastase inhibitory capacity, unlike the NMRI mouse, which has higher elastase inhibitory capacity and which did not develop emphysema. The degree of lung destruction correlated inversely with the elastase inhibitory capacity. It was therefore suggested that treatments that induce neutrophil influx into the lungs would only result in emphysema in animals with reduced elastase inhibitory capacity, an important consideration when developing a model of emphysema.

In a poster (outlined above), Dr M. Fitzgerald (Bayer) examined the effects of cigarette smoke exposure in two different strains of mice. Dr Fitzgerald suggested that, after long-term exposure, a faster development of emphysema (in approximately half the time) occurred in A/J mice when compared with C57Bl/6J mice. Those data also suggested a greater inflammatory response in the A/J mice after short-term exposure to cigarette smoke.

Dr G. Lungarella (Siena University, Siena, Italy) also stressed the importance of strain selection and stated that it is important to determine the antiprotease and antioxidant status of the chosen model. That investigator showed that C57Bl/6J and DBA/2J mice (reduced antielastase and increased sensitivity to oxidants) were more responsive to cigarette smoke exposure than were ICR mice (normal antielastase and lack of sensitivity to oxidants).

Conclusion

It was evident from this meeting that a great deal of effort is going on worldwide to produce animal models of COPD that are both predictive of the human condition and user-friendly to the experimentalist. Animal models that may be of great benefit to the study of the mechanisms involved in the development of COPD were described. The importance of animal and strain selection was stressed and the need to use cigarette smoke as a stimulus wherever possible was also highlighted, whereas other possible approaches to the induction of emphysema were also described. It was evident from the meeting that much more needs to be done in this field and that the importance of having robust animal models of the disease that are generally available is paramount. In conclusion, the meeting was very successful and provided plenty of food for thought for both the academic and industrial scientists.

Reference

1 Massaro GD, Massaro D: **Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats.** *Nat Med* 1997, **3**:675-677.