Innate immunity in paediatric viral wheezers is virus specific and not interferon dependent

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Up to a third of all children develop virus induced wheezing, but we still do not understand why some children wheeze with viral colds and others do not. We also do not know why only some viral wheezers progress to develop asthma and others do not. Data from the Childhood Origins of Asthma Study (COAST) have shown that children with at least one atopic parent who wheeze with viral infections in the first 3 years of life have a significantly increased risk of developing asthma.[1] Specifically, wheezing with human rhinovirus (HRV) in the third year of life was associated with up to 30-fold higher risk. However, this association did not delineate whether virus infection caused asthma, or underlying susceptibility to asthma or early sensitisation resulted in altered immune responses to viral infections which subsequently resulted in an asthma phenotype. We now know that an underlying susceptibility is an important determinant since variants at the 17q21 locus were associated with asthma in children who had had HRV wheezing illnesses in COAST and another unrelated high risk birth cohort.[2] Moreover, allergic sensitisation precedes HRV induced wheezing and asthma development.[3] However, we still know very little about the nature of the immune responses to viral infection in susceptible children who may go on to develop asthma compared with those who are likely to outgrow their symptoms. A consequence of our limited understanding of the mechanisms underlying virus associated wheezing is that currently therapeutic options remain limited to bronchodilators and leukotriene receptor antagonists, which are frequently ineffective.[4] A further significant limitation in our approach to investigating mechanisms of preschool viral induced wheeze is the tendency of translating mechanistic findings from studies in adults of viral asthma exacerbations directly to children with viral wheeze.[5] Although it seems obvious that this is unlikely to be a fruitful approach because of differences in immune maturation with age, and the fact that preschool viral wheeze in no way equates to asthma, the potential difficulty in obtaining airway samples from preschool children has frequently been a deterrent to adopting the optimal scientific approach.

The study by Spann *et al*[6] is therefore to be commended since significant efforts have been made to obtain samples from both the upper and lower airways, from children with viral induced wheezing and healthy age matched controls, with the influence of atopy also being addressed. Importantly, the easy option of using cell lines to reflect immune responses was not adopted. In addition, the effects of two different viruses on epithelial immune responses were compared. The study has shown that unlike epithelial responses to HRV in asthma, primary epithelial cell cultures from children who have viral induced wheezing which are stimulated with either respiratory syncytial virus (RSV) or human metapneumovirus (hMPV) do not have altered interferon β or λ responses. However, a higher viral load was still associated with cells from children with viral wheeze, suggesting there is an underlying altered immune response in this condition, but the nature of this response remains unresolved.

Epithelial responses to RSV revealed altered interferon responses, but only in nasal epithelial cell cultures, not lower airway tracheal cultures. However, similar responses were seen in cells from both nasal and tracheal cells that were infected with hMPV. This highlights the importance of obtaining lower airway samples when determining mechanisms underpinning childhood airway diseases. Ease of access makes it tempting to use nasal or upper airway samples as a surrogate to investigate lower airway functional responses, but a direct comparison of responses to virus has been shown in this study to produce different results. It is becoming increasingly apparent that, especially when investigating the function of structural airway cells in the pathogenesis of asthma, upper airway samples may not represent functional responses of the lower airway.[7]

A comparison of immune responses to two different viruses in this manuscript has highlighted the importance of considering virus-specific effects, which may impact on identifying novel therapies. However, a limitation was the absence of stimulation with HRV as a comparator, especially since this is the commonest virus to infect children in the age group studied, and immune responses to rhinovirus have been most extensively published in paediatric asthma.[8 9] Comparisons of the effect of HRV with RSV and hMPV may have helped to determine whether mechanisms underpinning viral exacerbations in children with asthma (who are known to have altered epithelial interferon responses[10]) are similar to those in children who wheeze only with viruses, but do not have asthma. Potential differences in immune responses to viruses between the two phenotypes could help to explain why steroids are beneficial in viral induced asthma exacerbations, but not in viral induced wheezing without asthma.[11 12] It is also possible that the specific pattern of immune responses to virus determines whether or not a child who wheezes with colds will develop asthma.

Although wheezing with viruses is more common in infants and preschool children, the age range of children included in this study was wide, ranging from 2 to 9 years, with a mean age between 4 and 6 years in each group. Since numbers in each group were small, a split between preschool and school-aged children was not possible. However, future assessments of innate immunity in preschool compared with school-aged children should be considered to further elucidate how host maturation affects immune responses.

This manuscript makes several significant additions to the current paediatric literature concerning mechanisms underlying the development of wheezing and asthma in children. It is the first to look at epithelial immune responses to virus infection in children with viral induced wheeze and/or atopy, but without a clinical diagnosis of asthma. The authors' intention was to determine whether ultimately epithelial immune responses may help to identify those viral wheezers that are more likely to develop asthma. Although not answerable yet, this is the first study that has addressed this question. The differences found in immune responses to two viruses, even though both were from the same family, show the importance of considering virus-specific effects especially for future therapeutic approaches, and also highlight that altered immune responses are not restricted

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to rhinovirus infection, but also result from infection with RSV and hMPV. The manuscript has also shown that abnormal interferon responses are not the only pathway affected in viral wheezing; this may of course only be relevant in children, but highlights the need to investigate alternative pathways. Finally, the importance of obtaining primary airway samples from the appropriate age group has been demonstrated. Even though this is more difficult than using peripheral blood samples, cell lines or samples from adult patients and means numbers of patients recruited is often small, this study has shown that the data obtained from optimal samples from carefully clinically characterised patients are meaningful even with small sized groups. It is apparent that the mechanisms underlying the pathogenesis of childhood viral wheeze and asthma are complex, but if we are to progress to identifying effective therapeutic interventions and achieving disease modification and asthma prevention, then we must accept that studies of this nature carry much more weight than those using less demanding approaches. If this is not realised, then the data published will be no more translatable to clinical practice than that from contrived in vivo experimental models.[13]

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