EDITORIAL

Repeated low dose allergen exposure: a new investigational model of asthma as a persistent disease?

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Asthma is a persistent disease, characterized by episodic chest symptoms and variable airways obstruction [1]. Its pathogenesis is determined both by genetic factors [2, 3] and by environmental exposures among which allergens [4, 5] and respiratory virus infections [6, 7] seem to predominate.

The pathology of asthma is characterized by features of acute and chronic airways inflammation, such as epithelial desquamation, leucocyte infiltration, mucosal and adventitial swelling, smooth muscle hyperplasia or hypertrophy, and subepithelial collagen deposition [8]. There is increasing evidence that the eosinophilic infiltrate [9] and the expression of the cytokines interleukin (IL)-4 and IL-5 [10] within bronchial biopsy specimens are associated with the clinical characteristics of asthma.

Human investigational models of asthma

The acute inflammatory events in patients with asthma have largely been unravelled by using challenges with pro-inflammatory stimuli, such as (single-dose) allergen provocation [11, 12] or experimental virus infection [13, 14]. However, such models are almost invariably based on acute flare-ups of airways inflammation, whereas the development and consequences of its chronicity still remain to be resolved [15]. The latter seems to be of vital importance since:

1) chronic features of inflammation, such as structural remodelling due, for example, to subepithelial fibrosis [16], smooth muscle growth [17], increased vascularity [18], and airway wall thickening (as measured by high resolution computed tomography (HR-CT) scan [19] or by histology [20]), appear to be major determinants of the severity of airways obstruction in asthma [21].

2) chronic exposure to allergens might "prime" the response to acutely encountered pro-inflammatory stimuli, thereby potentially facilitating asthma exacerbations due to subsequent high dose allergen exposure [22] or respiratory virus infections [23, 24].

Hence, understanding the chronicity of airways inflammation will be essential for developing new and specific therapeutic targets for asthma, particularly those with more sustained activity than the ones currently available.

Repeated low-dose allergen exposure

Apart from descriptive studies in moderate-to-severe asthma, the chronicity of airways inflammation can be investigated experimentally by repeated, low-dose allergen inhalation. Such controlled laboratory conditions mimic the patient’s natural exposure to environmental allergens.

In the present issue of the Journal, SULAKVELIDZE et al. [26] present the clinical, physiological and cellular consequences of repeated low-dose allergen exposure in patients with asthma. Allergen or its diluent were inhaled on five subsequent days, the allergen dose being chosen such that it caused about a 5% fall in forced expiratory volume in one second (FEV1) only. The results show that in the absence of meaningful bronchoconstriction to the allergen exposure, the patients developed night-time symptoms and increased their β2-agonist usage. In addition, during these exposure days there was a steady worsening of hyperresponsiveness to methacholine, associated with increases in induced sputum of: eosinophils; EG2+ stained eosinophils; metachromatic cells; eosinophil cationic protein (ECP); and IL-5 levels [26]. This indicates that this model provides a realistic gradual worsening of asthma, under well-controlled laboratory conditions. Importantly, the study also shows that these changes are well tolerated and transient, underlining the safety and ethical acceptability of this investigational model.

Others have recently published similar results in abstract form. In these studies low-dose allergen exposure produced variable airways obstruction [27], elevated serum ECP [28], and an increased IL-4 to interferon (IFN)-γ ratio in stimulated peripheral blood mononuclear cells ex vivo [29]. However, at present it is unknown whether this is accompanied by features of chronic airways inflammation, which could eventually lead to structural airways remodelling.

A model of chronic airways inflammation?

In experimental animals some major features of chronic airways inflammation have been established following repeated low-dose allergen exposure. These studies have demonstrated the induction of (apart from leucocyte infiltration): airways hyperresponsiveness to cholinergic agonists [30, 31], but not to allergen [30]; an increase in smooth muscle shortening capacity [32]; smooth muscle...
growth [33–36]; epithelial damage [35] and proliferation [34]; subepithelial collagen type III and VI deposition [31]; goblet cell proliferation [31, 36]; sub-mucosal gland hypertrophy and hyperplasia [35]; and impaired nitric oxide production [37].

The development of such changes in response to repeated allergen exposure has not yet been confirmed in asthmatics, even though single-dose allergen challenge has been reported to increase the number of myofibroblasts in bronchial biopsy specimens [38]. It can be envisaged that well-controlled repeated low-dose allergen exposure is a promising approach to investigate the cellular and molecular pathways for the development of airways remodelling [15, 39]. Then it may be possible to describe not only the presence of growth factors, such as transforming growth factor (TGF)-β, within the airways in asthma [40, 41], but also to investigate the dynamics of these factors and their consequences, as induced by allergen, in more detail [42]. If the induced changes appear to be reversible, as appears from the study by Sulaveldi et al. [26], then there do not seem to be major ethical restrictions to this kind of research.

Perspectives

It can be envisaged that human laboratory allergen challenges will evolve towards more realistic research models of environmental allergen exposure in asthma. This will certainly allow progress in the research on the pathogenesis of acute as well as chronic airways inflammation in asthma. Interestingly, the repeated low-dose allergen model might be applicable to the careful investigation, in the laboratory setting, of the interaction between multiple environmental exposures in asthma, for instance between allergens and photochemical air pollution [43] or the occurrence of a respiratory virus infection on top of seasonal chronic allergen exposure [44]. Needless to say, the combination of challenges with low-dose allergen [26] with air pollutants [45] or experimental virus infection [14] also has prospects for well-controlled intervention studies with newly developed drugs.

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