Molecular Immunology 66 (2015) 97–105

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Asthma "of horses and men"—How can equine heaves help us better understand human asthma immunopathology and its functional consequences?

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ARTICLE INFO

Article history:
Received 15 July 2014
Received in revised form
30 November 2014
Accepted 7 December 2014
Available online 26 December 2014

Keywords:
Animal model
Asthma
Immunology
Horse
Airway remodeling
Inflammation

ABSTRACT

Animal models have been studied to unravel etiological, immunopathological, and genetic attributes leading to asthma. However, while experiments in which the disease is artificially induced have helped discovering biological and molecular pathways leading to allergic airway inflammation, their contribution to the understanding of the causality of the disease has been more limited. Horses naturally suffer from an asthma-like condition called "heaves" which presents sticking similarities with human asthma. It is characterized by reversible airway obstruction, airway neutrophilic inflammation, and a predominant Th2 immune response. This model allows one to investigate the role of neutrophils in asthma, which remains contentious, the regulation of chronic neutrophilic inflammation, and their possible implication in pulmonary allergic responses. Furthermore, the pulmonary remodeling features in heaves closely resemble those of human asthma, which makes this model unique to investigate the kinetics, reversibility, as well as the physiological consequences of tissue remodeling. In conclusion, heaves and asthma share common clinical presentation and also important immunological and tissue remodeling features. This makes heaves an ideal model for the discovery of novel pathways implicated in the asthmatic inflammation and associated tissue remodeling.

1. Introduction

Major discoveries related to human diseases have been gained through animal experiments. It is undoubted that mice models have helped uncovering novel immunological mechanisms responsible for the development of different disease processes. Nevertheless, therapeutic strategies derived from these studies have been for the most part disappointing when translated to human diseases, including asthma (Clienti et al., 2011; Giembycz and Newton, 2011; Nair et al., 2012). This may be in part due to different transcriptional responses to acute inflammatory insults in mice and men (Seok et al., 2013).

Development of animal models better mimicking human diseases not only in their clinical presentation, but also taking into account genetic diversity and the complexity of immunopathological mechanisms leading to disease ontogeny, is considered crucial for the discovery of novel therapeutic approaches (Hein and Griebel, 2003). Domestic animal species spontaneously develop diseases having striking similarities with human conditions. Lifespan and size of large animals are more similar to men than to rodents, as is their developmental, innate, and mucosal immunity. For instance, mice lack the gene encoding for the interleukin-8 (Hol et al., 2010), a cytokine implicated in severe neutrophilic asthma and in respiratory virus-induced asthma exacerbations (Nakagome et al., 2012; Rohde et al., 2014), and also essential for neutrophil recruitment in men, cattle, and horses (Caswell et al., 1999, 2001; Cook et al., 2009; Douglass et al., 1996; Franchini et al., 1998; Kaur and Singh, 2013).

2. Equine heaves, as a naturally occurring model of asthma

Horses naturally develop an asthma-like condition currently known in the veterinary scientific community as "heaves" or RAO (recurrent airway obstruction) (Robinson, 2001). This condition has also been known in the past as chronic bronchiolitis, broken-wind, hay sickness, emphysema, small airway disease, allergic airway disease, and chronic obstructive pulmonary disease. As "heaves" was the term used to introduce the horse as an animal model for asthma,

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http://dx.doi.org/10.1016/j.molimm.2014.12.005
0161-5890/

we will employ this term in this review. The name "inflammatory airway disease" (IAD) has been coined to describe a milder form of equine respiratory inflammatory disease in which no respiratory effort is observable at rest. It is characterized by mild clinical signs (nasal discharge, cough, decreased athletic performance) detected in the presence of inflammatory abnormalities of the bronchoalveolar lavage fluid (BALF) cytology (Couetil et al., 2007). It has recently been proposed that heaves and IAD in all their clinical variants are grouped together under the definition of "equine asthma" (Lavoie, personal communication).

Both human asthma and equine heaves are heterogeneous diseases which might present in a variety of clinical forms depending upon the stage of the disease, the chronicity of the condition, and possibly upon different pathogenetic pathways leading to its development. We recognize that not all forms or stages of human asthma necessarily share the same attributes as equine heaves. Based on the definition of the most recent GINA guidelines (GSAMP, 2014), we believe that heaves represent an ideal animal model for the study of non-allergic asthma, late-onset asthma, and severe asthma.

2.1. "Heaves" and asthma

Heaves is a chronic obstructive respiratory condition naturally affecting 10–15% of adult horses living in temperate climates (Hotchkiss et al., 2007). It shares remarkable similarities with human asthma (Table 1). In heaves, disease exacerbations, during which horses suffer from respiratory distress episodes comparable to those affecting severe asthma patients, are triggered by inhalation of environmental antigens (Pirie et al., 2003). It had been postulated that heaves was analogous to allergic pneumonitis in man (Farmer's lung disease), as moldy hay is an important triggering factor for both diseases. However, these two conditions are otherwise different in their clinical presentation, lung pathology, and underlying immunopathological mechanisms. For instance, bronchiolitis and alveolitis with granuloma formation and extensive fibrosis leads to a restrictive respiratory pattern in allergic pneumonitis (Costabel et al., 2012), while in heaves these changes are not present.

The exposure to hay and dusts leading to heaves is rather a consequence of the human influence on horses' natural environment. Molds and fungi are indeed common antigens in the stables, suggesting that heaves is a disease of "domestication". However, horses can develop a similar condition while at pasture, with grass pollen being then the likely triggering factor (Dixon and McGorum, 1990; Seahorn and Beadle, 1993). Therefore, the antigens toward which horses develop an asthma-type response vary according to environmental exposure.

During clinical exacerbation of heaves, horses develop a pulmonary neutrophilic inflammation (Jean et al., 2011) (Fig. 1). While asthma is commonly described as an eosinophilic disease, it is now recognized that neutrophilic inflammation may be present in asthma of all severities, although it is more common in severe asthmatic patients and during acute disease exacerbations (Nakagome et al., 2012; Qiu et al., 2007; Wenzel, 2012). Eosinophils, metachromatic cells, or neutrophils may infiltrate the airway lumen when horses develop the mild-to-moderate asthmatic-type response seen in IAD.

Both heaves and asthma are characterized by reversible airflow obstruction, as a consequence of bronchospasms, increased mucus production, airway hyperresponsiveness, and pulmonary remodeling (Fig. 2). During periods of remission of the disease, when offending antigens are removed from the horses' environment,

Table 1
Similarities and differences between equine respiratory conditions and asthma.

	IAD	Heaves	Mild asthma	Severe asthma
Epidemiology and etiology				
Naturally occurring disease				
• Early in life	√	†	√	√
• Adult-onset	√	√	√	√
Environmental component	√	√	√	√
Genetic component		√	√	†
↑ Endotoxin sensitivity	√	√	√	√
Pathophysiology				
Airway hyperresponsiveness	√	√	√	√
• Early phase		–	√	√
• Late phase		√	√	√
Airway obstruction	Sub-clinical	Reversible*	Reversible	Partly reversible
High temperature/humidity induced exacerbations	?	√	√	√
Tissue remodeling				
• ↑ ASM mass	?	√	√	√
• ↑ ECM mass	?	√	√	√
• ↑ basal membrane thickness	?	†	√	√
• ↑ mucous producing cells	?	√	√	√
• Associated bronchiectasis	?	†	†	†
Hypercoagulability state	?	√	√	√
Immunology				
Airway neutrophilia	†	√	†	†
Airway eosinophilia	†	-	†	†
Airway mastocytosis	†	† (rare)	†	
Tissue inflammation	?	√	√	√
Th2-mediated inflammatory response	√	√	√	√
Th1-mediated inflammatory response	√	√	†	†
Th17-mediated inflammatory response	†	√	√	√
IgE mediated response	?	†	√	√
Associated atopy	?	†	†	†
Innate immune activation				
• Systemic inflammation	†	√	†	√
• ↑ Endotoxin sensitivity	†	√	√	√

√: present †: may be present. *: may be only partly reversible. ?: Not evaluated to our knowledge.