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Viral-Induced Wheeze and Asthma Development

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Amaziah Coleman, James E. Gern
Departments of Pediatrics and Medicine, University of Wisconsin-Madison, Madison, WI, USA

Introduction

Wheezing illnesses occur in up to 50% of children by age 6 years[1] and are almost always initiated by viral infections. Respiratory syncytial virus (RSV) and rhinovirus (RV) infections are the two major causes of preschool wheezing illnesses, and there are a number of other viruses that cause smaller numbers of cases. Viral lower respiratory illnesses (LRI), with or without wheezing, are the most frequent cause of hospitalization in young children, and unfortunately specific treatments are lacking. Thankfully, for most children virus-induced wheezing episodes are transient and cease to occur after the preschool years. However, some children who wheeze in early life go on to develop persistent childhood asthma. It is important to define risk factors for the transition from recurrent virus-induced wheeze to persistent childhood asthma, to develop new strategies for asthma prevention. This review will focus on the epidemiology and etiology of virus-induced wheezing in early life and the relationship of viral LRI in early life to the subsequent development of asthma.

Longitudinal studies of childhood wheezing

One of the first large birth cohort studies in the United States to evaluate the natural history of childhood wheezing and risks associated with wheezing and asthma development was the Tucson Children's Respiratory Study.[2,3] An important finding of the study was the description of distinct wheezing phenotypes that occur during childhood: transient, nonatopic, and atopic.[4] Investigators later modified and identified four distinct wheezing patterns: never wheeze, transient early wheeze, late-onset wheeze, and persistent wheeze. Never wheeze was described as never having had a lower respiratory wheezing illness from birth to age 6 years. Transient early wheeze was described as having a wheezing lower respiratory illness before age 3 years only. Late-onset wheeze was described as wheezing at age 6 years only, and persistent wheeze was described as having a wheezing lower respiratory illness before age 3 years and wheezing after age 6 years.[5] Long-term follow-up of children in Tucson and other cohorts indicate that children with a persistent wheeze phenotype are at greater risk for subsequently developing asthma. Interestingly, the risk of asthma is not linked to viral infections per se; rather, the clinical response to infection seems to be most important. For example, the German Multicentre Allergy Study (MAS)

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Table 1 **Modified asthma predictive index**[10]

Modified asthma predictive index		
≥ 4 wheezing episodes in a year, plus:		
At least 1 major	**OR**	**At least 2 minor**
Parental asthma		Wheezing unrelated to colds
Atopic dermatitis		Eosinophils ≥ 4% in circulation
Allergic sensitization to at least one aeroallergen		Allergic sensitization to milk, eggs, or peanuts

reported that frequent episodes of upper respiratory illness marked by runny nose were inversely related to the development of asthma at age 7 years, whereas viral wheezing illnesses were positively related to the same outcome.[6]

The Tucson study also developed an Asthma Predictive Index based on risk factors for the transition between wheezing in infancy and asthma (Table 1).[7] This index can be used in the clinic to predict which children with recurrent wheeze have a high versus low probability of developing asthma in the next few years. It has been validated in other populations,[8] and a version modified to include more objective criteria has been used in clinical research studies to identify high-risk preschoolers.[9,10] Additional indices have been developed from other study populations, with similar performance characteristics.[11,12] Many of the risk factors for asthma onset after recurrent wheeze in childhood are related to personal or parental atopy (e.g., eczema, blood eosinophilia, or parental asthma).[13,14] Other factors include male sex, preterm delivery, and a history of wheezing apart from colds.[7,11,12]

Two of the longest longitudinal studies of wheezing illnesses and asthma were conducted in Australia and New Zealand. The Melbourne Asthma Study followed a group of children from age 7 years through adulthood. At age 42 years, study participants who had asthma as children were most likely to have significant wheezing into adulthood, with remarkable tracking of lung function and asthma severity.[15] Participants of the Dunedin, New Zealand, birth cohort were followed from birth through age 26 years. Over 25% of children had wheezing that persisted from childhood to adulthood or that relapsed after remission. Other factors that predicted persistent wheezing or wheezing relapse in this group included atopic sensitization, airway hyperresponsiveness, female gender, smoking, and early age of wheezing onset.[16] These longitudinal studies with extended periods of follow-up suggest that outcomes of asthma in adulthood are largely predetermined early in childhood (Table 1).

Etiology of wheezing illnesses in infancy

Most wheezing illnesses in the first few years of life are caused by respiratory viruses (Table 2).[17–21] Many viruses can cause wheezing illnesses in infancy, but the two most common are RSV and RVs.[21] Other frequent causes of wheezing illnesses include

Table 2 Pathogens associated with acute wheezing illnesses in infancy

Viruses	Bacteria
RSV	*Streptococcus pneumonia*
RV	*Moraxella catarrhalis*
Metapneumovirus	*Haemophilus influenzae*
Parainfluenza viruses	*Bordetella pertussis*
Coronaviruses	
Enteroviruses	
Bocavirus	
Influenza viruses	
Polyomaviruses	

metapneumovirus, coronaviruses, parainfluenza viruses, and bocaviruses. Coinfections with more than one virus are most common in young children and can result in greater severity of illness.[19,22] Prolonged illnesses are often caused by sequential infections with more than one virus.[23]

Respiratory syncytial virus

Respiratory syncytial virus is a medium-sized, negative-stranded ribonucleic acid virus of the family *Paramyxoviridae*, which causes a range of respiratory illnesses in infants and children. It can present as a benign upper respiratory illness or as severe bronchiolitis, especially in high-risk infants with prematurity of chronic lung disease. Respiratory syncytial virus infections are the most common cause of bronchiolitis in the first year of life, and nearly all children have had an RSV infection by age 3 years.[24]

Rhinoviruses

Rhinoviruses are members of the genus *Enterovirus* of the family *Picornaviridae* and are classified into three species (A, B, and C). More than 160 RV types have been identified to date.[25] Rhinoviruses are responsible for most upper respiratory tract infections (common colds) and, after RSV, are the viruses most often detected in wheezing infants. For years it was assumed that RV infection was confined to the upper airway and did not affect the chest except under unusual circumstances. Initial studies demonstrated optimal RV replication at 33–35 °C, and it was assumed that higher temperatures in the lower airways would limit RV replication. Contrary to these initial assumptions, direct measurements in the lower airways have shown that large and medium size airways are at the ideal temperature for RV replication.[26] Furthermore, some RV types, including C-species viruses, replicated equally well at 33 °C and 37 °C.[27,28] In addition, cultured lower airway epithelial cells support RV replication in vitro at least as well as, and perhaps even better than, cells derived from the upper airways.[29,30] Rhinovirus has been detected in sputum and bronchial biopsy specimens after experimental inoculation of

the upper airway[31–33] and is frequently detected in lower airway biopsies from infants with recurrent wheezing.[34] These findings provide strong evidence that RV can infect the lower airways, especially in young children. The species of RV affects its virulence, because RV-A and RV-C cause more severe illnesses in infants[35,36] and are more likely to cause exacerbations of childhood asthma.[37,38]

Bacteria and wheezing illnesses

It has been demonstrated that bacterial infections may also be associated with wheezing illnesses. The bacteria most commonly implicated include *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae*.[39] Furthermore, in a Danish birth cohort study, colonization with these common bacterial pathogens soon after birth was associated with increased incidence of recurrent wheeze and asthma in early childhood.[40] Viruses may precede overgrowth of respiratory pathogens, and both the virus and secondary changes in airway bacteria may contribute to the severity of acute illnesses.[41–44] However, serious bacterial infections accompanying bronchiolitis are rare,[45] and a meta-analysis found no evidence that antibiotics such as azithromycin or ampicillin are efficacious for treatment of bronchiolitis.[46] Because of the close relationships between viral and bacterial infection in the pathogenesis of other diseases such as otitis media and sinusitis,[47,48] understanding the role of airway bacteria in acute wheezing illnesses is a priority.

Risk factors for virus-induced wheezing

There are a number of risk factors for acute wheezing illnesses in early childhood (Figure 1).[1,49–51] These include factors related to genetics and lung structure and function (e.g., small lung size, prematurity). Environmental factors that can influence wheezing illnesses include siblings, day care attendance, stress, and exposure to

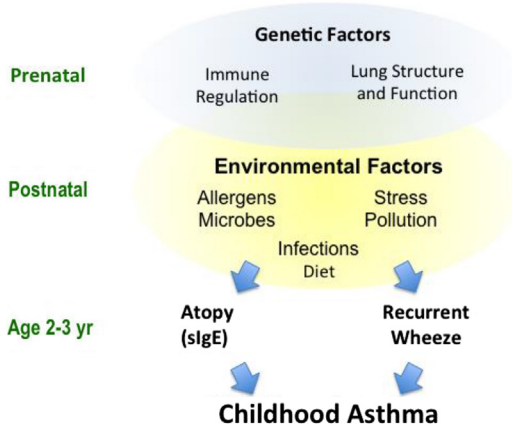

Figure 1 Risk factors for virus-induced wheezing and childhood asthma.

tobacco smoke, especially during the prenatal period. Other risk factors for viral LRI with wheeze include male sex, race, and low socioeconomic status. For RSV bronchiolitis, the relationship of birth date to peak RSV season is important; a birth date that occurs approximately 120 days before the peak of RSV season confers the highest risk.[51] For RV-induced illnesses, moderate-to-severe colds are more likely to occur in the wintertime, even after controlling for seasonal variation in the prevalence of different RV species.[35] Immunologic risk factors for viral LRI include low interferon responses from cord blood mononuclear cells and reduced numbers of plasmacytoid dendritic cells (pDCs), which are important sources of type I interferons.[52–55]

Genetics

Immune pathways that modify the risk of bronchiolitis have also been identified using genetic studies (Table 3). Several studies using a candidate gene approach have implicated genes encoding cytokines, chemokines, and antiviral effectors.[56–62] In addition, several studies have linked the severity of RSV illness to variation in surfactant and vitamin D pathways.[63] Fewer genetic associations of RV-induced wheezing have been identified. A study of infants hospitalized for their first episode of wheezing identified viral etiology and observed these infants for 2 years to assess recurrent wheezing. Investigators found that recurrent wheezing after RV bronchiolitis was associated with IL4RA, IL4RG, and MAP3K1 polymorphisms.[56] Finally, polymorphisms in the 17q12 region have been strongly linked to RV wheezing illnesses and to childhood asthma. In the Childhood Origins of Asthma (COAST) birth cohort study, there was an interaction between these outcomes; 17q12 genotype was strongly related to asthma, but only in children who had experienced RV wheezing illnesses in the first 3 years of life.[64]

Role of atopy

Personal or family history of atopy is an important risk factor for recurrent wheezing. Infants whose parents, especially mothers, had atopy or asthma are at increased risk for viral wheezing.[65] Sensitization to food proteins or aeroallergens in infancy is a risk factor for recurrent wheezing episodes.[66] Viral respiratory illnesses and wheezing

Table 3 Genes associated with viral-induced wheezing in infancy[56–58,61–64,110–113]

Cytokines and chemokines	Receptors	Other
Genes associated with RSV wheezing		
IL4, IL6, IL10, IL13, IL19, IL20, IFNG, IFNA5, CCL5, CXCL8, TGFB1, IL4RA, TNF	TLR4, CCR5, CD14, VDR	SPA, SPD, MBL, VDBP, JUN, NOS2, ADAM33
Genes associated with RV wheezing		
IL10	IL4RA	MAP3K1, 17q21

are more common in infants with atopic dermatitis, especially when the dermatitis is persistent.[67] Likewise, mutations in the *FLG* gene (encoding filaggrin) are associated with more significant atopic dermatitis and also with early wheezing illnesses.[68]

Microbial exposures

In addition to bacterial pathogens, there is interest in defining relationships between microbial exposures and colonization and the risk of wheezing illnesses. In western Europe, rural infants from farm families are less apt to develop transient wheeze, likely of viral origin.[69] Findings from other studies suggest that farm-related microbial exposures are likely to mediate protective effects against allergies, wheezing, and asthma.[70,71] Children growing up in poor urban neighborhoods have different exposures, with high rates of cockroach allergens, stress and violence, and pollutants. Even so, high-level exposure to microbes in house dust in the first year of life is associated with a reduced risk of atopy and atopic wheeze.[66] Children with the lowest risk of atopic wheeze are those who have increased exposure to both microbes and allergens.[66] These findings suggest that environmental microbial exposures in early life could be important in modifying the immune response to respiratory infections, either directly or indirectly through effects on atopy.

Progression from virus-induced wheezing to asthma

Role of atopy

Longitudinal cohort studies have established that there are strong and dose-related effects of early life sensitization on the development of asthma. For example, prospective studies of high-risk children in Perth, Australia demonstrated that serum immunoglobulin E (IgE) levels to house dust mite at age 2 years had a dose-related association with recurrent wheeze at age 5 years.[72] In this study, the number of LRIs and mite-specific IgE both contributed to risk for subsequent wheezing episodes.[72] In the MAS cohort, children with atopic wheeze lost lung function relative to children with nonatopic wheeze after age 5 years and lung function was lowest in children who were both sensitized and had exposure to the same allergen.[73] A latent class analysis of children in a population-based cohort identified multiple early sensitization to allergens as an important risk factor for recurrent wheezing and asthma at age 8 years.[74] Children who were polysensitized to multiple allergens before age 2 years have especially high risk for developing virus-induced wheezing episodes and subsequently, asthma. Polysensitization was also related to lower lung function and airway hyperresponsiveness.[74]

Respiratory syncytial virus and asthma

Respiratory syncytial virus bronchiolitis is associated with an increased risk for recurrent wheezing in the months after the acute infection, and up to half of children who are hospitalized with RSV bronchiolitis are subsequently diagnosed with asthma.[75]

These associations have been consistently observed in birth cohort studies and those with long-term follow-up of hospitalized infants. For example, Sigurs and colleagues conducted a case–cohort study of 93 Swedish children hospitalized for RSV bronchiolitis in infancy and 47 matched control children. Those with early RSV bronchiolitis were found to have recurrent wheezing or asthma, allergic sensitization, airway obstruction, and airway hyperreactivity in early adolescence.[76] This same group of children were followed into early adulthood and found to have an increased prevalence of allergic asthma.[77] Relationships with atopy and asthma have also been evaluated in birth cohort studies, with slightly different findings. For example, the Tucson Children's Respiratory Study observed children from birth and found that RSV lower respiratory illnesses in early childhood were a risk factor for recurrent wheezing up to age 11 years, but not age 13 years.[78] Unlike the Sigurs study, there was no association between RSV bronchiolitis and the prevalence of atopy later in childhood. Similarly, data from a large British birth cohort study (Avon Longitudinal Study of Parents and Children) found that hospitalization with RSV bronchiolitis in infancy was associated with asthma (odds ratio [OR], 2.5 [1.4, 4.3]) but not with atopy (OR, 0.7 [0.2, 1.7]) at age 7 years.[79]

There have also been efforts to identify risk factors for development of asthma after hospitalization with RSV bronchiolitis. In a prospective cohort study of 206 infants hospitalized with RSV, risk factors for subsequent asthma development included maternal asthma, exposure to dog allergen, and allergic sensitization by age 3 years.[75]

Intervention studies for RSV

Palivizumab is a monoclonal antibody to the RSV F protein that inhibits binding of the virus to cellular receptors. When administered preseasonally to high-risk infants, palivizumab reduces the rate and severity of RSV infections and the incidence of RSV bronchiolitis. Because of the high cost of this medication, its use is limited to infants who are at increased risk for adverse outcomes such as hospitalization for bronchiolitis.

Several studies have now tested whether prophylaxis with palivizumab reduces subsequent rates of recurrent wheezing and childhood asthma. A prospective nonrandomized study involving centers in Canada and Europe explored the influence of RSV prophylaxis on subsequent wheezing and found an 80% decrease in the risk of recurrent wheezing from ages 2 to 5 years in nonatopic children, but no effect in atopic children.[80] More recently, healthy preterm infants born at 33–35 weeks' gestation were enrolled in a double-blind, placebo-controlled trial of palivizumab prophylaxis and were monitored for 1 year to determine effects on recurrent wheeze. All of the children were age 6 months or less at the start of RSV season. In this study, palivizumab treatment led to a 61% relative reduction in the total number of wheezing days in the first year of life.[81] A case–control study in Japan enrolled a similar population of 444 infants with mild prematurity, 349 of whom were treated with palivizumab. The children were monitored for 3 years, and recurrent wheezing was significantly less common in the treated versus untreated groups (6.4% versus 18.9%; $P < .001$).[82]

Rhinovirus and asthma

Several studies have identified a relationship between the viral etiology of wheezing illnesses in infancy and the risk of developing asthma. In a study of children aged less than 2 years who were hospitalized for acute wheezing illnesses, RV was the predominant virus seen in these children after age 5 months. When followed up 5 years after hospitalization, 60% of children who wheezed with RV in the first 2 years of life had asthma.[83] Researchers from the same group found that hospitalization for RV-induced wheezing before age 2 years predicted the risk for asthma during the teen years.[84] The COAST birth cohort is a high-risk cohort of children observed prospectively through adolescence. In this cohort, outpatient RV wheezing illnesses during the first year of life are a significant predictor of recurrent wheezing through age 3 years.[19] Furthermore, RV wheezing illnesses in infancy significantly predicted development of asthma at age 6 years, especially among children with evidence of aeroallergen sensitization by age 3 years.[85] Similar findings were reported in an Australian birth cohort study involving high-risk children; early life infections with RV or RSV were associated with an increased risk of asthma, but only in children who had developed aeroallergen sensitization by age 2 years.[13] Several studies have linked the susceptibility of RV-wheezing illnesses to allergic predisposition in infants of atopic families.[86] These findings suggest that RV wheezing illnesses and early onset of atopy are both strongly associated with childhood asthma.

Do severe viral respiratory infections in infancy cause asthma?

Observational studies have defined a strong and consistent association between viral LRI with wheezing in infancy and subsequent childhood asthma, but this type of study cannot definitively establish causality. There are at least three possible hypotheses to explain the nature of this association: (1) there is a common predisposing factor that increases the risk of both viral wheezing and asthma; (2) children who are predisposed to asthma are more likely to wheeze during viral infections; or (3) viral respiratory illnesses contribute to the causation of asthma. There are data to support each of these possibilities, as discussed in the following sections.

Hypothesis 1: Infants who are already predisposed to asthma are more likely to wheeze when they develop viral illnesses. This hypothesis implies that asthma, or at least a predisposition to asthma, can be established early in life or perhaps during the prenatal period. Viral respiratory infections, which are a significant source of lower airway inflammation, merely reveal the underlying asthma and serve as a signaling event rather than having a causal role. In other words, children who are predisposed to virus-induced wheezing are also predisposed to asthma.

In support of this theory, asthma risk can be passed from parents to offspring through genetics (and perhaps epigenetic modifications) and also from mother to child via environmental exposures (e.g., tobacco smoke) in utero. To investigate maternal effects on RV- and RSV-induced wheezing illnesses, the Tennessee Children's Respiratory

Initiative conducted a longitudinal analysis of mother–infant dyads in which mothers were classified in four groups according to the presence or absence of atopy and asthma.[65] Results indicate that clinically significant RV illnesses during infancy were associated with a maternal history of atopic asthma. Maternal atopic asthma was also associated with increased severity of RV infection in infancy, which suggests that infants with RV wheezing in early life are more likely to have a familial predisposition to atopic asthma.[65] This association could help to explain why infants who experience RV wheezing illnesses are most likely to develop asthma subsequently.

Several twin studies have investigated a causal link between RSV infection in infancy and childhood asthma, but the results supported that susceptibility to asthma predetermines RSV infection.[87–89] In addition, studies of infant lung function suggest that reduced neonatal lung function is a risk factor for virus-induced wheeze[90,91] and asthma later in childhood.[92,93] The results of these studies provide evidence that predisposing factors such as lung function or familial atopy can influence the risk of virus-induced wheezing and asthma.

Hypothesis 2: Viral respiratory illnesses contribute to the causation of asthma. This hypothesis implies that viral infections can damage the structure or alter the function of the lower airways in such a way as to promote asthma. In fact, viruses that infect the lower airways lyse airway epithelial cells and induce inflammatory responses that cause further damage to the airways. The potential to cause persistent effects on the lower airway is greatest when viral LRIs occur in early life during rapid lung growth.[94] Animal models provide evidence that viral LRI in early life can have long-lasting effects on airway epithelial cell and macrophage inflammatory responses,[95] and can induce abnormalities in the morphology of small airways.[96]

Respiratory syncytial virus infections are seasonal, and analysis of the seasonal patterns of birth date, RSV wheezing illnesses, and incident asthma support a causative effect of viral illnesses on subsequent asthma. In a study involving over 95,000 infants in a Tennessee Medicaid database, the risk of developing asthma corresponded with the timing of infant birth in relationship to the winter virus peak.[51] Infants born approximately 4 months before the winter virus peak had the highest risk of developing RSV bronchiolitis and also the highest asthma risk (adjusted OR, 1.29; 95% confidence interval, 1.19–1.40) at age 5.5 years.

Intervention studies provide valuable insights into disease causation, and as outlined earlier in this review, studies of prophylactic use of palivizumab provide convincing evidence that prevention of RSV LRI in the first year of life reduces the risk of recurrent wheeze for 1–5 years.[80,81] To date, palivizumab has not been shown to prevent allergic asthma, and so far studies of effects on asthma have been restricted to infants who were born prematurely. Nonetheless, these findings demonstrate that prevention of acute virus-induced lung injury leads to beneficial effects on airway physiology for several years.

Clinical evidence supporting an association between RV wheezing illnesses and subsequent childhood asthma is strong, but in contrast to RSV, currently no interventions can prevent RV illnesses to assess effects on asthma. Nevertheless, other experimental evidence strongly suggests that RV infections can contribute to causation of asthma. One unique feature of RV infection is that with over 160 types,[97,98] a child who

is susceptible to RV LRIs with wheezing can develop multiple infections per year. RV infections probably cause less lower airway damage per infection compared with more virulent viruses such as RSV and influenza, but cumulative damage to the airways from multiple RV infections could be substantial. Notably, RV infections can induce factors (e.g., *vascular endothelial growth factor*, transforming growth factor-β)[99,100] that have been linked to airway remodeling, and in murine models, RV infections of young animals can induce mucoid metaplasia and airway hyperresponsiveness.[101]

Hypothesis 3: There is a common predisposing factor that increases the risk of both viral wheezing and asthma. This is a joint effect theory, in which a predisposing factor would cause viral wheezing *and* asthma, but viral wheezing is not causal for asthma. A number of factors could increase the risk of both virus-induced wheeze in early life and childhood asthma. Examples include atopy, immunologic factors (low interferon responses or bias toward type 2 T-cell responses), and lung factors (low lung function at birth or poor epithelial cell barrier function). It would be difficult to prove this theory because one would need to prove that the predisposing factor caused both viral wheezing and asthma, and that an intervention targeting viral wheezing would not affect asthma incidence.

Atopy, virus-induced wheeze, and the complex causality of childhood asthma

The three theories listed above are not mutually exclusive, and each could contribute to the association between viral wheezing and childhood asthma. As stated above, there is evidence that predisposing factors increase viral wheezing, and that viral wheezing can damage airway structures and promote remodeling. With the growing understanding that asthma has multiple endotypes and that the genetic and environmental influences (including viral respiratory infections) on childhood asthma onset are complex, there is no doubt that asthma causation is also multifaceted.

As an example, RSV and RV are the two viruses most closely associated with wheezing, but differences in the viruses and natural histories of illness likely translate into different relationships with asthma causation. Respiratory syncytial virus is the more virulent of the two viruses, and babies who develop severe RSV illnesses are at risk for recurrent wheezing that may persist for several months up to 10 years. Mechanisms for post-RSV recurrent wheezing are still speculative, but likely involve airway injury, and remodeling of the airway structures and perhaps neural elements.[102,103] After the initial infection, activation of the adaptive immune response reduces the risk of a second RSV LRI, and serious illnesses with subsequent RSV infections are uncommon.

The effects of RV and interaction with host effects could be different. RV wheezing illnesses are less common that RSV illnesses until year 2. There appear to be some common risk factors for wheezing with RV versus RSV (e.g., small lung size[90,91]), but there are some differences as well. Atopy appears to be an important risk factor for RV wheezing, but it is less of a factor for wheezing with other viruses.[104] Similarly, maternal asthma increases the likelihood of wheezing with RV infections but does not affect the risk of wheezing with other viruses.[65] Interestingly, for children who progress from RV recurrent wheeze to persistent asthma, the number of RV wheezing illnesses

in the first few years increases, and this is in distinct contrast to the stepwise reduction that is observed in children who do not develop asthma.[85] This temporal increase in susceptibility to RV wheezing occurs concurrently with increasing sensitization to aeroallergens. In fact, a temporal analysis in the COAST birth cohort demonstrated that atopy generally precedes RV wheezing episodes, rather than the converse (wheezing episodes preceding the onset of atopy).[105]

These findings raise the possibility that atopy might impair the immune response to viral respiratory infections, and several potential mechanisms have been described. For example, pDCs are potent sources for type I and III interferons, which have strong inhibitory effects on RV infections. pDCs are responsive to allergic inflammation because they express the high-affinity IgE receptor (FcεRI) on the cell surface. Notably, cell surface expression of FcεRI is inversely related to the virus-induced interferon secretion.[106] Furthermore, cross-linking FcεRI markedly impairs interferon responses to influenza virus or RV,[106,107] suggesting that the combination of allergy and allergic inflammation could inhibit antiviral responses at the mucosal surface. In epithelial cells, allergic inflammation and RV infection can induce mucus metaplasia through mechanisms that involve induction of the transcription factors forkhead box protein A3 (FOXA3) and SAM pointed domain containing ETS transcription factor (SPDEF).[68,108] FOXA3 expression in epithelial cells can inhibit antiviral responses (e.g., type I interferons) and enhances expression of pro-allergic factors such as TSLP.[109] During acute viral infections, the function of FOXA3 may be to limit inflammatory responses as the infection resolves, but chronic expression in the context of allergic inflammation could instead inhibit antiviral responses, potentially leading to more severe illness.[109]

Considered together, effects of more severe infections with RSV, RV, and other pathogens (including bacterial) could represent repeated insults to the developing lung and immune system that promote the development of asthma. Respiratory syncytial virus bronchiolitis can cause significant damage to the airways during a particularly vulnerable period with respect to lung growth and differentiation. In infants who develop allergic sensitization, repeated RV LRI could provide repeated insults to the developing small airways. Repair of virus-induced damage may remodel the airways, thus increasing the risk for asthma, especially in children who are at increased risk because of genetic factors or exposed to adverse environmental stimuli.

Conclusions

There is a close relationship between virus-induced wheezing in infancy and the onset of childhood asthma. The associations are well documented, but important questions remain about causality. These questions are best answered with interventional studies; results of observational studies indicate that strategies to target respiratory viruses and those directed at prevention of atopy are warranted. Defining relationships between viral infection, atopy, and lung development in early life could lead to new strategies for the prevention or treatment of viral LRI and, ultimately, the prevention of childhood asthma.

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