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Patrick G. Holt and Peter D. Sly

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Interaction Between Adaptive and Innate Immune Pathways in the Pathogenesis of Atopic Asthma

Operation of a Lung/Bone Marrow Axis

Patrick G. Holt, DSc; and Peter D. Sly, DSc

Atopic asthma is the most common form of asthma, particularly during childhood, and in many cases it persists into adult life. Although atopy is clearly a risk factor for development of this disease, only a small subset of subjects sensitized to aeroallergens express persistent symptoms, suggesting that additional pathogenic mechanisms are involved. Recent studies have implicated respiratory viral infections as key cofactors in asthma development in atopic patients. In relation to initial expression of the asthma phenotype in early childhood, it has been shown that although both atopic sensitization and early severe lower respiratory tract infections can operate as independent asthma risk factors, the persistence of asthma is most frequent among children who experience both insults, suggesting that the relevant inflammatory pathways interact to maximally drive disease pathogenesis. Importantly, it has been established that both these factors must be operative contemporaneously for these interactions to occur (ie, the interactions are likely to be direct). Recent studies on viral-induced asthma exacerbations in atopic children have provided a plausible mechanism for these interactions. Notably, it has been demonstrated that signals triggered during the innate immune response to the virus can lead to the release of large numbers of migrating high-affinity IgE receptor-bearing bone marrow-derived precursors of mucosal dendritic cells into the blood. The subsequent trafficking of these cells to the infected airway mucosa where dendritic cell turnover is very high provides a potential mechanism for recruitment of underlying aeroallergen-specific T-helper 2 immunity into the already inflamed milieu in the infected airway mucosa.

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Abbreviations: DC = dendritic cell; FcεR1 = high-affinity IgE receptor; hRV = human rhinovirus; IFN = interferon; LRI = lower respiratory tract infection; RSV = respiratory syncytial virus; Th = T helper

Asthma is a complex disease manifesting as two major phenotypes, nonatopic or “intrinsic” asthma, and atopic asthma, which is the focus of this brief review. Atopic asthma is the dominant form of the disease throughout the school years and into young adulthood,^{1,3} whereas the nonatopic form becomes increasingly more prominent among older age groups. It has been argued that these two persistent respiratory disease phenotypes, and possibly COPD, may share a common stem^{4,5} in the form of gene/environment interactions in early life that shape the trajectory of subsequent age-dependent changes in lung functions during and beyond childhood and set susceptibility thresholds to airborne environmental stimuli.⁴ A key common factor in these interactions

may be airway inflammatory responses to respiratory pathogens, which in all three diseases are the principal triggers for severe exacerbations. Patients with asthma or COPD are clearly more prone to develop severe airways symptoms associated with respiratory infections than the population at large, and a more complete understanding of why this occurs is likely to provide novel insights relevant to development of improved treatments. In this review, this issue is addressed in the specific context of atopic asthma in children. We acknowledge that the mechanisms discussed herein are unlikely to operate in precisely the same way in all three diseases, but the approach described here to elucidate them in atopic asthma may be more broadly applicable.

ASTHMA-ASSOCIATED PHENOTYPES IN EARLY LIFE

Studies conducted in longitudinal birth cohorts, such as the Tucson Children's Respiratory Study⁶ and Western Australian Pregnancy Cohort (Raine study)⁷ have defined a number of asthma phenotypes based on when children wheeze, how long wheezing persists, and what triggers the wheeze. Wheezing in infancy is common, with up to 30% having at least one episode of wheeze. The Tucson group defined transient infantile wheeze as a condition in which children wheezed in the first 3 years of life, often but not always associated with viral respiratory infections.^{6,8} This was associated with low premorbid lung function when measured in a subset in the first weeks of life,^{6,9} and maternal smoking during pregnancy is a risk factor for this type of wheeze in many studies.¹⁰

Perhaps the most common asthma-associated phenotype is intermittent or viral-associated wheeze, which describes children who wheeze with viral respiratory infections and have few symptoms in between episodes. Although precise estimates of the frequency of this phenotype are lacking, clinically up to 70% of children who earn the diagnostic label of asthma are likely to have this phenotype.¹¹ Many of these children will lose their asthma symptoms by mid-childhood.^{8,10} In the Tucson study, this phenotype was not associated with low premorbid lung function and was also not associated with lower lung function later in life.⁹ In addition, this phenotype is not associated with an increased prevalence of atopy.^{6,8,10,11}

Longitudinal cohort studies have also shown that the asthma-associated phenotype that is most likely to persist into adult life is atopic asthma, especially when allergic sensitization occurs in early life (reviewed in Reference 2). Classically, atopic asthma is described as presenting somewhat later in childhood; however, increasingly data from longitudinal studies are showing that wheezing with viral infections in early life, especially in the presence of early allergic sensitization, is

a major risk factor for persistent atopic asthma.^{12,13} Recently, a task force from the European Respiratory Society has suggested renaming this phenotype as multitrigger wheezing to recognize that triggers other than respiratory viruses may precipitate symptoms in these children.¹¹ Unfortunately, the European Respiratory Society classification depends very heavily on parental reports and has been shown to be unstable over time, in that children classified as having multitrigger wheeze on one occasion may be classified differently 3 months later.¹⁴

These epidemiology-based phenotypes all rely on detecting the presence and pattern of wheezing. Physiologically, wheeze occurs predominantly during expiration and simply indicates that expiratory flow is limited by the physical properties of the airways. Expiratory flow limitation can occur in anatomically small airways (such as with maternal smoking during pregnancy) or in airways narrowed by edema (eg, in viral infections) or by bronchospasm. Wheezing can also occur with structurally abnormal airways (eg, tracheal stenosis) or airways with abnormally high airway wall compliance (eg, as may be seen in bronchopulmonary dysplasia). Thus, wheeze is not a specific indicator of asthma.

Wheezing with viral respiratory infections in early life is a major risk factor for asthma. Until recently, much of the literature on this association focused on the respiratory syncytial virus (RSV) and suggested that bronchiolitis in early life "caused" asthma, presumably by damaging the developing airways. However, the bulk of this literature reported on the associations between severe bronchiolitis requiring hospital admission and recurrent episodes of wheeze over early childhood. In the Tucson study, wheezing with RSV in the first 3 years of life was a risk factor for wheeze in mid-childhood but not by adolescence.⁸ Recent community-based cohort studies have clearly demonstrated that viruses other than RSV may be associated with wheezing in early life and that these are associated with an increased risk of subsequent asthma.^{12,13} Human rhinovirus (hRV) was once believed to be limited to causing common colds; however, these studies have clearly shown that hRV can be associated with wheezing lower respiratory illnesses. In our own studies, the increased asthma risk with wheezing illnesses was only seen in children who also developed allergic sensitization by the age of 2 years.¹² The question as to whether any virus-specific factors are involved in increasing the asthma risk or whether wheezing with viral infections simply identifies a susceptible host has still not been settled (reviewed in Reference 15).

As outlined previous, low lung function increases the risk of wheezing. The airway branching pattern is fully developed by 17 to 18 weeks' gestation, but alveolar

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Affiliations: From the Telethon Institute for Child Health Research and the Centre for Child Health Research (Dr Holt), The University of Western Australia, Perth, WA; and the Queensland Children's Medical Research Institute and University of Queensland (Dr Sly), Brisbane, QLD, Australia.

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Correspondence to: Patrick G. Holt, DSc, Division of Cell Biology, Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, PO Box 855, West Perth, WA 6872, Australia; e-mail: patrick@ichr.uwa.edu.au

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growth does not begin until late in the third trimester and continues after birth. Lung function at birth is a major determinant of lung function later in life. Lung function has been shown to track along percentiles¹⁶⁻¹⁸ unless lung growth is compromised by adverse environmental exposures. The relationship between asthma and lung function is complex. Cross-sectional studies generally show lower lung function in patients with asthma,¹⁰ and longitudinal studies report low lung function in patients with asthma, generally at the earliest time point measured.¹⁹ Serial lung function testing in the Childhood Asthma Management Program (CAMP) has shown that mild to moderate asthma results in a pattern of airway obstruction that increases with age and is not modified by treatment.²⁰ Whether low lung function is a risk for asthma²¹ or asthma limits growth in lung function is not completely clear. Lung function is known to be heritable, and recent data suggest that genetically determined lung function may contribute to asthma risk independent of other genetic predispositions contributing to asthma.^{20,22,23}

DEVELOPMENT OF THE PERSISTENT ATOPIC ASTHMATIC PHENOTYPE

The broad association between atopy and asthma symptoms during childhood has been recognized for many years,²⁴ and the strength of this relationship during the school years has been confirmed via the results of recent prospective cohort studies. The particular issue of whether the atopic phenotype per se can alone account for this association (eg, by increasing risk for development of inappropriate proinflammatory T helper [Th] 2-associated immunity against any class of inhaled antigen) is still debated. However, recent studies have demonstrated quantitative relationships between the level of sensitization in children as determined by measurement of aeroallergen-specific IgE titers and likelihood of expression of asthma symptoms,^{1,25} arguing that simple binary assessment of atopic status is inadequate for determination of disease risk. Moreover, the earlier sensitization develops during childhood,²⁶⁻²⁸ particularly severe sensitization,²⁹ the more likely it is that persistent asthma will follow. Collectively, these latter findings implicate atopic sensitization as a potentially important etiologic factor in early asthma but leave unresolved the issue of whether atopy can act alone in this context or whether it interacts with other factors to drive the disease.

A partial answer to this question again comes from a series of prospective birth cohort studies. First, we reported several years ago the results of the 6-year respiratory assessment of an unselected community sample of 2,640 children followed from birth. Among

these subjects, sensitization at outcome age was associated with significantly increased risk for current asthma, and even higher risk was observed among children who had experienced severe lower respiratory tract infections (LRIs) during infancy.³⁰ Although these factors could apparently act independently, maximum risk was observed among children who experience both sensitization and early respiratory tract infections.³⁰ We have suggested^{2,31} that interactions between inflammatory pathways triggered in the airways by these disparate stimuli during this period of rapid lung growth and remodeling may perturb normal tissue differentiation programs and result in disturbed respiratory function that “tracks” for long periods into later childhood. Indirect support for such interactions was provided from a second cohort of “high-risk” children from atopic families, in which prospective monitoring was more intensive.¹² In particular, every reported infection episode in these children up to age 5 years was assessed by a medical team, and the chronology of sensitization was determined by annual skin prick tests and serum IgE assays.³² Several crucial observations have come from these studies. First, the results confirmed that maximum risk of persistent asthma is found in the children who were both atopic and experienced early LRIs, and second, the bulk of the infection-associated asthma risk in this population was accounted for by subjects in whom sensitization occurred before age 2 years (ie, contemporaneous with the LRIs most strongly associated with subsequent asthma development).³² Additionally, and consistent with results from the Childhood Origins of Asthma (COAST) birth cohort,³³ the viral pathogen most strongly associated with risk for asthma development was hRV.³²

More recent analyses have further highlighted the quantitative nature of the relationship between early sensitization and early LRIs and the risk for subsequent asthma. The data in Figure 1 are derived from logistic regression analyses using information on the cumulative number of severe LRIs (with accompanying wheeze and/or fever) experienced by each child before age 2 years and their respective IgE titers against the aeroallergen (house dust mite) responsible for the bulk of sensitization in this population. Considering first the children in whom specific IgE was essentially undetectable (log titer -1.8), risk for wheeze at age 5 years increased eightfold from approximately 0.1 to approximately 0.8 across the range of infection frequencies observed.³² Focusing next on children who remained free of severe LRIs, their risk increased approximately 5.5-fold across the range of sensitization levels observed; this “amplifying” effect of sensitization on infection-associated asthma risk was evident across the full spectrum of observed infection frequencies, being most marked in the range

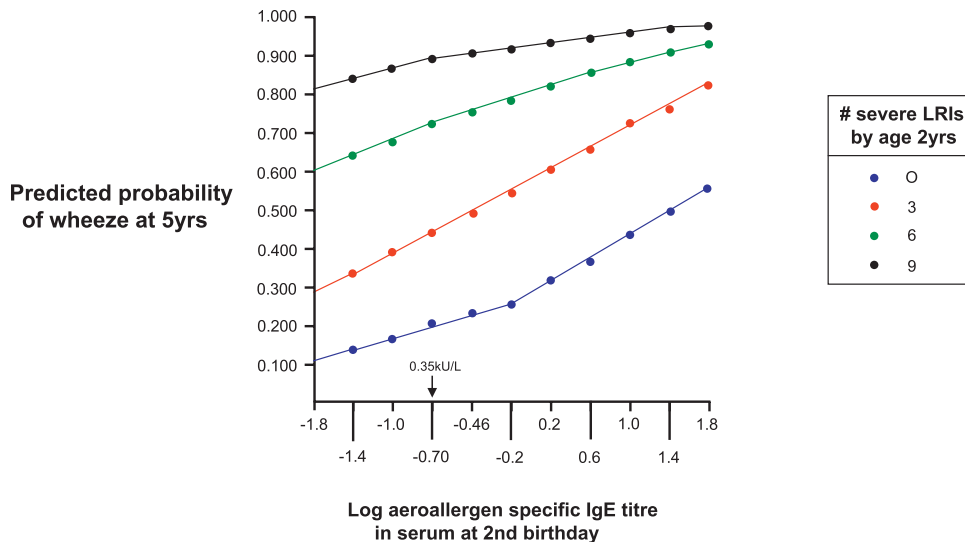


FIGURE 1. Early sensitization to aeroallergens amplifies the asthma-promoting effects of LRIs. In a cohort of 240 high-risk children, all “severe” LRIs (accompanied by wheeze and/or fever) were recorded up to age 2 years, together with serum titers of house dust mite-specific IgE at the same age. These data were used to compute probability of wheeze at outcome age 5 years via logistic regression (details in Reference 32). LRI = lower respiratory tract infection.

(three to four LRIs) most frequently encountered in this population.³²

ACUTE ASTHMA EXACERBATIONS: SIMILAR INTERACTIONS AT PLAY?

The importance of respiratory viral infections as triggers of acute severe asthma exacerbations has been recognized for many years,^{2,34} particularly in children. However, the underlying mechanisms are incompletely understood, partly because of the logistic and ethical difficulties associated with obtaining relevant clinical material for study at the time of acute symptoms. The development of highly sensitive genomics-based techniques for expression profiling, which require only nanogram levels of RNA, has opened up a range of new possibilities for addressing this complex question, two recent examples of which are discussed next.

The most severe examples of acute asthma exacerbations are those requiring hospitalization. Among children these occur most frequently in association with respiratory viral infections (especially hRV), particularly in atopic children, but the basis for these comorbidities has until recently been unknown. We have used this genomics-based technology to readdress this issue, guided by a precept established in the inflammation biology literature for > 30 years, notably that during episodes of inflammation the lung signals to the bone marrow to recruit myeloid cells (now recognized to include both monocytes and dendritic cells [DCs]) to replenish populations turning over rapidly at the challenge site.³⁵ More-

over, it has also been recognized that these signals (chemokines, cytokines, and so forth) also direct the functional maturation of myeloid cells prior to their release from the bone marrow, programming them optimally to meet the specific challenge responsible for generation of the signals.³⁶ In the specific context of atopic asthma, there is clear evidence of upregulation of eosinophil/basophil precursor populations in the bone marrow of patients with asthma following inhalation challenge with aerosolized allergen.^{37,38} This concept applies to all peripheral sites, one of the best understood examples being helminth parasite-infested GI tract tissues that generate signals upregulating antiparasite effector mechanisms in myeloid precursors prior to their release from the bone marrow.³⁶

We have recently demonstrated a similar sequence of events during viral infection-associated exacerbations in children with atopic asthma. Our approach involved genome-wide expression profiling of paired samples of peripheral blood mononuclear cells collected at the time of hospitalization for severe asthma exacerbation vs during convalescence.³⁹ Most prominent among the expression signatures associated with exacerbation were genes downstream of type 1 interferon (IFN) and IL-4/IL-13 and follow-on studies using flow cytometry localized the signatures predominantly to the monocyte and DC components of the peripheral blood mononuclear cells population; in contrast, Th cells displayed the postactivation (“exhaustion”) phenotype, suggesting participation in the inflammatory process at an earlier stage.³⁹ The standout marker detected on circulating myeloid

populations (monocytes and both myeloid and plasmacytoid DCs) during acute exacerbation was the high-affinity IgE receptor (FcεR1), which increased on a log scale, implying that the incoming replacements of airway mucosal DCs, which are turning over rapidly during the infection-triggered event,⁴⁰ arrive pre-equipped with these receptors.^{39,41} A precedent for this finding is high-level FcεR1 expression on DCs in lesions of active atopic dermatitis, in which FcεR1-bound IgE functions to enhance trapping/processing of specific allergens for subsequent local presentation to (and activation of) Th2 cells,⁴² a process that is believed to be central to atopic dermatitis pathogenesis. We hypothesize that in the case of atopic asthma, a similar mechanism functions to “recruit” underlying aeroallergen-specific Th2 memory cells into the inflammatory milieu of the infected airway mucosa.⁴¹ Based on recent animal model findings⁴³ and our *in vitro* human studies,³⁹ the initial trigger may be virally initiated local production of type 1 IFN acting to upregulate expression of the γ chain of FcεR1 on resident airway mucosal DCs. In this regard, it is known that FcεR1 on myeloid cells is a complex of the α and γ chains of the receptor⁴⁴ and also that atopic patients constitutively hyper-express the gene encoding the FcεR1-α chain on myeloid cells⁴⁵; surface expression of the α/γ complex on myeloid cells is limited in atopic patients by the availability of the γ chain,⁴² and, hence, upregulation of FcεR1-γ by type 1 IFN facilitates accelerated intracellular assembly of the complete receptor and thus amplifies its surface expression. As illustrated in Figure 2, this will potentially result in a cascade initiated locally in the airway mucosa via type 1 IFN and sustained/amplified via a feed-forward loop mediated by the effects of type 1 IFN and, in particular, Th2 cytokines on myeloid precursors in the bone marrow.⁴¹ An intriguing additional finding was the apparent dualistic effect of type 1 IFN in this cascade, as sufficiently high levels of this cytokine eventually inhibit IL-4/IL-13-mediated activation of the FcεR1-α chain gene.³⁹ Thus, type 1 IFN may also serve as an off switch to limit progression of this response toward a chronic state, and this may account in part for the association between type 1 IFN “deficiency” and increased risk for asthma.⁴⁶

An additional approach to understanding these complex interactions involves application of the same genomics-based technology to the study of cell populations in sputum collected during acute asthma exacerbations. In an exciting proof-of-concept study, Bosco and colleagues⁴⁷ collected induced sputum at the time of a moderate exacerbation and after convalescence in a group of children with asthma and compared genome-wide patterns of gene expression in sputum cells. Their results confirmed FcεR1 upregula-

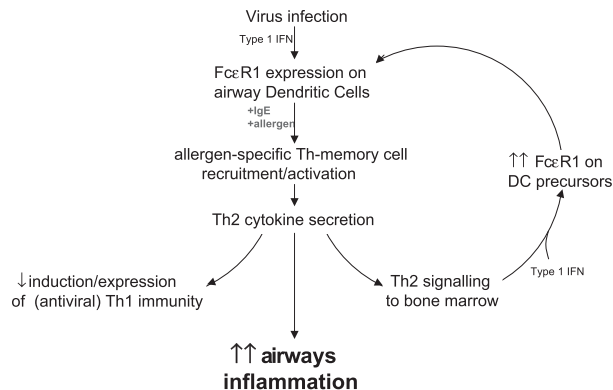


FIGURE 2. Operation of a lung/bone marrow axis during virally triggered acute severe asthma exacerbations. This schema is based on primary data from Reference 39 and discussion in Reference 41. In summary, signals triggered as a result of viral infection in airway tissue result in upregulation of FcεR1 on local DCs that turn over rapidly during infection and also in their precursors within bone marrow. In atopic subjects with a ready supply of aeroallergen-specific IgE and concomitant exposure to specific allergens, this sets the scene for a potentially self-sustaining inflammatory cascade. DC = dendritic cell; FcεR1 = high-affinity IgE receptor; IFN = interferon; Th = T helper.

tion and, in addition, demonstrated that the activation of Th1-like/cytotoxic and IFN signaling pathways during exacerbations is decreased in children with asthma with evidence of chronic airflow obstruction. Moreover, regardless of the presence or absence of chronic airflow obstruction, acute exacerbations were associated with markers of invariant natural killer T cells, and the latter were highly correlated with cytokines that promote Th1/cytotoxic responses (IL-12A, IL-21).

CONCLUSIONS AND SPECULATION

The findings presented here are derived principally from studies focusing on atopic asthma and demonstrate the potential for amplification of airways inflammation initiated locally by a microbial pathogen through effects induced in myeloid precursor populations at a distal site (the bone marrow). This may be mediated either via soluble cytokines/mediators secreted into the blood and/or via cytokine-secreting cells (notably activated Th cells) migrating from the inflammatory site into bone marrow.⁴⁸ As noted previously, this “axis” linking the bone marrow with sites of inflammation in the lung also operates outside the context of viral infections, and in particular provides an explanation for earlier observations that during active (as opposed to quiescent) atopic asthma, allergic rhinitis, and atopic dermatitis, FcεR1 expression is amplified “systemically” on myeloid cells at nonlesional sites.⁴⁹

In relation to viral infections in atopic patients, it appears implausible that triggering this cascade

facilitates viral clearance, given that Th2 immunity is known to antagonize the Th1-associated effector mechanisms that are central to host defense. Moreover, IgE triggering of FcεR1 on plasmacytoid DCs has recently been shown to impair their antiviral responses.⁵⁰ It is, thus, more likely that this overall process instead represents another example of viral evasion of the mammalian immune system via various forms of immune deviation, a survival strategy that is exploited by a variety of pathogens.⁴¹ In this regard, it is also noteworthy that the studies mentioned previously were restricted to severe grades of acute asthma associated with infection, but given the fundamental nature of the underlying inflammatory mechanisms, it is likely that the same processes operate at a less intense level during all infectious episodes. An important question that remains to be answered is whether the nature of the pathogen is an important determinant of the severity of these types of responses. Recent evidence from studies on post-nasal aspirates from the same cohort of children with severe asthma used to define the pathway in Figure 2 suggests that hRV type C represented the most common viral trigger of exacerbations in this group⁵¹; however, more detailed evidence is required from other studies to resolve this issue. Additionally, it is noteworthy that evidence is mounting in support of a role for bacterial colonization of the airway mucosa in susceptibility to asthma and other chronic inflammatory respiratory diseases.^{52,53} Given the strong evidence that bacterial-derived inflammatory signals can create unique activation signatures in bone marrow myeloid precursors,³⁶ it is tempting to speculate that breaching of epithelial barriers during viral-induced asthma exacerbations by mucosal-dwelling bacteria may also contribute to the local inflammatory milieu via a similar bone marrow-associated mechanism. It is interesting to note in this context our recent findings on the complex relationship(s) between immunity to mucosal bacteria-specific antigens in teenagers and their susceptibility to asthma,⁵⁴ and this is likely to become an increasingly important area of research in the short-term future.

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Patrick G. Holt and Peter D. Sly
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