EBioMedicine 19 (2017) 12–13

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Mucosal Lining Fluid Biomarkers in Asthma: Basis for Rational Use of New Targeted Therapies?

Rudolf Valenta *

Div. of Immunopathology, Dept. of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria

Asthma is a frequent, disabling chronic disease which is characterized by respiratory symptoms (wheeze, breathlessness, chest tightness and cough) and chronic airway inflammation. It affects more than 300 million people world-wide and represents a heavy economic burden to health care systems (Kaur et al., 2015). The syndrome asthma is caused by several underlying diseases and trigger factors of which the most frequent ones are IgE-associated allergies and respiratory virus infections (Kim et al., 2010). Although there are obviously a range of different pathomechanisms operative in asthma, for decades the treatment has been based mainly on symptomatic therapy aimed at bronchodilation and reducing inflammation (i.e., pharmacological bronchodilation and corticosteroids). However, the introduction of IgE-targeting therapies for the treatment of allergic asthma has emphasized the need to identify patients by accurate stratification to allow accurate administration of anti-IgE and other new IgE targeting therapies (Incorvaia et al., 2017; Lupinek et al., 2017). Through the characterization of the diseases-causing allergens by molecular cloning techniques, new forms of molecular allergy diagnosis based on allergen molecules have emerged (Lupinek et al., 2014). The new molecular tests allow not only to discriminate between clinically relevant and irrelevant IgE-sensitizations but also to establish IgE reactivity profiles associated with allergic asthma (Resch et al., 2015) and, even to predict the development of respiratory allergy early in childhood (Westman et al., 2015). Furthermore, it seems possible for allergen-derivatives lacking IgE reactivity to discriminate mechanisms of allergen-IgE-mediated allergic inflammation from non-IgE-mediated allergic inflammation, which may help to direct IgE-mast cell-targeting treatments and T cell targeting therapies (Campana et al., 2016).

In patients suffering from allergic asthma, allergen-specific immunotherapy (AIT) is currently emerging as an alternative to symptomatic treatment. In fact, several clinical studies have shown that AIT is effective for asthma (Yukselen, 2016). Moreover, new forms of AIT based on recombinant hypoallergenic allergen-derivatives have been shown to be effective in clinical studies (Zieglmayer et al., 2016). These new forms of molecular AIT have major advantages over allergen-extract-based AIT such as reduced side effects and thus increased safety, coverage of the relevant allergens, convenient, few-dose applications as well as lack of allergenicity and thus have great potential to improve the treatment of allergic asthma.

Regarding asthma caused by respiratory virus infections the causal relationship between human rhinovirus HRV, which is thought to be the most relevant virus involved in asthma exacerbation, has been only established by relatively ambiguous nucleic acid-based test methods. However, it has been found that HRV infections induce IgG and IgA responses mainly against an N-terminal peptide of the HRV coat protein VP1. Then it has been demonstrated that serologically detectable increases of the VP1-specific antibody responses occur in patients who have experienced HRV-induced asthma attacks by natural infections as well as by experimental inoculation and can be measured by serological testing (Niespodziana et al., 2014). Available data thus suggest that the increases of VP1-specific antibodies reflect the severity of airway symptoms and may allow identification of the disease-causing HRV groups, indicating that serological tests will become available soon, and allow the identification of persons suffering from HRV-induced asthma attacks.

Using the aforementioned experimental model for HRV-induced asthma exacerbations, Hansel et al. in this issue of *EBioMedicine* use novel sampling of cytokines and chemokines to provide potential biomarkers for HRV-induced asthma (Hansel et al., 2017). The authors developed nasosorption and bronchosorption sampling devices for collection of mucosal lining fluid, in which they measured airway mucosal cytokine and chemokine responses following experimental HRV infection. A major finding of the study was that asthmatic individuals developed higher nasal mucosal lining fluid levels of an anti-viral cytokine/chemokine pathway and in some subjects there was also induction of a type 2 inflammatory pathway which one would consider to be associated with allergic asthma. At a first glance, it may appear confusing to see an antiviral and a type 2 inflammatory pathway taking place in some subjects with HRV-induced asthma. However, there is good evidence that HRV-infections and allergen-induced asthma are connected. In fact, the subjects with HRV-induced asthma exacerbations who were investigated in this study had an atopic back ground. There is also evidence that HRV infections and allergen-exposure may potentiate each

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2017.03.033.

* Division of Immunopathology, Dept. of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Waehringer Guertel 18-20, 3Q, 1090 Vienna, Austria.

E-mail address: rudolf.valenta@meduniwien.ac.at.

http://dx.doi.org/10.1016/j.ebiom.2017.04.016

other and HRV-infections were shown to damage respiratory epithelium and allow increased allergen penetration associated with increased allergic inflammation (Gangl et al., 2015).

An interesting feature of the manuscript by Hansel et al. is that 34 different nasal cytokines and chemokines are shown as figures in a "warts and all" manner in a variety of modes: including individual data points over time (linear and logarithmic) and medians. In addition there are heat maps to show correlations and individual responses, as well as volcano plots and receiver operating characteristic (ROC) curves, with an extensive supplement of 6 figures and 12 tables. Notably, the authors do not present peak value data for nasal responses after HRV infection, since this approach has been criticized in relation to IL-33 (Hilvering et al., 2015). An exciting feature of the current study is that nasosorption IL-5 and IL-13 are elevated in allergic asthmatics prior to rhinovirus challenge: offering the possibility for patient selection for biologics directed against type 2 inflammation. Furthermore, the technique of bronchosorption is promising for a range of respiratory diseases, since soluble mediators are present at higher detectable levels than in BAL and can be expressed in terms of known dilution.

The identification of cytokines and chemokines which are elevated after HRV-induced asthma may also have clinical importance. In fact, there are currently several treatment options emerging for asthma which are based on biologics which target inflammatory cytokines (Heck et al., 2015). Some of these biologics appear to be very effective but there have been also less successful studies and critical comments have arisen (Bagnasco et al., 2016). Also one might get the impression that the efficacy of the new forms of cytokine-targeting treatments could be increased if patients suitable for the new forms of treatment can be better identified. The measurement of cytokines and chemokines associated with HRV-induced asthma, as demonstrated by Hansel et al., may in fact help refine the selection of patients who are suitable for the newly emerging cytokine-targeting biologics. However, some important questions remain open. One of these questions is: What are the mechanisms of HRV-induced tissue damage responsible for triggering asthma attacks? This question has not been answered in the current study because it has not been investigated if HRV occurs also in the lungs of the infected subjects. Another open question is if HRV directly damages the respiratory tissues and thus is the cause of the asthma attack or if the cytokines released in the course of the HRV-infection have a causal role in inducing asthma. The latter question is of particular importance because otherwise the risk is that one does not treat the cause of the disease but rather an epiphenomenon. In this context one would like to know what the pathophysiologic contribution of the elevated anti-viral and type 2 inflammatory cytokines to asthma exacerbations is. Otherwise we cannot be sure if we are treating the hen or the egg.

Disclosure

R.V. receives grant support from the Austrian Science Foundation (FWF), from Biomay AG, Vienna, Austria and Viravaxx, Vienna, Austria. He serves as a consultant for Biomay AG, Vienna, Austria, Viravaxx, Vienna, Austria, Fresenius Medical Care, Bad Homburg, Germany and Thermofisher, Uppsala, Sweden.

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