

Viral infections and asthma inception

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Respiratory tract infections caused by viruses have been implicated in the pathogenesis of asthma. Of these respiratory pathogens, viruses have been demonstrated to be associated with asthma epidemiologically in at least 3 ways (Fig 1). First, during infancy, certain viruses have been implicated in the inception of the asthmatic phenotype. Genetic susceptibility, particularly genes coding for atopic phenotypic characteristics, might differentiate, at least in part, those children who are destined to have persistent wheezing, asthma, or both later in childhood. Second, repeated exposure to infectious viruses in daycare centers or in households with multiple older siblings increases the number of respiratory infections, but in doing so, it might paradoxically reduce the long-term risk of allergies and asthma through either pre-existing or newly formed alterations in cytokine response profiles. Third, in patients with established asthma, particularly children, viral upper respiratory tract infections play a significant role in producing acute exacerbations of airway obstruction that might result in frequent outpatient visits or in hospitalizations. This review will highlight available data on respiratory syncytial virus infections and their relationship to asthma inception in childhood. (*J Allergy Clin Immunol* 2004;114:1023-6.)

Key words: Respiratory syncytial virus, rhinovirus, asthma, cytokine, virus

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS AND WHEEZING

The epidemiologic association of infantile viral-induced bronchiolitis with the subsequent development of recurrent wheezing, asthma, or both has intrigued many clinicians-scientists for decades. Of the various respiratory viruses linked to these relationships, respiratory syncytial virus (RSV) is the most commonly implicated. RSV is categorized within the family of Paramyxoviridae and the genus of *Pneumovirus*. It is an enveloped, medium-sized virus (120-300 nm) consisting of a single strain of

Abbreviation used

RSV: Respiratory syncytial virus

nonsegmented RNA. RSV has 2 major immunogens primarily responsible for the formation of neutralizing antibody: the fusion (F) protein and the attachment (G) protein. The G protein mediates attachment of the virus to target epithelial cells in the host, whereas the F protein facilitates fusion of the virus lipid membrane with the cellular lipid membrane, permitting insertion of the RNA into the host cell. The F protein also promotes fusion of uninfected cells, leading to syncytial formation (thus the name). In both murine and human *in vitro* experiments, it has been noted that the G protein elicits a predominant T_H2 immune response, whereas the F protein produces a predominant T_H1 response. Two types of RSV (A and B) are recognized that differ primarily on variations in the structure of their G protein. The clinical significance of subtype differentiation remains uncertain because infection with subtype A does not protect the host from future infection with the same subtype, nor does it guarantee that subsequent subtype A infections will be less severe.¹

Although numerous studies have implicated RSV infections with recurrent wheezing, airway hyperresponsiveness, and subsequent asthma,¹ data pertaining to these associations have been difficult to interpret definitively because of a number of methodological concerns. However, 2 recent prospective studies have been able to document that antecedent RSV infections are risk factors for both recurrent wheezing² and physician-diagnosed asthma.³ An interesting paradox of these observations has been the fact that nearly 100% of children have been infected with RSV by age 2 years.

Two possible explanations for these associations have been proposed. The first is that RSV persists or in some way affects the immature respiratory and immune systems of the neonate, predisposing the host to recurrent respiratory tract infections, bronchial hyperresponsiveness, and long-term pulmonary and immunologic sequelae (the consequential hypothesis). The second is that susceptible infants might have pre-existing diminished lung function, genetic susceptibility to the development of lung disease, or both (the common causal hypothesis).¹ It is possible that a combination of both could be true. Thus the elucidation of genetic, environmental, epidemiologic, and immunologic factors that

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Supported by National Institutes of Health grant 1P01AI50500.

Received for publication August 5, 2004; revised August 5, 2004; accepted for publication August 9, 2004.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.08.031

TABLE I. Genetic associations with more severe RSV infections

Genes encoding for:	Function	Associated outcome	Study design	Reference
<i>CCR5</i>	Receptor for chemokines (RANTES)	More severe hospitalized patients	Case control and transmission disequilibrium	Hull et al ¹²
<i>IL4</i>	T _H 2 differentiation, promotes IgE synthesis	Hospitalization	Case control	Choi et al ¹¹ and Hoebee et al ¹³
<i>IL4Ra</i>	Receptor subunit for IL-4 and IL-13	Hospitalization	Case control and transmission disequilibrium	Hoebee et al ¹³
<i>IL8</i>	Neutrophil chemoattractant		Transmission disequilibrium	Hull et al ⁹
<i>IL10</i>	Anti-inflammatory cytokine	Hospitalization	Case control and transmission disequilibrium	Hoebee et al ¹⁰
Surfactant protein D	Airway surfactant	Hospitalization		Lahti et al ¹⁴
<i>TGFB1</i>	Fibrosis, anti-inflammatory effects	Wheezing	Birth cohort	Hoffjan et al ¹⁵

predispose certain individuals to the development of chronic lower respiratory tract sequelae after these infections has been the subject of intense study.

IMMUNE RESPONSE

T_H1-T_H2 imbalance

Immunologic mechanisms that have been explored have focused primarily on cytokine dysregulation by using an imbalance of T_H1-T_H2 cytokine response patterns as a major area of investigation in both human and animal models. In human subjects reduced IFN- γ expression in PBMCs of infants with severe RSV disease has been observed,⁴ as has diminished PBMC production of IFN- γ both during and months after RSV-induced bronchiolitis in only those children who have subsequent asthma.⁵ In contrast, analyses of IFN- γ levels obtained from upper airway secretions during episodes of viral-induced wheezing have demonstrated an increased level of this T_H1 cytokine.⁶ PBMC secretion of the regulatory cytokine IL-10 has been reported to be increased during the convalescent phase in hospitalized children with RSV-induced bronchiolitis, and levels were significantly higher in children with recurrent wheezing.⁷ In this study no association was found between IFN- γ responses, IL-4 responses, or IFN- γ /IL-4 ratios and recurrent wheezing. A recent report on cytokine response profiles in high-risk babies (at least one atopic asthmatic parent) during a documented RSV illness contrasts with these findings.⁸ During their acute illness, nasal lavage IL-4/IFN- γ and IL-10/IL-12 ratios in infants who had bronchiolitis were significantly increased compared with those in infants who did not. Similar evidence for T_H2-polarized responses was seen when PBMC mRNA levels were evaluated: IL-18 levels were reduced, and the IL-4/IFN- γ ratio was increased.

Chemokines

Recent data indicate that additional immunoinflammatory mechanisms might be contributory. The chemokines

RANTES and macrophage inhibitory protein 1 α have been found to be increased in nasal lavage fluids from infants with RSV-induced bronchiolitis compared with levels in infants with RSV but without bronchiolitis and in infants without RSV but with acute respiratory illnesses. Although both of these chemokines are capable of attracting lymphocytes, eosinophils, or both to infected tissues, it is not clear whether high levels of these chemokines are important in disease pathogenesis. Genetic variants of the major receptor for these chemokines, CC chemokine receptor 5, were recently evaluated to address this question. Two single nucleotide polymorphisms (–2459G and –2554T) were found to be associated with severe bronchiolitis. Several other genes have been related to adverse outcomes with RSV infection (Table I),^{9–15} and this has spurred intensive efforts to determine the mechanisms underlying these relationships.

LUNG FUNCTION

Premorbid measurements of lung function indicate that children with reduced levels of lung function in infancy appear to be at increased risk of chronic lower respiratory tract sequelae after viral infections.¹⁶ It is doubtful that this defect is solely responsible for the development of chronic lung disease, and additional host factors are currently being evaluated. Furthermore, the ability of one virus (ie, RSV) to be more likely responsible for these outcomes (because of either virus- or host-specific factors) has also not been well defined. Indeed, recent data would indicate that rhinovirus-induced bronchiolitis, although less frequent than that induced by RSV, might cause more severe patterns of disease during infancy.¹⁷

ANIMAL MODELS

Several animal models have been used to evaluate the types of changes that occur in the airways as a result of infections with respiratory viruses. RSV infections have been most extensively studied in mice, and these murine

Relationship of Viral Infections to Asthma Pathogenesis

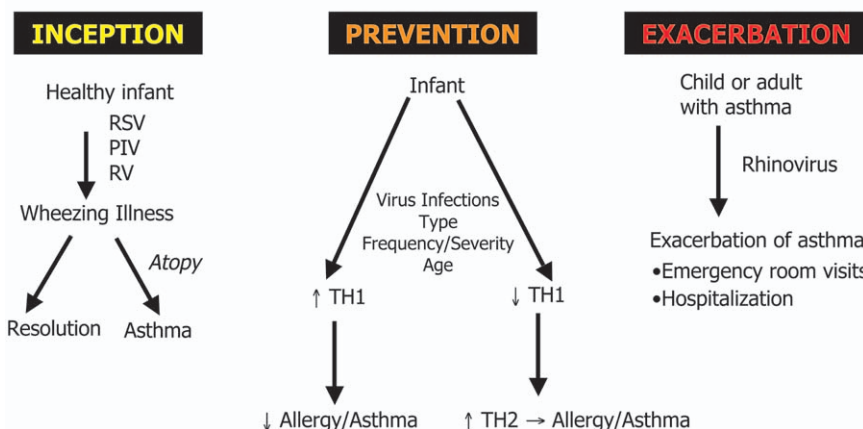


FIG 1. Viral infections have been implicated in at least 3 ways with asthma pathogenesis: inception, prevention, and exacerbations. Asthma inception after early childhood respiratory tract infections might be influenced by genetic (atopy), environmental (type of virus and concomitant allergen exposures), and developmental (age at which these events occur) factors. Repetitive infections might confer protection on the basis of their ability to skew the immune response away from T_H2 cytokine responses. Once the asthmatic phenotype develops, viruses might cause periodic exacerbations. PIV, Parainfluenza virus; RV, rhinovirus.

infections result in airway inflammatory and physiologic changes reminiscent of those seen in human asthma. The results of these evaluations indicate that RSV has the potential of inducing polarized cytokine response patterns (T_H1 vs T_H2) on the basis of differential responses to 2 of its structural constituents (F and G proteins),¹⁸ and this might be particularly likely if the animals are infected at a young age.¹⁹ IL-13 seems to be important in inducing a state of airway hyperresponsiveness after infection,²⁰ whereas prior airway exposure to allergen increases viral-induced airway hyperresponsiveness.²¹

Parainfluenza 1 (another member of the paramyxovirus family) infections in weanling rats can induce the development of a chronic asthma phenotype.²² The infection must occur in a genetically susceptible strain (T_H2 skewed) at a critical time point in the development of the animal to induce this response.²² Interestingly, the selective administration of IFN- γ to these animals after infection inhibits the development of the chronic airway dysfunction.²³ Cytokine dysregulation in these rats is related to aberrancies in natural killer cell numbers and functions as part of the innate immune response to viral infection.²⁴ In mice the timing of RSV infections in early life also influences the subsequent development of immune response profiles to reinfection.²⁵ Taken together, these findings strongly support the concept that viral infections might have to occur in a genetically susceptible host at a critical time period in either the development of the immune system, the lung, or both for asthma inception to occur in early childhood.

NON-RSV PATHOGENS

From a number of epidemiologic observations, it appears that other viral infections during infancy and early childhood that have a predisposition for lower airway involvement (eg, parainfluenza, influenza A, and metapneumovirus) can also be associated with chronic lower respiratory tract symptoms, including asthma.²⁶ The recent discovery of a previously unrecognized pathogen, metapneumovirus, indicates that it has contributed significantly to lower respiratory tract illnesses in early childhood.²⁶ Rhinovirus infections associated with wheezing during infancy have also been potentially implicated with the subsequent development of childhood asthma.²⁷ The precise contribution of these infections to the development of asthma remains to be determined.

CONCLUSIONS

Viral respiratory tract infections that induce acute lower airway symptoms have the potential of predisposing infants and toddlers to the development of asthma. Because a number of viruses have been implicated, it appears that host-related factors, which might involve immune system abnormalities based on genetic susceptibility or developmentally regulated processes, are the predominant influences on these outcomes. Nonetheless, because RSV infections have been most frequently documented with regard to asthma

inception, it is possible that immune responses unique to this virus might also play a role in these outcomes. Untangling these relationships will require prospective birth cohort studies designed to address these important unanswered questions.

REFERENCES

1. Openshaw PJ, Dean GS, Culley FJ. Links between respiratory syncytial virus bronchiolitis and childhood asthma: clinical and research approaches. *Pediatr Infect Dis J* 2003;22(suppl 2):S58-64.
2. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541-5.
3. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161:1501-7.
4. Aberle JH, Aberle SW, Dworzak MN, Mandl CW, Rebhandl W, Vollnhöfer G, et al. Reduced interferon- γ expression in peripheral blood mononuclear cells of infants with severe respiratory syncytial virus disease. *Am J Respir Crit Care Med* 1999;160:1263-8.
5. Renzi PM, Turgeon JP, Marcotte JE, Drblik SP, Bérubé D, Gagnon MF, et al. Reduced interferon- γ production in infants with bronchiolitis and asthma. *Am J Respir Crit Care Med* 1999;159:1417-22.
6. van Schaik SM, Tristram DA, Nagpal IS, Hintz KM, Welliver CII, Welliver RC. Increased production of IFN- γ and cysteinyl leukotrienes in virus-induced wheezing. *J Allergy Clin Immunol* 1999;103:630-6.
7. Bont L, Heijnen CJ, Kavelaars A, Van Aalderen WM, Brus F, Draaisma JT, et al. Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. *Am J Respir Crit Care Med* 2000;161:1518-23.
8. Legg JP, Hussain IR, Warner JA, Johnston SL, Warner JO. Type 1 and type 2 cytokine imbalance in acute respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med* 2003;168:633-9.
9. Hull J, Thomson A, Kwiatkowski D. Association of respiratory syncytial virus bronchiolitis with the interleukin 8 gene region in UK families. *Thorax* 2000;55:1023-7.
10. Hoebee B, Bont L, Rietveld E, van Oosten M, Hodemaekers HM, Nagelkerke NJ, et al. Influence of promoter variants of interleukin-10, interleukin-9, and tumor necrosis factor- α genes on respiratory syncytial virus bronchiolitis. *J Infect Dis* 2004;189:239-47.
11. Choi EH, Lee HJ, Yoo T, Chanock SJ. A common haplotype of interleukin-4 gene IL4 is associated with severe respiratory syncytial virus disease in Korean children. *J Infect Dis* 2002;186:1207-11.
12. Hull J, Rowlands K, Lockhart E, Moore C, Sharland M, Kwiatkowski D. Variants of the chemokine receptor CCR5 are associated with severe bronchiolitis caused by respiratory syncytial virus. *J Infect Dis* 2003;188:904-7.
13. Hoebee B, Rietveld E, Bont L, Oosten M, Hodemaekers HM, Nagelkerke NJ, et al. Association of severe respiratory syncytial virus bronchiolitis with interleukin-4 and interleukin-4 receptor α polymorphisms. *J Infect Dis* 2003;187:2-11.
14. Lahti M, Lofgren J, Marttila R, Renko M, Kilaavuniemi T, Haataja R, et al. Surfactant protein D gene polymorphism associated with severe respiratory syncytial virus infection. *Pediatr Res* 2002;51:696-9.
15. Hoffjan S, Ostrovskaja I, Nicolae D, Newman DL, Nicolae R, Gangnon R, et al. Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. *J Allergy Clin Immunol* 2004;113:511-8.
16. Castro-Rodríguez JA, Holberg CJ, Wright AL, Halonen M, Taussig LM, Morgan WJ, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthma-like symptoms and pulmonary function during childhood: a prospective study. *Am J Respir Crit Care Med* 1999;159:1891-7.
17. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111:66-71.
18. Johnson TR, Parker RA, Johnson JE, Graham BS. IL-13 is sufficient for respiratory syncytial virus G glycoprotein-induced eosinophilia after respiratory syncytial virus challenge. *J Immunol* 2003;170:2037-45.
19. Culley FJ, Pollott J, Openshaw PJ. Age at first viral infection determines the pattern of T cell-mediated disease during reinfection in adulthood. *J Exp Med* 2002;196:1381-6.
20. Tekkanat KK, Maassab HF, Cho DS, Lai JJ, John A, Berlin A, et al. IL-13-induced airway hyperreactivity during respiratory syncytial virus infection is STAT6 dependent. *J Immunol* 2001;166:3542-8.
21. Makela MJ, Tripp R, Dakhama A, Park JW, Ikemura T, Joetham A, et al. Prior airway exposure to allergen increases virus-induced airway hyper-responsiveness. *J Allergy Clin Immunol* 2003;112:861-9.
22. Kumar A, Sorkness R, Kaplan MR, Castleman WL, Lemanske RF Jr. Chronic, episodic, reversible airway obstruction after viral bronchiolitis in rats. *Am J Respir Crit Care Med* 1997;155:130-4.
23. Sorkness RL, Castleman WL, Kumar A, Kaplan MR, Lemanske RF Jr. Prevention of chronic post-bronchiolitis airway sequelae with interferon- γ treatment in rats. *Am J Respir Crit Care Med* 1999;160:705-10.
24. Rosenthal LA, Mikus LD, Tuffaha A, Mosser AG, Sorkness RL, Lemanske RF Jr. Attenuated innate mechanisms of interferon- γ production in rats susceptible to postviral airway dysfunction. *Am J Respir Cell Mol Biol* 2004;30:702-9.
25. Culley FJ, Pollott J, Openshaw PJ. Age at first viral infection determines the pattern of T cell-mediated disease during reinfection in adulthood. *J Exp Med* 2002;196:1381-6.
26. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004;350:443-50.
27. Kotaniemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy—the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111:66-71.