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Murine models of hapten-induced asthma

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ABSTRACT

Asthma is a chronic inflammatory disorder of the respiratory tract that is characterized by reversible airflow obstruction and airway hyperresponsiveness. The non-atopic variant of asthma that appears later in life has no allergic background and is more severe and resistant to standard treatment. Hapten-induced asthma models can be utilized to investigate mechanisms behind the development of non-atopic and occupational asthma, in which non-allergic processes seems to play significant role. The development of adequate animal models of non-allergic asthma is a necessary prerequisite both for understanding the pathophysiology of non-allergic asthma and for the possibility of testing new therapies. Still, there is no ideal model that represents all the hallmarks of this complex disease. In this review, we examine the most popular hapten-induced murine models of occupational and non-atopic asthma. For this reason, we describe the most popular sensitizing haptens, sensitization and challenge protocols, symptoms produced by asthma, and advantages and disadvantages of the models.

1. Introduction

According to World Health Organization, asthma is a chronic inflammatory disorder of the respiratory tract that is characterized by reversible airflow obstruction and airway hyperresponsiveness (WHO, 2007). Asthma, which affects about 300 million people worldwide, poses a serious global health problem (GINA, 2018). Although prevention and treatment of the disease are in place, many issues should be investigated. In this respect, experimental animal models of asthma play important roles; the mouse is the most frequently used species. There are many reasons to choose mice in pre-clinical asthma studies. First, a large number of inbred strains are well described. Numerous immunological reagents are available, creating the opportunity to examine specific mechanisms of inflammatory reaction in airways (Shin et al., 2009). Moreover, mouse transgenic models have been developed to assess the influence of particular mediators on asthmatic response (Lloyd, 2007). Other advantages are the shortness of the gestational period, ease of breeding, and the relatively low cost of gaining (Shin et al., 2009). In contrast, due to anatomical differences in airways between mice and humans, translating findings from animal studies to clinic practice should be rational. Additionally, mice do not respond to constrictive activity of histamine. There are difficulties in designing chronic models of diseases that could be conducted over many months (Patel and Chorawala, 2011). Despite the noted above, mouse models are widely used in both the atopic and non-atopic phenotype of the disease. Bronchial asthma is a heterogeneous disorder that can be distinguished depending on the occurrence of allergic background. In the most common experimental model, the sensitizing compound is a protein allergen, ovalbumin (OVA). The use of the latter leads to allergic variant of asthma with characteristic features of eosinophilia and increased level of IgE antibodies in serum (Zhang et al., 2017; Hwang et al., 2017; Venturini et al., 2018). The pathomechanism of the non-allergic type of the disease has been investigated to a much lesser extent, and the number of animal models is limited.

Non-atopic variant of asthma, also called 'intrinsic asthma' due to the inability to identify external factors causing reaction, is characterized by negative results of allergy skin tests, as well as a lack of increased total IgE concentration and absence of specific IgE in serum (Humbert et al., 1999). A typical feature is an elevated number of neutrophils, which rarely occurs in the airways of atopic asthmatics (Amin et al., 2000). In addition, intrinsic patients display initial signs of the disease later in their lives; no familial predispositions to allergy and

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asthma are observed (Dahlberg and Busse, 2009). Although clinical symptoms in both phenotypes are similar, non-atopic asthma tends to be more severe and resistant to standard doses of inhaled glucocorticoids (Barnes, 2009). Epidemiological studies indicate that association between atopy and asthma concerns less than half of the cases and that a higher proportion can result from an imprecise definition of atopy. As a result of this overestimation, other possible mechanisms of pathological reaction might be insufficiently analyzed (Pearce et al., 1999).

One variant of asthma in which non-allergic processes may play significant role is occupational asthma (Douwes et al., 2002). This phenotype is described as a variable airflow limitation in response to agents present in the workplace (Bardana, 2003). It is estimated that approximately 40% of occupational asthma incidents are caused by chemical substances, including low molecular weight compounds (LMW) (Bernstein, 2003).

A number of studies indicate that mice models of hapten-induced asthma can be utilized to investigate mechanisms behind the development of work-related asthma, as well as non-atopic asthma in the general population. Unfortunately, available models are not uniform in respect to induced reaction, since many of them share both allergic and non-allergic features of asthma. Thus, there is no perfect model that will represent all the hallmarks of this complex disease. The aim of the present review is to present a brief summary of available murine models of occupational and non-atopic asthma, with cross-references including recently published reports.

To this end, a description of most popular sensitizing haptens, sensitization and challenge protocols, produced symptoms of asthma, and advantages and drawbacks of the models are presented.

2. Haptens in murine models of asthma

Haptens are LMW agents (< 5000 Da) that have the ability for unique binding with immunoglobulins and T lymphocyte receptors (antigenicity), but they are not able to elicit an immune response by themselves (immunogenicity). They obtain the latter feature only when attached to large carrier, e.g. a protein molecule. In response to complete adduct, B lymphocytes recognize the hapten and Th lymphocytes protein carrier (Gołąb et al., 2017). There are many compounds classified as chemical sensitizers. Some of them are used in experimental models of asthma, including toluene diisocyanate (TDI), trimellitic anhydride (TMA), dinitrofluorobenzene (DNFB), and picryl chloride (PCL). They can be then divided into those that cause IgE-dependent or IgE-independent asthma (Van Houwelingen et al., 2002). Hypothetical mechanism of hapten-induced non-atopic asthma is presented in Fig. 1.

2.1. Toluene diisocyanate model

One of the most common respiratory irritants is toluene diisocyanate, which occurs as a mixture of the 2,4- and 2,6-isomers. It is mainly used in the production of polyurethane foams. Chronic exposure, via inhalation, to 2,4-TDI causes asthma-like symptoms in humans, manifested by bronchial constriction, wheezing, and dyspnea (PubChem, CID = 11443). Highly reactive diisocyanates include diphenyl-methane diisocyanate and hexamethylene diisocyanate (Świerczyńska-Machura et al., 2012). However, TDI is the most frequently used compound in hapten-induced asthma in mice.

There are numerous experimental protocols with different sensitization and challenge periods (see Table 1). In some of them elevated serum levels of Th2 cytokine, e.g. IL-4 and IgE antibodies, indicate possible allergic mechanism of the reaction (Sun et al., 2007). Although the functional and clinical features of TDI-induced response are similar to those observed in allergic asthma, there are still controversies about substantial differences, including neutrophil-dominated lung inflammation (Sun et al., 2007), low association with atopy, and cause of the pathological process (Park et al., 2012).

Matheson et al. (2005) described two models in which the effect of low-level subchronic exposure to TDI inhalation (20 ppb of TDI for six weeks) and high doses of acute exposure (500 ppb TDI for 2h) were compared. Mice from the subchronic regimen group demonstrated significant allergic reaction including airway inflammation, eosinophilia, Th1/Th2 cytokine expression in the lung, increased level of serum IgE, and airway hyperresponsiveness (AHR). In contrast, mice that underwent acute exposure showed considerable AHR and specific IgG antibodies, yet there was no increased IgE in the

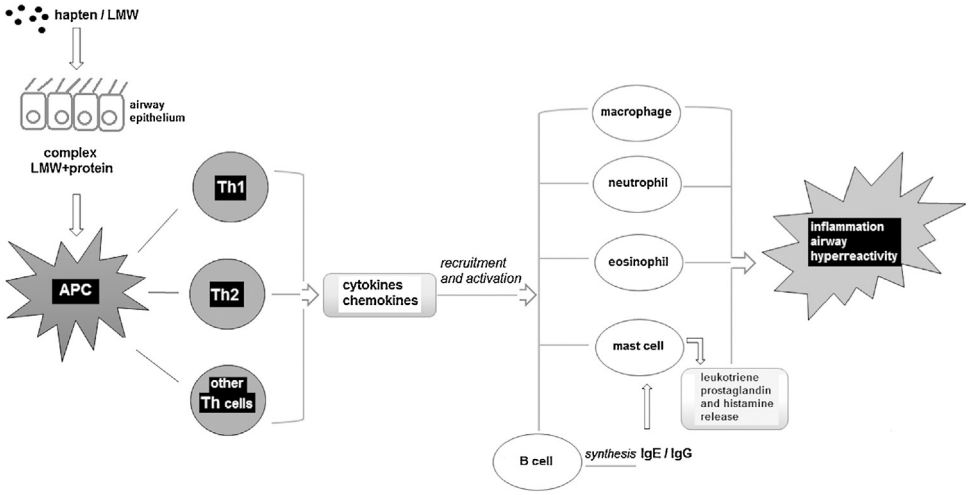

Fig. 1. Hypothetical mechanism of hapten-induced non-atopic asthma. Hapten after conjugation with protein is processed by antigen presenting cells (APC), which leads to differentiation and proliferation of T helper cells. T lymphocytes release cytokines and chemokines triggering recruitment and activation of inflammatory cells including B-cells and mast cells, which also release mediators of bronchoconstriction. DNFB induces mast cell activation and neutrophilic phenotype of asthma, while TDI and TMA eosinophilic, neutrophilic or mixed type depending on protocol applied. TDI and TMA elevate IgE production.