IFN- α /IFN- λ responses to respiratory viruses in paediatric asthma

To the Editor:

We read with interest the paper by BERGAUER *et al.* [1] on innate immune responses to viral infection in paediatric asthma. The paper confirms previous reports on impaired interferon responses in stable asthma [2–4], but describes a hyperactive interferon production during asthma exacerbations associated with rhinovirus infection. The authors conclude that, despite impaired immune condition at stable state, the ability to upregulate type I interferons during the acute phase is preserved in asthmatic children. However, what is lacking from this study is the information on interferon production during acute rhinovirus infection in an age-matched group of non-asthmatics. Thus, how can it be conclusively excluded that the production of interferon is impaired during the rhinovirus-induced acute phase of asthma in the absence of such a comparative control group? A study which examined nasal washes of children during acute episodes of wheezing or rhinitis, reported lower levels of IFN- λ in children with wheezing than in those with acute rhinitis, even if the differences were not statistically significant [5]. The fact that asthmatic patients, once infected, have more severe manifestations of the infectious diseases [6] could possibly suggest an impaired response also in the acute phase, but conclusive data are lacking.

Notably, and interestingly, children enrolled in this study had a very high prevalence of rhinovirus infections at stable state (up to 50%), which is higher than that previously reported [7]. We should carefully consider the implications of those findings, with a particular focus on the clinical background on which such a high viral detection occurs in stable asthma. For instance, was this a subset of children prone to frequent respiratory infections? Furthermore, children were stable for asthma, but could they have experienced coryzal symptoms in proximity to sampling?

Finally, the authors state that they did not see any relationship between IFN- α regulation and the allergic status in their patients; yet nonatopic children were scant in their population (four out of 24). We have previously shown that rhinovirus-induced interferon production from bronchial epithelial cells in preschool children was inversely related to circulating IgE levels [4], confirming the counterplay between IgE and innate immune responses to viral infections [8–11]. To support the clinical importance of these findings, it has been shown that pre-seasonal modulation of IgE results in an enhanced rhinovirus-induced interferon production and in decreased incidence of asthma exacerbations in autumn [12].

To conclude, several publications suggest the presence of an impaired innate immune response to rhinovirus in stable asthma, starting from the early stages of the disease. The study by BERGAUER *et al.* [1] adds to this information highlighting the complexity of the interplay between viral infections and asthma exacerbations. It remains to be established whether the impaired interferon production documented at baseline occurs also during rhinovirus-induced acute asthma attacks or whether it is confined to the stable state.

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Does impaired interferon production in stable asthma also occur during rhinovirus-induced acute asthma attacks? <http://ow.ly/kgVe309GazS>

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References

- 1 Bergauer A, Söpel N, Kroß B, *et al.* IFN- α /IFN- λ responses to respiratory viruses in paediatric asthma. *Eur Respir J* 2017; 49: 1600969.
- 2 Contoli M, Message SD, Laza-Stanca V, *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; 12: 1023–1026.
- 3 Bufe A, Gehlhar K, Grage-Griebenow E, *et al.* Atopic phenotype in children is associated with decreased virus-induced interferon-alpha release. *Int Arch Allergy Immunol* 2002; 127: 82–88.
- 4 Baraldo S, Contoli M, Bazzan E, *et al.* Deficient antiviral immune responses in childhood: distinct roles of atopy and asthma. *J Allergy Clin Immunol* 2012; 130: 1307–1314.
- 5 Kennedy JL, Shaker M, McMeen V, *et al.* Comparison of viral load in individuals with and without asthma during infections with rhinovirus. *Am J Respir Crit Care Med* 2014; 189: 532–539.
- 6 Corne JM, Marshall C, Smith S, *et al.* Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet* 2002; 359: 831–834.
- 7 Johnston SL, Pattemore PK, Sanderson G, *et al.* Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; 310: 1225–1229.
- 8 Gill MA, Bajwa G, George TA, *et al.* Counterregulation between the Fc ϵ RI pathway and antiviral responses in human plasmacytoid dendritic cells. *J Immunol* 2010; 184: 5999–6006.
- 9 Sriram U, Biswas C, Behrens EM, *et al.* IL-4 suppresses dendritic cell response to type I interferons. *J Immunol* 2007; 179: 6446–6455.
- 10 Contoli M, Ito K, Padovani A, *et al.* Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. *Allergy* 2015; 70: 910–920.
- 11 Subrata LS, Bizzintino J, Mamessier E, *et al.* Interactions between Innate Antiviral and Atopic Immunoinflammatory Pathways Precipitate and Sustain Asthma Exacerbations in Children. *J Immunol* 2009; 183: 2793–2800.
- 12 Teach SJ, Gill MA, Togias A, *et al.* Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015; 136: 1476–1485.

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From the authors:

The letter by S. Baraldo and co-workers raises some interesting points. It is correct that we cannot exclude the possibility that interferon upregulation during the acute phase in asthmatics, though existent, is suboptimal if compared to healthy subjects. It is also possible that there might be differences in kinetics, with peak expression reached at different time points in different groups. What we have established is that interferon deficiency in asthma is more complex than a simple on/off mechanism.

However, it should be noted that the authors are comparing studies with completely different experimental design. Since the discovery of interferons in 1957, research on interferons has developed by highlighting the heterogeneity of these factors, their different mechanisms of production and action. In fact, type I interferons (α and β) have kinetics of production that are strictly dependent on the system analysed. In our prospective European multicentre study PreDicta, we analysed IFN- α and IFN- λ (IFN type III) levels in serum of children with and without asthma and subgrouped the children in accordance to the presence or absence of rhinovirus in their airways *in vivo* [1]. By contrast, in other studies, IFN- λ [2], or IFN- β and IFN- λ levels [3] were analysed in supernatants of bronchial epithelial cells (or airways cells) after rhinovirus infection *in vitro*, or IFN- λ was analysed in nasal washings [4]. In spite of the different systems analysed, in the presence of rhinovirus, IFN- λ release shows the same trend [1, 2].

It is also known that the kinetics of interferon type I production are completely different *in vivo* and *in vitro* and it is thus difficult to compare *in vitro* and *in vivo* results. In addition, IFN- α production has been analysed in cultured blood cells or peripheral blood mononuclear cells challenged with Newcastle virus (not rhinovirus) [5].

In conclusion, under our different conditions, we could confirm and extend the existing literature.

It is also important to consider that interferons (at least interferon type I) have a very high biological action and are active at very low doses and they can also cause severe secondary disease, especially at the early stages of life, and even some symptoms of exacerbation are effects related to interferon.

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Analysis of acute infections that cause asthma exacerbation should be included in future studies
<http://ow.ly/GKcM309Gi9R>

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In relation to the effects of the atopic background, it is also true that small differences would not have been able to appear significant due to sample size. Nevertheless, there is no obvious qualitative difference. In all, we agree with the authors that the innate immune response to rhinovirus in asthma is complex. Future studies addressing this complexity would need to evaluate the response dynamics.

To conclude, we are only at the beginning of understanding the dysregulated innate immune response to rhinovirus in stable asthma, starting from the early stages of life, but we learned from our study PreDicta that infections that cause asthma exacerbation should be also included in our future analysis because they can help us to better understand the pathogenesis of this increasingly prevalent disease.

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References

- 1 Bergauer A, Söpel N, Kroß B, *et al.* IFN- α /IFN- λ responses to respiratory viruses in paediatric asthma. *Eur Respir J* 2017; 49: 1600969.
- 2 Contoli M, Message SD, Laza-Stanca V, *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; 12: 1023–1026.
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- 4 Kennedy JL, Shaker M, McMeen V, *et al.* Comparison of viral load in individuals with and without asthma during infections with rhinovirus. *Am J Respir Crit Care Med* 2014; 189: 532–539.
- 5 Bufe A, Gehlhar K, Grage-Griebenow E, *et al.* Atopic phenotype in children is associated with decreased virus-induced interferon-alpha release. *Int Arch Allergy Immunol* 2002; 127: 82–88.

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