EDITORIALS

Asthma and the Dysregulated Immune Response to Rhinovirus

Acute asthma remains a serious and underappreciated problem that we are only now slowly beginning to understand (1). Epidemiological studies first demonstrated how important acute asthma was in early childhood and how it was overwhelmingly triggered by viral infections, although this also reflects a pattern of illness that afflicts people with asthma of all ages (2). In children it was appreciated that sensitization to aeroallergens (especially dust mite) increased the risk and severity of acute asthma (3). The association with acute asthma and virus infection was found to be strongest with rhinovirus (RV), and recurring wheeze with RV infection and allergic desensitization both independently predict the development of asthma by age 6 years (4). It then became clear that in preschool children the virus most often associated with acute asthma and the most severe exacerbations was the newly discovered RV-C (5).

How, though, can asthma, a disease characterized by active airway inflammation and type 2 immune responses, leave otherwise well children and adults susceptible to the effects of viral infections? *In vitro* experiments on peripheral blood monocytes from children with asthma when exposed to RV demonstrated a relatively impaired type 1 or IFN-γ response (6), first hinting at specifically impaired antiviral immunity. Paradoxically, in adults and adolescents with established asthma, control of underlying type 2 airway inflammation by inhaled corticosteroids dramatically reduced the risk of asthma exacerbations, despite the fact they have no effect on enhancing immune responses to RV. A similar effect is now clear in preschool children, where in those with recurring wheeze, the use of regular or intermittent inhaled corticosteroids reduces the frequency of exacerbations (7), with the effect greatest in those with sensitization to aeroallergens and blood eosinophil counts >300 μl. Controlling type 2 airway inflammation clearly reduces the susceptibility to RV infection. Although enhancing antiviral responses in asthma would seem to be a natural extension, the impact does not seem as important as controlling type 2 inflammation. When adults with asthma received nebulized IFN-β at the commencement of a cold, a benefit could only be seen in those in whom regular therapy with inhaled corticosteroids could not control their disease (8).

This subtle impaired immune response is present in those destined to develop asthma even before allergic sensitization developing. Severe bronchiolitis in the first year of life is associated with the later development of asthma, but this risk varies. Recent evidence demonstrates children with bronchiolitis display a heterogeneous immune response, with three profiles seen (9). The most common profile is bronchiolitis triggered by respiratory syncytial virus, with moderately severe acute disease, but this group does not have an increased asthma risk at 3 years (9). Those with the most severe acute illness, again mostly due to respiratory syncytial virus, have a modest heightened risk of asthma. But those who had the greatest risk of asthma had a history of eczema, bronchiolitis caused by RV, higher blood eosinophils, and a microbiome dominated by *Haemophilus influenzae* and *Moraxella*, suggesting a dysregulated mucosal immune response to pathogens. These effects were independent of all other environmental factors known to influence asthma development. This suggests an immune phenotype characterized by impaired responses to RV and predisposed to asthma has evolved in these children and is evident within the first year of life (9).

The nasal secretions from children during acute asthma exacerbations also demonstrate two distinct immunophenotypes differentiated by the master regulator of type I and type III IFN responses, IRF-7 (10). Those who were IRF-7 high had a more robust IFN-α/γ response and less severe illness, while those who were IRF-7 low had a longer illness, with relatively poor IFN-α/γ responses (10). Differences in innate immune responses from children with asthma have also been seen in their T-cell responses. Using peptides from RV-A and RV-C, CD4 and CD8 cells from children were activated and underwent proliferation similar to control children, but in asthma there were fewer T regulatory (Treg) cells present and they were less responsive (11). RV-C peptides demonstrated even fewer Treg responses. Tregs are critical immunomodulating cells that mitigate the effects of acute inflammation. Interestingly although Tregs have been observed to be reduced in asthma, their numbers can be enhanced by use of inhaled corticosteroids (12).

In this issue of the *Journal*, Anderson and colleagues (pp. 202–209) have taken us a step further in understanding these immune responses in early-life acute asthma, assessing the peripheral blood monocytes from a cohort of 17 children with asthma and 19 control subjects, and stimulating T cells with conserved peptides from RV-A and RV-C (13). They noticed two important responses. First, in both subjects with asthma and control subjects, RV-A peptides led to a more robust response, with upregulation of significantly more differentially expressed genes (DEGs) and, specifically, enhanced (T-helper cell type 1 [Th1]) IFN-γ/STAT-1 as well as CXCL-9, 10, 11, and Th17 responses. RV-C stimulated an increase in STAT-1 but not IFN-γ and quantitatively led to reduced DEGs compared with RV-A. Interestingly, RV-C stimulation in both subjects with asthma and control subjects was associated with increased release of CCL-24 (eotaxin). Although it is clear that early-life virus-induced wheeze is not associated with increased type 2 airway inflammation acutely, a signal that attracts and activates eosinophils and mast cells, especially if it is recurring, in the setting of allergic sensitization could enhance the development of eosinophilic airway
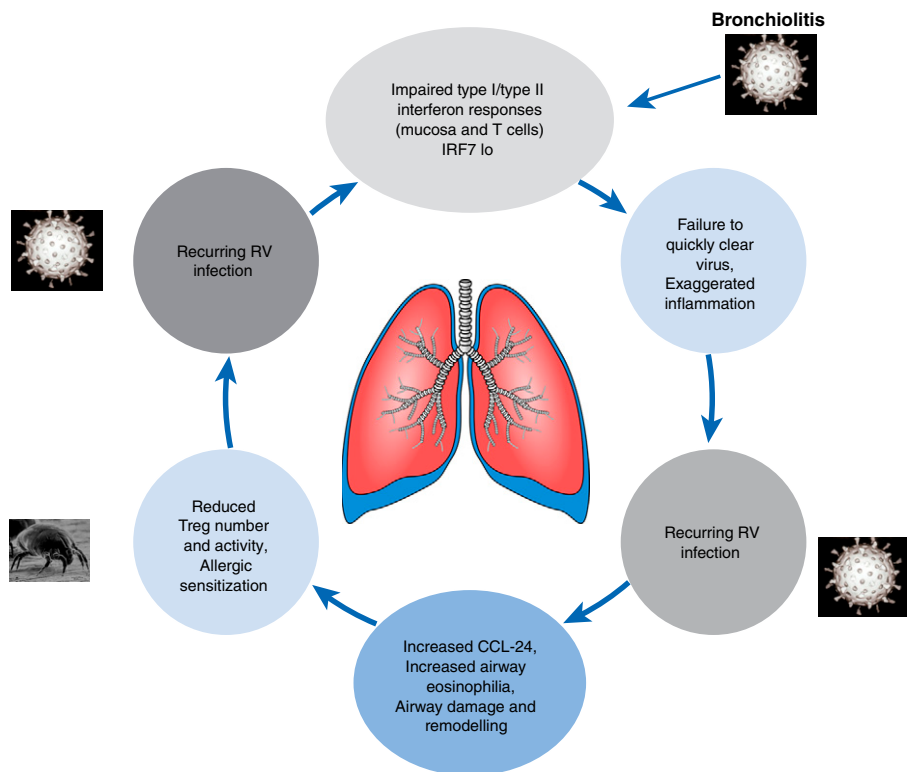
Figure 1. A proposed series of early-life events may predispose someone to develop asthma. Susceptible individuals in the first year of life display impaired type I and type II IFN responses (IRF7 lo), giving them an impaired antiviral immune phenotype. A viral infection leads to intense acute airway inflammation in the first year of life, resulting in bronchiolitis. Those with impaired immunity (IRF7 lo) have impaired IL-6 responses and are slower to clear the virus; they suffer more intense airway inflammation, and recurring infection develops with viruses such as rhinovirus-C (RV-C). The exaggerated airway inflammatory response continues and is now augmented by increased CCL-24, and airway eosinophilia develops. Reduced T-cell immune responses and recurring airway inflammation are associated with reduced T-regulatory (Treg) numbers and function, failing to control airway inflammation. In the airway, a cycle of damage and remodeling develops. Susceptible individuals develop sensitization to aeroallergens, especially dust mite. Type 2 airway inflammation becomes established. This in itself can predispose an individual to recurring RV infection that further exacerbates the impaired antiviral immunophenotype. Asthma is established, characterized by type 2 airway inflammation and recurring exacerbations triggered by RV-A and RV-C.

inflammation and airway remodeling. Second, although the qualitative responses were no different between subjects with asthma and control subjects, the z-scores for DEGs were substantially reduced in those with asthma, suggesting a very poor T-cell response to the presence of RV-A and RV-C. This again appears to be consistent with the story that there is a subtle but critical impairment of antiviral responses in asthma. This was illustrated by the blunted IL-6 response that was seen in the children with asthma, although on face value this seems a paradox, as IL-6 is often seen to be elevated in asthma. In the context of acute virus infection, IL-6 plays a critical role in the early response to viruses such as influenza, promoting survival of neutrophils, and an impaired IL-6 response is associated with delayed viral clearance and more severe illness (14).

What we now understand is that children who go on and develop asthma in early life appear to display from a very early age an immune phenotype that is susceptible to infection with RV (Figure 1). This phenotype is worsened by the development of type 2 airway inflammation associated with allergic sensitization, and recurring infections with agents like RV-C and RV-A are likely to have a positive feedback effect, worsening this process. These features may then characterize asthma at all ages. The impact

is lessened, though not resolved, by treating type 2 airway inflammation. We still do not understand why this impaired immune phenotype evolves, why it is so closely linked to type 2 airway inflammation, or how we can prevent it or reverse it once it is present. These remain as key questions to answer, and until they are resolved it is difficult to see that we will make important advances in controlling and preventing acute asthma. ∎

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The Origins of Chronic Obstructive Pulmonary Disease: Sometimes the Journey Matters More than the Destination

Fundamentally, chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder, and over the past 40 years, there have been great advances in clarifying this heterogeneity to the point that we now have a number of candidates that can be considered veritable COPD endotypes (1). Despite this progress, spirometry is still required to diagnose COPD, and the constraint to meet this spirometric criteria has obscured an important truth: a post-bronchodilator FEV_1/FVC ratio less than 0.70 only defines a destination but does not reveal how the patient arrived there (2). After all, one of the main goals of COPD research is to help clinicians predict how their patients' diseases will evolve and to map out individual natural histories such that timely interventions can be applied to slow or halt lung function decline. In reality, these paths and roads stretch both forward and backward, and thus it is perhaps prudent to examine where we came from as well as where we are going.

A discussion of the natural history of COPD necessarily begins with the work of Charles Fletcher and Richard Peto, but the dogma of accelerated FEV_1 decline was challenged in 2015 when Lange

and colleagues demonstrated that the inability to attain maximal lung function in early adulthood contributes significantly to COPD development (3, 4). In that landmark study, an analysis of pooled participants from three large longitudinal cohorts revealed distinct lung function trajectories when the results were stratified based on whether the study participant had normal FEV_1 at cohort inception (4). Four divergent trajectories were modeled, of which two outlined markedly different pathways to COPD: some subjects with normal FEV_1 at study onset developed COPD as a result of accelerated lung function decline, whereas an equal number had low or submaximal FEV_1 at study onset and developed COPD despite having a normal rate of decline. In this issue of the *Journal*, Marott and colleagues (pp. 210–218) provided an insightful update on one of these three cohorts, the Copenhagen City Heart Study (5). After 20 years of follow-up, 144 of 1,170 participants in this cohort developed COPD, including 79 who were in the "normal maximally attained FEV_1" trajectory and 65 in the "low maximally attained FEV_1" trajectory. These two subpopulations were equivalent in age, smoking habits, asthma history, and FEV_1 at the time of diagnosis, but predictably, participants who attained normal maximal FEV_1 had a FEV_1 rate of decline that was twice as high as those who had low maximal FEV_1. After another 10 years of follow-up, the rate of FEV_1 decline in these two COPD subgroups converged, but their mortality curves separated, with individuals in the normal maximally attained FEV_1 trajectory having increased all-cause mortality as well as nonmalignant respiratory mortality. There were several limitations to this study, the most important of which being the dwindling of the study population