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Establishing the phenotype in novel acute and chronic murine models of allergic asthma

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Abstract

Allergic asthma is a chronic disease of the airways, with superimposed acute inflammatory episodes which correspond to exacerbations of asthma. Two novel models of allergic asthma have been developed in mice receiving the same allergen sensitisation, but with acute or chronic allergen exposures, the latter to mimic the human situation more closely. Ovalbumin-sensitised mice were challenged by ovalbumin inhalation twice on the same day for the acute model, and 18 times over a period of 6 weeks for the chronic model. Lung function was monitored in conscious, unrestrained mice immediately after the last challenge for up to 12 h. Airway responsiveness to inhaled methacholine and serum antibody levels were determined 24 h after challenge. Bronchoalveolar inflammatory cell recruitment was determined at 2 or 24 h.

Acute and chronically treated mice had similar early and late asthmatic responses peaking at 2 h and 7–8 h, respectively. IgE and IgG antibody levels, compared with naïve mice, and eosinophil infiltration, compared with naïve and saline challenge, were elevated. Airway hyperresponsiveness to methacholine was observed 24 h after challenge in both models. The acute model had higher levels of eosinophilia, whereas the chronic model showed hyperresponsiveness to lower doses of methacholine and had higher levels of total IgE and ovalbumin-specific IgG antibodies. Both novel murine models of allergic asthma bear a close resemblance to human asthma, each offering particular advantages for studying the mechanisms underlying asthma and for evaluating existing and novel therapeutic agents.

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1. Introduction

Ascertaining whether asthma is present in humans is usually based on the presence of clinical symptoms such as episodic cough, wheezing, breathlessness and chest tightness and on a characteristic history and variability in lung function measured

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with spirometry or peak-flow measurements [1]. However, a diagnosis based largely on consistent symptoms and home peak-flow reading is often inaccurate due to poor patient technique and compliance, requiring further investigation [2]. *In vivo* animal models of the disease help to understand the pathogenesis of asthma permitting the study of parameters that would be difficult to assess in humans and have ethical problems. An ideal animal model should resemble the major features of human asthma. Asthma is a chronic disease of the airways characterised by the chronic presence of inflammatory cells such as eosinophils, mast cells and T lymphocytes, with superimposed acute inflammatory episodes which correspond to exacerbations of asthma [3—5]. In addition, asthmatic airways undergo chronic airway remodelling that, together with the accumulation of inflammatory cells, may contribute to the development of airway hyperresponsiveness (AHR). This consists of an exaggerated response of the airways to a variety of non-specific stimuli contributing to exacerbations of asthma [6,7].

Allergic asthma is the most prevalent type of asthma affecting two thirds of the total asthmatic population and 80% of asthmatic children and adolescents [8,9]. The acute asthmatic response after antigen inhalation in sensitised atopic asthmatic patients results in an early asthmatic response (EAR) which develops immediately after challenge reaching a maximal bronchoconstriction between 15 and 30 min and generally resolving within 1—3 h [10,11]. The EAR is the result of an immediate IgE-dependent type I hypersensitivity reaction driven by the activation of mast cells, alveolar macrophages, dendritic cells and airway epithelial cells among others [12]. These cells release mediators such as histamine, prostaglandins, leukotrienes and thromboxanes that are involved in the bronchoconstriction, mucus secretion and microvascular leakage observed during the EAR. In addition, these mediators release cytokines and chemotactic factors that are essential for the recruitment and activation of further inflammatory cells involved in the development of the late asthmatic response (LAR) in some patients [10,12]. Depending on the intensity and duration of the stimuli, approximately 60% of asthmatic patients are dual responders eliciting two temporally distinct bronchoconstrictor responses [13,14]. This LAR is characterised by a slowly progressive and persistent bronchoconstriction that begins 3—4 h after allergen provocation, peaks between 6 and 12 h and generally resolves within 24 h [13]. The late phase response develops as a result of activation of inflammatory cells which release pro-inflammatory mediators contributing to the development of allergen-induced AHR [11] and perpetuating the asthmatic inflammatory response [12] typical of chronic human asthma.

Animal models have been developed to study the pathogenesis of asthma. Guinea-pig models of asthma can provide the essential hallmarks of asthma, including dual bronchoconstrictor responses (EAR and LAR) [15—18]. However, asthma models in mice are potentially more useful due to the fact that their immune system has been extensively characterised, genetically modified animals (knockout, transgenic and immunodeficient mice) are available and a wide range of species-specific reagents can be obtained [9,19]. Different protocols have been employed for induction of allergic asthma in mice, and can be differentially classified into acute or chronic models depending on the number of exposures to the allergen. Acute models of allergic asthma expose the animals to the allergen over a relatively short period of time, obtaining an asthma-like phenotype that resembles human asthmatic airways during exacerbations of the disease. On the other hand, chronic models expose the animals to the allergen over longer periods to mimic the recurrent long-term exposure to low concentrations of allergen experienced by people with asthma [9]. In this report, we compare the effects of acute and chronic exposure to allergen on asthmatic hallmarks developed in two novel murine models of allergic asthma receiving the same sensitisation. While there have been a number of studies using acute and chronic exposures of mice to allergen, this study describes for the first time a chronic murine model of allergic asthma that displays both EAR and LAR, alongside measures of AHR, serum antibody levels and lung inflammatory cell counts.

2. Methods

2.1. Sensitisation and challenge

Male BALB/c mice weighing 20—25 g were maintained under conventional animal housing conditions receiving food and drinking water *ad libitum*. All studies complied with the guidelines for the care and use of laboratory animals according to the Animals (Scientific Procedures) Act 1986. All mice except the naïve animals were sensitised on days 0 and 5 by i.p. injection of ovalbumin (OVA, 100 μg/mouse) and aluminium hydroxide (10%, 50 mg/mouse) in phosphate-buffered saline (PBS). Twelve days after the last injection, mice in the acute group (Ac O/O) were challenged by inhalation of a 0.5% (w/v) OVA aerosol in 0.9% sodium chloride solution (saline) twice on the same day, 4 h apart. Mice in the chronic group (Ch O/O) were challenged over a period of 6 weeks by inhalation of a 2% (w/v) OVA aerosol in saline for 30 min/day on 3 days/week (18 challenges). The choice of the sensitisation protocol was based on preliminary studies in our laboratories involving a fully characterised asthmatic model in guinea-pigs [20], whereas the choice of challenge protocols was based on successful models described in the literature for acute [21] and chronic [22] models. We used a higher concentration of OVA in the chronic model because it is known that tolerance can develop to repeated exposures to inhaled antigen in both humans [23] and mice [24]. The aerosols were delivered by a PulmoStar nebuliser (Sunrise Medical, Stourbridge, U.K.) to a polystyrene exposure chamber (14.5 cm×28.5 cm×15 cm) in which groups of mice were contained. Mice in control groups Ac O/S and Ch O/S were sensitised with OVA and aluminium hydroxide but challenged with saline for the same period of time as the respective group O/O. Naïve animals were not challenged.

2.2. Non-invasive determination of airway function

Airway function was measured in unrestrained, conscious mice by barometric plethysmography using a single chamber, whole-body plethysmography (WBP) system (Buxco Research Systems, Winchester, U.K.) according to the manufacturer's instructions. Enhanced pause (Penh) was used as a measure of airway responsiveness as described by Hamelmann et al. [25]. For determination of allergen-induced changes in airway function (EAR and LAR), Penh was assessed by placing the animals in the chamber singly for a period of 1 min. Penh values were measured before the challenge (baseline reading) and then at 0, 20, 40, 60, 90 and 120 min after the last OVA or saline challenge for all groups. Penh was then assessed every 60 min during the first 10 h after challenge with a final readout 24 h after the first challenge for the acute groups and 24 h after the last challenge for the chronic groups. Results are expressed as mean

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