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Severity of virus-induced asthma symptoms is inversely related to resolution IFN-lambda expression

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To the Editor

Asthma exacerbations have been shown to be a major cause of morbidity and mortality and up to 80% of exacerbations are linked to viral infections. Therefore, how interferon responses in infected airways relate to the severity of illness is of great interest. Some studies have demonstrated that asthma is associated with reduced in vitro production of interferon (IFN)- λ and IFN- β ,^{1, 2} and that allergic inflammation can down regulate virus-induced interferon responses,^{3, 4} suggesting that virus-induced interferon responses are reduced in asthma. In contrast, other studies have reported positive associations between interferons, measured in respiratory secretions, and the severity of illness in patients with asthma. For example, Miller et al. described increased levels of IFN- λ in the nasal lavage fluid of wheezing asthmatic children compared to non-wheezing asthmatic children with upper respiratory infections.⁵ In addition, we have shown that during the acute phase of naturally-acquired colds, expression of IFN- γ and IL-13 mRNA in sputum cells is increased in adult patients with asthma exacerbations compared to asthmatics with uncomplicated colds.⁶ Furthermore, sputum IFN- α , IFN- β , and IFN- γ mRNA expression also correlated with severity of asthma symptoms. One potential explanation for the disparate findings is that the timing of interferon expression might be important in determining the relationship to illness severity. We therefore sought to determine whether expression of interferons in sputum cells following recovery from the illnesses (reflecting basal levels of expression) was related to the severity of asthma symptoms with viral colds.

As previously described, 30 asthmatic subjects, age 16-60 yrs with a virus positive cold, participated in the clinical study of viral exacerbations in asthma (VIAX, University of Wisconsin Institutional Review Board approved protocol H-2005-0070).⁶ The protocol included clinical characterization and collection of induced sputum samples following the resolution of symptoms of a viral infection, typically 6 weeks later. The mRNA from sputum cells was isolated and analyzed by quantitative RT-PCR for the expression of IL-13

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(n=27) and IFN- α (n=25), - β (n=25), - γ (n=27), and - λ (n=24) (see online supplement for details). The severity of asthma symptoms and categorical designation of exacerbations were based on the Asthma Index Score.⁶⁻⁸

There were no significant differences in sputum eosinophils, neutrophils, lymphocytes or macrophages between those who experienced an exacerbation and those who did not at resolution as previously reported.^{6, 7} However, subjects with exacerbations (Figure 1A) or more severe asthma symptoms (Figure 1B) had reduced resolution expression of IFN- λ mRNA (categorically, $p=0.01$ and by correlation, $R=-0.51$, $P=0.01$), while expression of IFN- β , - α , or - γ were not related to exacerbations or illness severity. IL-13 mRNA expression at resolution was not related to illness severity during the exacerbation (online supplement), but there was a significant inverse correlation ($R=-0.47$, $P=0.02$) between resolution IFN- λ and IL-13 mRNA expression during exacerbation (Figure 2).

These observations suggest that lower levels of interferon expression (IFN- λ) *after resolution of a* viral infection are related to more severe asthma symptoms and possible exacerbation. Based on our previous study, greater expression of interferons (IFN- α , IFN- β and IFN- γ) *during* the viral infection correlates with more severe asthma symptoms and the presence of an exacerbation. Thus, the “sample timing” can explain some of the differences seen in previous studies of interferons during colds and exacerbations of asthma.

IL-13 has been shown to suppress IFN- λ production by airway cells stimulated with double stranded RNA.⁹ Given the finding of an inverse relationship between IL-13 expression during a viral infection and IFN- λ expression at resolution, it is possible that increased IL-13 synthesis associated with airway inflammation in asthma suppresses expression of IFN- λ . This effect may inhibit antiviral responses during the early phases of viral infection, and thereby increase the risk for exacerbation in patients with asthma.

One of the limitations of this analysis is the use of a 6 week post-viral infection sputum sample. These samples may represent a “baseline” for individuals, however it is possible that the previous viral infection/exacerbation or medications influenced the values (online supplement). These possibilities are unlikely given the transient nature of viral infections and illnesses and limited use of add-on medications, and it is worth noting that recovery of peak flow typically occurs within 2 weeks of an exacerbation and the sputum neutrophil counts showed significant decrease 6 weeks following an exacerbation.⁷ Furthermore, the specificity of our observation for IFN- λ 1 at the resolution visit suggests there is not a broad suppression of inflammatory gene expression. Another potential limitation is the measurement of gene expression from sputum cells but not bronchial epithelial cells, which could exhibit different patterns of gene expression. However, it is recognized that macrophages and dendritic cells, which are captured with sputum analysis, are also important sources of interferon expression.

In a recent clinical trial for the use of inhaled IFN- β by Djukanovic et al., subjects with asthma who were treated with interferon therapy at the initiation of a cold had no significant overall improvement in the ACQ6 scores.¹⁰ Based on these findings and our data, it would be intriguing to determine whether the interferon treatment during peak viral seasons prior to

viral infection might reduce the frequency and severity of virus-induced asthma symptoms and/or exacerbations.

The role of interferons in viral induced exacerbations of asthma is complex. The severity of asthma and regulation of interferon expression may both be critical determinants for outcomes of viral infection and illness. This report supports the timing of interferon gene expression as an important determinant of infectious outcomes in asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Capsule Summary

Lower airway IFN λ 1 expression following viral upper respiratory infection corresponds to greater asthma symptoms and likelihood of exacerbation during the infection. This suggests lower baseline interferon expression may increase risk for viral induced asthma exacerbations.

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Figure 1.

Panel A. Baseline sputum cell interferon mRNA expression with or without asthma exacerbation. Interferon gene expression was normalized, log transformed and presented as box plots for patients with or without exacerbation (Exac). Significant P-value is indicated.

Panel B. Baseline sputum cell interferon mRNA expression correlation with asthma index. Interferon gene expression was normalized, log transformed and correlated with asthma index, the data is presented as dot plots, with fitted regression lines. Significant Spearman R-value and P-value is indicated.

Figure 2.

Baseline sputum cell mRNA expression of IFN-λ1 negatively correlates with IL-13 sputum mRNA expression at the time of exacerbation. Interferon gene expression was normalized and log transformed, the data is presented as dot plots, with fitted regression lines. Spearman R-value and significant P-value is indicated.