

Do the current house dust mite driven models really mimic allergic asthma?

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To the Editor,

Animal models play a key role in helping us determine the pathogenesis of diseases and they are vital for discovery of new therapies and the improvement of existing medication. To do this the model(s) need to closely mimic the clinical features and, where possible, be relevant to the disease in humans. Classically the innocuous antigen ovalbumin (OVA) has been used to induce an allergic reaction in animals, and whilst it is possible to reproduce many of the features of the asthmatic lung, i.e. specific IgE levels, Th2 associated eosinophilic inflammation, early and late asthmatic responses (EAR and LAR) and airway hyperresponsiveness (AHR) and associated tissue remodelling, researchers began to question the clinical relevance of using OVA as a model allergen [1]. In addition, it was commonly felt that the need for systemic delivery of OVA, with an adjuvant such as aluminium hydroxide, did not correctly mimic how asthmatic patients become sensitised to aeroallergens. To circumvent these issues researchers switched to using topically delivered House Dust Mite (HDM) to model allergic asthma [1], a route which incidentally is reported to induce tolerance when using OVA [2, 3]. A large proportion of human asthmatic patients have raised levels of HDM specific IgE and after challenge with HDM exhibit EAR and LAR and increases in airway inflammation [4-7]. For these reasons the choice of HDM as the allergen to use in animal models seems like a logical one and explains the almost unilateral decision to switch to using them. Generally these models are based around giving HDM topically into the airways, normally via the intranasal route, daily, over multiple weeks. This results in airway inflammation which features an increase in eosinophilia. However, a source of concern is the lack of evidence to show that the inflammation is part of an *allergic* (i.e. presence of HDM-specific IgE, B cells and T cells) phenotype. Unlike the classical OVA model where without prior sensitisation airway inflammation is absent upon challenge, it is not clear whether HDM-induced inflammation is a truly *allergic* response or merely a consequence of repeated nasal insult with an inflammatory concoction. Indeed, it is possible to induced airway eosinophilia using a variety of non-IgE associated stimuli, i.e. with sephadex and endotoxin [8, 9].

The current dogma suggests that the line between “sensitisation” and “challenge” phases is blurred in the repeated HDM insult models. But yet if these models do have a strong allergic component one would expect more reports of the classical allergic asthma phenotypes such as increased HDM specific IgE and respiratory symptoms such as EAR and LAR. In contrast to the OVA-alum models that show high serum levels of specific IgE and antigen-induced mast cell degranulation (the prototypic type I hypersensitivity response) most studies using HDM models have either not measured specific IgE levels or have reported a very weak (approximately twofold

increase in OD) total or specific IgE response. Whereas in patients with HDM allergic asthma, serum levels of specific IgE are usually 100-fold higher compared to non-allergic (<0.35 kU/L) controls. What is more, if one uses the presence of specific IgG1 as a marker of HDM specific B and T cell clonal expansion, it would appear that this event occurs after much of the airway inflammation is observed (i.e. IL-5 and IL-13 production and airway eosinophilia) [10]. Studying the role of the key allergic asthma effector cells should help understand the mechanisms driving the repeat HDM challenge model. As yet, however, there are limited reports on the role of cells such as the mast cell, dendritic cell, B cell and the Th2 cell in these modelling systems. In addition, to recapture some of the allergic asthma phenotypes currently missing from the repeat HDM challenge models, we suggest it may be necessary to revert back to using a systemic sensitisation phase prior to HDM challenge.

Animal models do play a key role in helping us to determine the pathogenesis of diseases and they are vital for discovery of new therapies. However, we suggest one needs to understand the modelling systems we use, what limitations they have and how relevant they are to the human disease before they are utilised in the search for new therapeutic entities. It could well be that repeated topical HDM challenge does adequately model allergic asthma but equally we, as a community, could end up developing a therapy for HDM induced airway inflammation in rodents rather than a therapy to combat human disease.

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