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EDITORIAL

Respiratory syncytial virus and subsequent asthma: one step closer to unravelling the Gordian knot?

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Respiratory syncytial virus (RSV) is the most common respiratory pathogen in infancy, infecting nearly all children within the first 2 yrs of life [1]. There is growing evidence that severe RSV lower respiratory infection (LRI) early in life is an important risk factor for the development of recurrent wheezing and asthma in later childhood [2] but the field abounds with apparent controversy [3–13]. A recent paper from the Tucson Children's Respiratory Study in Arizona, USA has demonstrated that mild-to-moderate RSV LRI in the first 3 yrs of life is an important risk factor for subsequent wheezing [7, 8] up to 11 yrs of age, but this risk is no longer statistically significant by 13 yrs of age [8]. In this study, no relationship was found between the infection and development of atopy. In contrast, in Boras, Sweden, subsequent recurrent wheezing in later childhood (up to 7 yrs of follow-up) was observed in children with a history of severe bronchiolitis requiring hospitalisation in infancy [9, 10] and a significant association was found between RSV and atopic sensitisation, which was not explained by a family history of asthma or atopy. How does one reconcile these apparently discrepant observations? Clearly not all children with recurrent wheezing disease have been previously hospitalised with severe RSV bronchiolitis and not all children with RSV LRI go on to wheeze. The explanation for these observations is slowly unravelling.

It was initially suggested that RSV-specific immunoglobulin (Ig) E during acute infection and convalescence correlated with both the severity of RSV illness and subsequent wheezing [14]. This implied that the immune responses to RSV were implicit in the subsequent development of an asthmatic phenotype, and has in part driven some of the studies examining the relationship between RSV infection and the T-helper (Th) 2-type responses to RSV. This observation has not been consistently repeated [15, 16]. It has also been suggested that an imbalance in the Th2-Th1 memory response is involved in determining the atopic/asthmatic phenotype and that a priming RSV infection may be responsible for biasing children toward an atopic state by skewing immune responses towards a Th2-type response [17, 18]. However, this does not appear to be the complete explanation either, since interferon (IFN)-γ appears to be the predominant cytokine produced in infant airways in a primary RSV infection [19] and in peripheral T-cells [20]. The only positive correlate with recurrent wheezing in the first year of life appears to be interleukin (IL)-10, produced by cultured mononuclear cells from infants with severe RSV LRI [21]. While eosinophilia during the RSV LRI appears to correlate with the recurrent wheeze seen in older children (7 yrs of age), it does not appear to be correlated with either a Th1- or Th2-type response [22]. Rather the macrophage inhibitory protein (MIP)-1α, which is chemotactic for eosinophils and is increased in the airways of children with severe RSV LRI [23] along with increased production of MIP-1β and RANTES (regulated on activation, T-cell expressed and secreted) [24], may be responsible for these observations.

How then can one tie the clinical observations in with the pathogenetic mechanisms? An interesting paper in the previous issue of this journal [25] throws new light on the RSV-reactive airways disease (RAD) link. Children with a history of severe RSV bronchiolitis were found to have higher frequencies of RSV-specific IL-4 producing T-cells in their blood, whereas there was no difference in IFN-γ responses. Surprisingly, logistic regression analysis indicated that the frequency of IL-4 producing T-cells to RSV or to a chimeric FG protein did not correlate with the risk for asthma or wheeze, whereas the IL-4 response to the Fel d (cat) antigen did, accounting for about 15% of this association. Because the genetic background of the study population was similar, as suggested by the family history of atopy and similar IL-4 responses to tetanus toxoid, it is possible that the increased frequency of IL-4 producing T-cells is an acquired phenomenon caused by early RSV infection. Given that the Th2-type responses to RSV antigens themselves did not correlate with either wheeze or asthma, a possible hypothesis is that the RSV infection caused a significant epithelial break and exposure to aeroallergens in infancy (when these children had their RSV LRI, and when the inherent immune response is biased toward a Th2 type [26]) biasing their subsequent responses to allergens towards a Th2-type response. This data also explains the observation of sensitisation to allergens and the

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development of an atopic phenotype in this study population [9, 10]. RSV causes prolonged pulmonary inflammation that may exaggerate this response [27] and which anti-inflammatory therapy does not appear to mitigate [28]. However, prevention of both the severe RSV LRI and depression of the inflammatory responses, by monthly infusions of 750 $mg \cdot kg^{-1}$ of RSV immune globulin to infants with bronchopulmonary dysplasia has been shown to improve not only their pulmonary function but also to decrease their sensitisation to aeroallergens [29].

Thus, it is becoming apparent that the young age of acquisition of severe RSV LRI, the prolonged pulmonary inflammation [27], the Th2 bias of the immune responses early in life [26], especially in those with an atopic family background, may be part of the explanation for the RSV-RAD association. An article in this issue of the *European Respiratory Journal* illustrates the age dependency of the immune response, this time by neutrophils [30], showing that upper airway secretions from infants delay neutrophil apoptosis much more efficiently that in adults. Despite the fact that RSV does not affect this response, this is probably a protective mechanism which makes a larger number of viable inflammatory cells available for the first-line, nonspecific protection against respiratory infections in early life (when specific adaptive immunity is still immature). This study was performed using nasal lavage fluid, therefore, it is unclear whether this finding can be extrapolated to the lower airways, and the authors could not identify the heat-labile factor responsible for inhibiting apoptosis. Perhaps the most important message is that the immuno-inflammatory response to viral respiratory infections is exquisitely age-dependent, as suggested recently by studies conducted in an animal model of RSV infection [31, 32, 33].

Together, these studies give us new insight into the complexity of the interactions between RSV and innate and adaptive immunity. RSV infection is an important early event for the programming of immuno-inflammatory responses during development and has the potential of contributing to the emergence of an atopic/asthmatic phenotype. Another important aspect is the role played by innate immunity in protecting against early-life respiratory infections, which could also be one of the determinants of the age-related differences in the clinical expression of RSV disease.

Neural mechanisms may be important in this relationship and prolonged changes in the cholinergic and nonadrenergic, noncholinergic pathways innervating the airways occur with early-life RSV infections [34]. Recent studies in animal models suggest that remodelling of the submucosal neural network and the subsequent neuro-immune interactions may link RSV infections occurring during critical developmental "windows" with RAD in childhood. This process of virus-dependent neural remodelling appears to be particularly extensive when the infection occurs early in life, because of the much higher degree of neural plasticity that characterises infancy. Based on this model, during infancy, the lower airways would become hyperreactive due to the abnormal density and/or responsiveness of the afferent innervation, reprogrammed by virus-directed overexpression of specific neurotrophic factors [31]. Activation of these fibres by irritants would trigger a cascade-like series of events involving plasma exudation [32], recruitment and activation of polymorphonuclear and mononuclear leukocytes, and mast cell degranulation with release of leukotrienes [33] and other inflammatory mediators. The local tissue hyperreactivity caused by these dysfunctional neuro-immune feedback loops could be responsible for the recurring airway inflammation and subsequent narrowing, which continues after the acute RSV infection has cleared.

A lot of investigative work is necessary to explore further the immuno-inflammatory mechanisms activated by early RSV infection, because this work could lead to a better understanding of the ontogenesis of protective mechanisms and also shed new light on the early origins of asthma. The contribution of controlled, prospective interventional studies conducted in larger study populations, testing the effect of RSV-specific prophylaxis on the chronic sequelae of RSV infection will be particularly important. An example of the latter is a recently published study of children with chronic lung disease of prematurity that had received RSV immune globulin 7–10 yrs earlier [29]. Pulmonary function was significantly better in the treatment group than in matched control patients. Significantly less atopy and a lower likelihood of RAD attacks were observed. Based on this preliminary evidence, WENZEL *et al.* [29] suggested that RSV prophylaxis might have long-term benefit in reducing the risk of RAD. Being 50–100-times more potent than RSV immune globulin, palivizumab may be an important alternative in the prophylaxis of RSV and the avoidance of reversible airway obstruction.

A prospective, multicentre study to examine the effect of palivizumab prophylaxis on the incidence and degree of reversible airway obstruction in premature children is ongoing in Europe and Canada, the results of which are anticipated at the end of 2004.

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