Reply: Key role of dysregulated airway epithelium in response to respiratory viral infections in asthma

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From the authors:

We thank F. Moheimani and colleagues for their interest in our paper and their considerations, to which we like to respond.

Our paper in *ERJ Open Research* is a follow-up on our previous publication in *European Respiratory Journal* [1]. There, we described an intrinsic defect in translational control of response genes (*CXCL8* and *IL6*) in bronchial epithelial cells from asthma patients, due to a failing cytoplasmic translocation of the translational repressor TIAR. As the half-life of response transcripts can be very short, the defect is best visualised by prolonging the half-life of transcripts of response genes. In our studies, we used interleukin (IL)-17 to prolong the transcript half-life and tumour necrosis factor (TNF)-α to induce expression of response genes. The study reported in *ERJ Open Research* shows that upon an *in vivo* challenge with rhinovirus 16, the bronchial epithelial cells recovered from patients display further enhanced responses to IL-17 and TNF-α, whereas this is not the case for bronchial epithelial cells recovered from healthy individuals.

There have been several reports indicating that bronchial epithelial cells from asthma patients display intrinsically different responses (referred to in [1]), such as exaggerated production of inflammatory mediators and indeed the different response of microRNA (miR)22 as described by Moheimani *et al.* [2]. Whereas our findings for TIAR may underlie the exaggerated inflammatory mediator production and that of the bronchoconstrictor endothelin-1 in asthma, we have not addressed miR22. Interestingly, in their paper, Moheimani *et al.* [2] showed that expression of the transcription factor c-Myc was also enhanced after infection with influenza A virus (H1N1). An important difference between their and our study is that Moheimani *et al.* [2] triggered an epithelial response by infection with H1N1, whereas we exposed bronchial epithelial cells to TNF-α and IL-17, about 3 weeks after these cells had been exposed *in vivo* to rhinovirus 16. In view of that, the enhanced c-Myc expression is in response to a stimulus, *i.e.* infection with H1N1. As c-Myc is a typical response gene, it may well be that this enhanced expression is due to the TIAR-related defective translational control. Interestingly, two recent papers describe that TIAR also interacts with nuclear long noncoding RNA molecules, which are considered to regulate transcription of specific sets of genes. One of these papers, in fact, shows that TIAR controls c-Myc expression [3]. Although this remains to be shown for bronchial epithelial cells from asthma patients, it is in line with the TIAR-related effect on mitochondrial functioning in asthma [4].

We do agree with Moheimani *et al.* [2] that air–liquid interface (ALI) cultures of bronchial epithelial cells are more differentiated and thus may better reflect the *in vivo* status than submerged cultures. ALI cultures do lead to the expression of genes involved in the polarised phenotype of bronchial epithelial cells and, thus, defective translational control may lead to additional response genes being expressed in an exaggerated manner. Although we consider it formally likely, we have not yet shown that this defective translational control in submerged cultures of bronchial epithelial cells is also manifest in polarised bronchial epithelial cells from asthma patients.

As mentioned above, we used IL-17 to prolong half-lives of response transcripts in order to be able to visualise the defect in translational control. There are several mediators, such as IL-1β and lipopolysaccharide, but also conditions that are known to prolong half-lives of response transcripts. Partial

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The defective translational control in bronchial epithelial cells from asthma patients is reflected by enhanced responses to viral infection and (temporarily?) worsened by a respiratory viral infection
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inhibition of protein synthesis is one of these conditions that results in the marked accumulation of response transcripts (also known as superinduction), outcompeting other transcripts for remaining translation and even leading to an enhanced protein production [5]. During viral replication, eukaryotic protein synthesis is attenuated and that may be the reason why Moheimani *et al.* [2] saw an increased expression and translation in bronchial epithelial cells from asthma patients of c-Myc, which normally has a half-life of only ∼10 min. Whereas IL-17 exposure or viral replication may facilitate visualisation of the defective translational control, these factors will also markedly contribute to exaggerated responses *in vivo*. We have shown that for IL-17 in conjunction with neutrophilic inflammation in asthma [1]. For viral infections, it was shown that interferon and interferon-induced genes, most of which are typical response genes, are enhanced in bronchial epithelial cells from children with asthma upon respiratory syncytial virus infection *in vitro* [6] and we showed that with an *in vivo* challenge with rhinovirus 16 in adult patients with asthma [7]. This is despite the attenuated interferon response as reported earlier by Wark *et al.* [8], which among others, may relate to IL-33 [9].

The defective translational control varies between patients and, obviously, affects only the response genes that have been transcribed and that are dependent on TIAR for translational control; however, these are many [10]. This could explain the heterogeneity in asthma pathophysiology just as well as the proposed epigenetic mechanisms by Moheimani *et al.* [2].

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