

EDITORIAL

Clinical and Experimental Allergy

Deficient interferon in virus-induced asthma exacerbations

This editorial discusses the findings of the paper in this issue by Bullens et al. [16].

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Respiratory viral infections account for the majority of asthma exacerbations in both adults and children, and are therefore responsible for a large part of the morbidity, mortality and disease burden associated with asthma. Human rhinovirus (RV), an agent commonly associated with the common cold, is the main virus associated with asthma exacerbations, responsible for up to 80% of virus-induced asthma exacerbations [1, 2]. Asthma exacerbations are also not adequately controlled by corticosteroid-based treatments, the mainstay of asthma therapy [3], and finding better treatment alternatives or new therapeutic targets is a main research focus for the future.

Recently, much has been learnt regarding the pathogenesis of respiratory viral infections and how this may impact on asthmatic individuals. In a study of co-habiting asthmatic and non-asthmatic couples, Corne et al. demonstrated that while asthmatic and non-asthmatic individuals had similar rates of acute viral infections, the asthmatics had more severe and a greater duration of symptom scores, including lower respiratory tract symptoms, and a greater decrease in lung function [4]. This important finding was the first to suggest that there may be some inherent differences in the way that asthmatic and non-asthmatic individuals respond to respiratory viral infections, and such differences may be important in the role of viral infections in asthma. The exact differences at the time were unknown; however, previous data had shown that asthmatic tissues often had over-exuberant inflammatory responses, largely through the increased activation of NF- κ B or Rel family of transcription factors [5–7].

Wark et al. then provided a mechanistic insight into why asthmatics have a greater amount of virus-induced illness with studies involving cultured bronchial epithelial cells from adult asthmatic and non-asthmatic individuals obtained by fibre optic bronchoscopy, and infection with RV *in vitro* [8]. Surprisingly, asthmatic bronchial epithelial cells produced lower levels of the type I IFN- β , and also had higher levels of RV replication, assessed by both viral titration and quantitative PCR. RV induction of the pro-inflammatory cytokine IL-6, and CCL5/RANTES however were not different between the two groups strongly suggesting that the differences were specific to anti-viral IFNs, and the pro-inflammatory cytokine profile of these asthmatic tissues were normal. Importantly, deficient IFN- β expression was observed in both steroid-treated and steroid naïve asthmatics. The asthmatic bronchial epithelial cells responded to exogenous treatment with IFN- β , exhibiting reduced RV release, neatly demonstrating that the deficiency in asthmatic cells was associated with production of anti-viral IFN- β , rather than in the actions of IFN- β . Also, these pioneering studies forced a re-examination of type I IFN therapy in RV infections; type I IFN- α and IFN- β therapy which had previously been trialled in the context of the common cold, however, did not proceed further than phase two clinical trials [9, 10]. The use of IFN- β as a therapy for asthma exacerbations is therefore currently being considered.

The importance of anti-viral IFNs *in vivo* was later elegantly shown using a human experimental infection model of adult mild-moderate asthmatics. Contoli et al. obtained bronchoalveolar lavage (BAL) cells from uninfected asthmatics and non-asthmatics [11]. Upon culturing these BAL cells (mostly macrophages) with stimuli including RV and lipopolysaccharide (LPS), BAL cells from asthmatics had lower levels of RV and LPS induced type III IFN- λ , a newly described anti-viral IFN family, consisting of three members in humans, IFN- λ 1 (IL-29)

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and IFN- λ 2 (IL-28A), IFN- λ 3 (IL-28B). IFN- λ 2 and IFN- λ 3 are highly homologous and the whole family shares up to 80% homology, and use a unique receptor complex consisting of IL-10R β and IL-28R α chains [12, 13]. Deficient IFN- λ in asthmatic cells was also shown to be important in the pathogenesis of asthma exacerbations *in vivo*, abundance of IFN- λ was negatively correlated with airway symptom scores, changes in lung function, and viral load and markers of inflammation *in vivo*. These studies collectively heralded a new era for the understanding of the role innate immune responses to viruses play in asthma, as a striking link between disease and a deficiency in innate molecules related to host defence was established.

These two studies have been supported by other studies, for example, deficient IFN- α 2 in peripheral blood of asthmatic donors [14], and the observation that asthmatic bronchial epithelial cells grown in differentiated air-liquid culture systems also exhibit deficient IFN- β , IFN- λ upon infection with RV [15]. This latter study is important as it shows that different methods of cell culture *in vitro* (air liquid, differentiated vs. liquid, undifferentiated), does not alter their inability to make IFNs, compared with cells from non-asthmatics grown in the same way. In the present issue of *Clinical and Experimental Allergy*, Bullens *et al.* demonstrate that IFN- λ 1 but not IFN- λ 2/3 mRNA levels obtained from sputum cells negatively correlated with asthma symptoms in moderate-severe asthmatics, and again highlight a protective role for IFN- λ in asthma [16]. Both IFN- λ 1 and IFN- λ 2/3 mRNA levels correlated with CD3 γ mRNA levels, and IFN- λ levels were higher in steroid-treated individuals. While the true meaning of the results is unclear, IFN- λ levels in this study may be a marker of steroid-mediated control of asthma symptoms.

Currently, the mechanism behind deficient IFN expression remains unknown but vigorously debated. As asthmatics have deficient IFN- β , IFN- λ and perhaps some of the IFN- α s, a polymorphism in each of these structural genes or their promoters is unlikely to be the explanation. A mutation or polymorphism in a gene encoding a transcription factor, or signalling molecule required for the expression of all IFNs is one possibility. Also, the increased expression of a negative regulator of type I and type III IFN in asthmatic tissues, such as the recently described Pin1, NLRX1 or SIKE [17–19] are also worth investigation. The role of T helper type-2 cytokines, or ongoing inflammation within the asthmatic airway, also deserves consideration, and may potentially down-regulate bronchial epithelial cell or lung macrophage IFN gene expression, such as in a manner analogous to innate imprinting [20, 21]. Of equal significance is whether this deficiency is causative of asthma, or is merely a consequence of asthma. More studies are required to answer these important questions. Future studies, aimed at exploring the above possibilities, and also further sampling of the asthmatic population, including asthmatic

children and non-atopic asthmatics are likely to provide further mechanistic insights into this problem.

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