Published in final edited form as:

Curr Allergy Asthma Rep. 2012 December ; 12(6): 613–620. doi:10.1007/s11882-012-0295-y.

Role of Viruses in the Development of Atopic Disease in Pediatric Patients

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Abstract

The prevalence of atopic diseases continues to rise in modernized countries, without a clear explanation for this increase. One potential cause identified from epidemiologic studies of children is respiratory RNA viral infections leading to development of recurrent wheezing, asthma, and allergic sensitization. We review human epidemiologic data that both support and refute the role of viruses in this process. Exploring recent murine models, we document possible immunologic mechanisms that could translate a viral infection into atopic disease. We further discuss evidence for a post-viral “atopic cycle” that could explain the development of multiple allergen sensitization, and we explore data available to suggest a connection between viral infections of the gastrointestinal tract with the development of food allergy. Taken together, this review documents evidence to support the “viral hypothesis”, and in particular, the role of RNA viruses in the development of atopic disease.

Keywords

Virus; antiviral; immunology; atopy; asthma; food allergy; IgE

Introduction

Asthma affects more than 8% of the population and is the number one illness leading to school absences in the pediatric age group [1]. The prevalence of asthma has been increasing -- in fact, from 2001–2009 the prevalence of asthma in the U.S. increased by 12.3% [2]. Similar trends have been seen worldwide, especially in modernized countries [3]. However, it is important to note that all atopic diseases, not just asthma, have seen marked increases over the last few decades in modernized countries [4, 5]. The reasons for this increase remain incompletely understood.

Respiratory viral infections have been implicated in the development of childhood wheezing, asthma, and allergic sensitivity [6–10]. In addition to development of disease, these infections have been demonstrated to exacerbate already existent asthma [11, 12]. The mechanisms translating a viral infection into atopic disease development and/or

exacerbation have not been fully elucidated. It remains unclear whether viral infections directly impact the respiratory immune system in a way that results in asthma and atopy or viral infections simply uncover asthma in those predisposed to develop the disease [10].

In this review we explore evidence for and against viruses playing an active, causative role in the development of asthma and food allergy. Using a paradigm developed from our studies, we discuss data to suggest anti-viral IgE and the antiviral immune response lead to development of atopic disease. Using the terms virus, asthma, food allergy, atopy, and IgE, we examined original research and review articles from searches of MEDLINE (via PubMed). Articles were selected for their relevance to viruses and their apparent role in atopic disease.

Asthma

Epidemiologic connection

Often acute wheezing in young children is associated with lower respiratory tract viral infections [13]. Viruses of the families *Paramyxoviridae*, *Orthomyxoviridae*, and *Picornaviridae* are major causes of lower respiratory viral infections (LRI) [14]. Two recent meta-analyses found that respiratory syncytial virus (RSV; a Paramyxovirus) has caused more than 3.4 million episodes of acute LRI in 2005, while seasonal influenza (an Orthomyxovirus) caused more than 20 million episodes of LRI worldwide in 2008 [15, 16]. In asthmatics and the immunocompromised, rhinovirus (a Picornavirus) was shown to represent a significant disease burden [17]. Clearly, these single stranded RNA viruses account for the majority of LRI's seen in children, and are therefore well positioned to induce or exacerbate atopic disease.

Sigurs and colleagues reported that children who required hospitalization for RSV-induced LRI had a markedly increased risk of developing asthma (odds ratio [OR], 12.7) and allergic sensitization (OR, 2.4) when compared with control subjects who were never hospitalized for an RSV infection [6]. Subsequent follow-up studies on this cohort have demonstrated that the increased risk for asthma and allergic sensitization continues to persist through 18 years of age [8].

The Tucson Children's Respiratory Study is a large population-based birth cohort including more than 1200 healthy newborn babies, 800 of whom had documented RSV infection in infancy. Unlike the hospitalized subjects in the Sigurs' study, in the Tucson cohort RSV infections were mild and did not require hospitalization. Nonetheless, RSV was found to independently associate with recurrent wheeze in the first decade of life [18]. This wheeze could be predictive of the development of asthma, as the Tucson study further showed that recurrent wheezing at age 6 years predicted chronic asthma at 22 years of age [19]. A larger population-based birth cohort in the UK further demonstrated that when RSV bronchiolitis necessitated admission in the first year of life, the subject was left with an increased prevalence of asthma by age 7 years [20].

The largest birth cohort examined for the association of RSV and recurrent wheezing came from Northern California, where complete records of 71,102 children from a single integrated health care delivery system were scrutinized. The investigators found RSV to be a significant risk factor for recurrent wheezing at 3 years of age. Moreover, this study examined the risk of wheeze and severity of RSV symptoms. As expected, those infants who required hospitalization for RSV had an increased risk of wheeze by 3 years of age, which could be broken down based on whether the hospitalization was complicated or not. For those with uncomplicated RSV hospitalization, the OR for wheeze was 4.66, while prolonged RSV hospitalization led to an OR for wheeze of 3.42. Those who had symptoms

requiring only an outpatient visit, but not hospitalization, were still at an increased risk of recurrent wheezing (OR, 2.07) compared to the lack of increased risk in those individuals who had either a mild or asymptomatic RSV infection. The unified inpatient, outpatient, and laboratory databases for all 71,102 subjects add strength to this study despite its retrospective design. Supporting the data from Sigurs et al, this well-powered study further strengthens the idea that viral infections are driving the allergic phenotype [21].

Although RSV has long been recognized as a major cause of LRI, with the advent of more sensitive PCR based detection methods, other respiratory viruses have been found to cause many LRIs. In the Canadian Asthma Primary Prevention Study, nasopharyngeal aspirate samples were isolated at 2, 4, 8, and 12 months of age from 455 children of atopic families. Using PCR to detect viruses, the researchers found exposure to parainfluenza virus (also a Paramyxovirus) or RSV in the first year of life was associated with recurrent wheeze by 2 years of age [22]. Therefore, these studies support the idea that infection in infancy with single stranded RNA viruses (and the Paramyxoviruses, in particular) is likely sufficient to drive the development of wheeze and atopy.

Rhinovirus (RV), another single stranded RNA virus (although positive stranded, as opposed to the negative stranded viruses mentioned above), has emerged as a significant cause of both upper respiratory infections (URI) and LRI. Kusel and colleagues in Perth, Australia enrolled 263 healthy infants from birth, and measured lung function at 1, 6, and 12 months of life, as well as collecting nasopharyngeal aspirates with each acute respiratory illnesses. They found that while RSV was strongly associated with severe LRI requiring hospitalization, it was RV that was identified much more frequently in URI (> 10 times as often) and in LRI (> 3 times as often) [23]. Their data also showed that a LRI in the first year of life with RSV or RV was sufficient to drive the increased risk of wheeze or asthma by age 5 (OR 4.1). Interestingly, this increased risk appeared to only apply to children who had developed atopy (i.e., had antigen specific IgE) before 2 years of age [23]. This study clearly tied viral infections to asthma and atopy; however, it also raised the question of whether anti-viral IgE is an important risk factor in the development and exacerbation of asthma. We will discuss this issue in more detail when exploring possible mechanistic explanations for these findings.

Another study that identified RV as a risk factor for asthma was the Childhood Origins of ASThma (COAST) study, a birth cohort of 285 children selected for a strong family history of atopy. In the COAST cohort, RV was identified as the most important risk for development of wheezing at both 3 and 6 years of age [24] [9]. Supporting evidence that RV may be important in driving wheezing, asthma, and atopy came from a study of Finnish children where RV was the only respiratory virus that positively associated with allergic sensitization in 247 episodes of hospitalized wheezing [25]. These studies showed that although RSV is more associated with severe bronchiolitis, RV is an important pathogen associated with childhood wheezing and asthma--if only on the basis of the sheer number of exposures alone.

Mechanistic hypotheses

A potential mechanistic association of viral infections with development of atopic disease was first shown in 1979 when Frick and colleagues prospectively followed 13 children of atopic parents for up to 4 years with immunologic and clinical observations performed every 3–6 months. In this study, 11 of the 13 children developed clinical atopic disease by 5 years of age. Most interestingly, all 11 children had an URI 1 to 2 months prior to initial development of allergic sensitization [26]. This led the authors to hypothesize that viral infections might drive the development of atopic disease, but they stopped short of proposing an immunologic mechanism.

Once Ishizaka, et al, identified IgE as the reagent responsible for type I hypersensitivity in 1967 [27], investigators began to document that viral infections caused increased specific (anti-viral) and non-specific IgE [28, 29]. Several investigators reported RSV-specific IgE could be detected in both nasopharyngeal secretions and serum [30–36]. Although the exact function of antiviral IgE remains unknown, establishing that IgE is part of the immune response against such viruses as RSV allows for the hypothesis that IgE could link viral infections to atopic disease.

In the mouse, it was shown that RSV infection was sufficient to drive both increased airway hyperresponsiveness and enhanced sensitization to allergen [37]. Using different strains of RSV in mice, two groups have provided useful insights into how the anti-RSV response includes contributions from Th1, Th2 and Th17 cytokines [38–44]. However, there are limitations to the utilization of the RSV infection model in mice when exploring mechanisms that might drive the translation of viral into atopic disease since RSV is not a natural rodent pathogen.

To better understand the potential mechanisms that might drive the antiviral immune response to atopic disease, we utilized a different mouse model of paramyxoviral infection. This model uses the natural rodent pathogen, Sendai virus (mouse parainfluenza virus-1), which at the appropriate inoculum causes a severe infection that appears pathologically similar to human RSV bronchiolitis. Over the course of 7–10 days mice lose up to 20% of their body weight before clearing the virus and recovering. Once recovered, mice are left with a long-lasting, IL-13 dependent, mucous cell metaplasia and airway hyper-reactivity [45, 46]. Similar to acute infections with RSV and RV, Sendai virus infection is associated with an early and intense infiltration of neutrophils in the lung and alveolar space. Amongst these neutrophils is a distinct subset that expresses the α integrin CD49d. These CD49d+ neutrophils are able to act directly on lung conventional dendritic cells (cDC) through a type I IFN and CD11b dependent process to induce cDC expression of the high-affinity receptor for IgE, Fc ϵ RI [47]. At about the same time point in the infection, mice begin to produce both viral-specific and non-specific IgE. Cross-linking IgE-Fc ϵ RI on the cDC leads to production of CCL28, a chemokine that recruits IL-13 producing T helper type 2 cells in an antigen-nonspecific fashion, leading to post-viral atopic disease [45, 48].

While these studies provide a possible mechanistic pathway from a viral respiratory infection to an asthma-like phenotype, they do not address whether the mice become atopic (i.e., made IgE against specific antigens) as a result of the infection. To address this issue, we examined the effect of a single exposure to a non-viral antigen (ovalbumin) during the peak of the antiviral immune response. Surprisingly, a single intranasal (i.n.) exposure to antigen (without any adjuvant) was sufficient to drive marked production of anti-ovalbumin IgE, inducing levels that were similar to those seen with the more standard intraperitoneal injection of ovalbumin with alum adjuvant. Subsequent i.n. challenge with ovalbumin after resolution of the viral infection revealed that these mice had developed allergic disease (not just sensitization), as the resulting mucous cell metaplasia and airway hyperreactivity were significantly augmented over that seen with just a viral infection alone [49]. Together, this robust model has revealed a pathway that not only translates a respiratory viral infection into atopic disease, but also appears to drive a self-perpetuating loop, which we have termed the “atopic cycle”, that may begin to explain the atopic risk associated with severe respiratory viral infections [50]. Another group reported supporting data for this idea with the demonstration that i.n. exposure to house dust mites (HDM) during an acute influenza A infection could lead to enhanced sensitization to HDM and increased airway hyperreactivity [51]. Together, we believe that respiratory infections by RNA viruses may be sufficient to drive the development of atopic disease through the initial production of anti-viral IgE, as shown in the figure.

While this mechanistic pathway was originally outlined in a mouse model, components of this pathway have been validated in human studies--although not all aspects of this model are intact in humans. For example, while mouse cDC do not express FcεRI at baseline, we have shown that human cDC express FcεRI constitutively from as early as 1 year of age [52]. However, data do exist to support the idea that viral infections are sufficient to drive increased FcεRI expression on cDC (and plasmacytoid DC, pDC). For example, Subrata, et al, profiled peripheral blood cDC and pDC from atopic children hospitalized for severe viral-induced asthma and compared samples obtained during the acute illness with those obtained during convalescence. During the acute viral respiratory illness, in addition to an increase in serum total IgE, there was a marked increase in FcεRI expression on cDCs and pDCs [53]. Further evidence for the pathway in humans was shown by our demonstration that crosslinking FcεRI on peripheral blood cDC led to a significant increase in the release of CCL28 [54]. Of note, crosslinking of FcεRI on pDC has been shown to reduce type I interferon production by pDC, adding to the significance of IgE in the antiviral response [55–58]. Taken together, these data begin to provide evidence that the pathways found in the mouse model may be operative in humans, leading to a translation of a viral respiratory illness into atopic disease.

Supporting evidence from studies on treatment

If severe respiratory viral infections drive the risk for atopy, therapy to reduce the viral infection severity should also have a significant impact on the subsequent atopic disease. In a study of 84 children hospitalized for RSV and 91 age and season matched controls, Ribavirin therapy was found to be associated with a lower rate of physician-diagnosed wheezing (15% Ribavirin versus 34% no Ribavirin, $p<0.05$) and allergic sensitization (26% versus 75%, $p<0.01$) [59]. Therefore, treatment of the viral infection does seem to reduce the overall effect of viral infection on subsequent development of atopic disease.

Palivizumab is an anti-RSV monoclonal antibody with 80% efficacy in preventing RSV hospitalization in premature infants without chronic lung disease. Therefore, treatment with palivizumab should be expected to reduce RSV severity and prevent subsequent development of atopy. To test this hypothesis, Simoes et al followed a cohort of 191 preterm infants who received palivizumab prophylaxis during the first year of life, as well as a parallel cohort of 230 preterm infants who did not receive palivizumab prophylaxis. In support of the viral hypothesis, the incidence of recurrent wheezing was significantly lower in the palivizumab-treated subjects (13% treated versus 26% $p=0.001$) [60]. Interestingly, a subsequent study looking at the role of family atopic history in these subjects demonstrated that RSV prophylaxis decreased the relative risk of recurrent wheezing by up to 80%--but only in those subjects who had no family history of atopy [61]. These data would support the idea that there are those genetically predisposed to develop allergies, as well as others who have their immune responses reprogrammed toward an atopic phenotype by an early life, severe RNA respiratory viral infection.

Perhaps the strongest support yet for IgE and respiratory virus playing a central role in childhood asthma comes from results of the Inner-City Anti-IgE Therapy for Asthma study. In this study, 419 inner-city individuals 6 to 20 years of age with persistent allergic asthma were randomized in a double-blind, placebo-controlled, parallel-group, multicenter trial to either anti-IgE therapy (omalizumab) or placebo. Subjects that were treated with anti-IgE had significantly reduced rates of exacerbations, particularly during the common cold (URI/LRI) season [62]. While these data do not give us insight into the development of atopic disease, they do provide indirect evidence that anti-viral IgE may be important in exacerbation of asthma. Nonetheless, the role of respiratory viruses in the development and exacerbation of atopic disease remains controversial.

The counterpoint

Although many studies have documented an association between early life respiratory viral wheezing illness and asthma, the causal role that respiratory viruses may play has been hotly debated. Bisgaard and colleagues have asserted that severe RSV bronchiolitis is an early indicator of a shared genetic predisposition for asthma--not that asthma is the consequence of having had a severe RSV bronchiolitis. In a study of 8280 pairs of Danish twins they used a variety of mathematical models to explore the relationship between RSV infection and asthma. From this study, they argued that the model with the best fit to the data supported the hypothesis that asthma was a risk for RSV infection severity (and not the other way around) [63, 64].

This viewpoint has been shared by Stein and Martinez, who have argued that the lack of premorbid lung function measurement in the studies by Sigurs, et al, leaves open the possibility that low lung function has confounded the relationship between early life severe bronchiolitis and subsequent wheezing [65]. To support this contention, they point to findings in the Tucson study that children with lower lung function are more likely to wheeze with an LRI [66]. However, while in the Perth cohort infants who had bronchiolitis were in the lowest quartile for premorbid lung function values, it was the combination of an LRI in the first year of life with aeroallergen sensitization by 2 years of age that gave the most significant increase in risk for asthma. These data, therefore, argue against low premorbid lung function being the sole independent risk for the development of asthma [10].

Recently a Danish study examined whether lung function measurements and/or bronchial responsiveness to methacholine at 1 month of age were predictive of subsequent development of bronchiolitis. In this study, the investigators demonstrated that bronchial hyperresponsiveness, not low lung function, preceded severe bronchiolitis [67]. This same group performed another study of 37 monozygotic twin pairs discordant for RSV hospitalization, and they examined the association of RSV severity with subsequent atopic disease. The authors were unable to find evidence of a differential effect of RSV infection severity on the development of asthma and allergy, arguing for the viral hypothesis and against the idea that asthma predisposes one to severe viral bronchiolitis [68].

Also hotly contested is whether IgE against aeroallergens must occur before or after the viral associated wheeze and asthma. Recent statistical modeling of data from the COAST cohort makes the claim that sensitization to aeroallergen primarily precedes any RV-associated wheezing, while the reverse could not be true [69]. This finding appears to argue against viral LRI being causative in subsequent aeroallergen sensitization. However, it should be noted that the statistical model used for this study assumed continuous monitoring of both wheezing and sensitization. In fact, the cohort was continuously monitored for wheezing but only annually assessed for sensitization to aeroallergens. Therefore, while this study supports the findings from the Perth cohort (i.e., that early sensitization and viral LRI have apparent synergy in asthma) it cannot refute the possibility that viral LRI could be causative in initial allergic sensitization.

Whether respiratory viral infections in early childhood have a direct etiologic role in the development of asthma and atopy in humans likely will not be determined quickly given the inherent challenges with epidemiologic studies. However, there is ample evidence in support of viral infections participating in the pathophysiology of chronic asthma, and there are mechanistic studies in animal models that provide direction for future human studies. And, in fact, the beneficial effects of early RSV prophylaxis and anti-IgE treatment have demonstrated that therapeutic possibilities do not require the clear definition of who is the chicken or the egg.

Food Allergy

In contrast to asthma, relatively few studies have looked for a connection between viral infections and food allergy. Although many of the studies discussed above have found associations between viral LRI and development of allergic sensitization—including food allergens—none of them has reported a causal role for the respiratory viral LRI in the development of clinical food allergy [6–9, 23, 24]. In addition, a positive relationship between food allergen sensitivity and wheezing has been reported [70]. Since most wheezing episodes studied were a result of a viral LRI, these data can be taken as indirect support for a relationship between respiratory viral infections and food allergy. However, it seems that respiratory viral infections would involve the wrong mucosal immune surface in the translation of viral into atopic disease. Therefore, a more fitting question would be whether viral infection of the gastrointestinal tract can lead to the development of clinical food allergy. While no human study has been published that directly addresses this question, it may be possible to examine the disparate prevalence of food allergy in different environments to gain some insight. While the prevalence of food allergy in developed countries may have reached a plateau, it remains well above that found in developing countries [4]. This is relevant because bacteria (e.g., *Shigella*, enteropathogenic and enterotoxigenic *E. Coli*) are far more common causes of pediatric diarrhea in developing countries, whereas the majority of pediatric diarrhea in developed countries is of viral origin (e.g., rotavirus) [71–73]. Therefore, these data provide circumstantial evidence that viral gastrointestinal infections may associate with the development of food allergy.

We have found that during an acute infection with the murine norovirus type 1 (MNV-1, a single-stranded RNA virus of the family *Caliciviridae*), FcεRI can be induced on gastrointestinal lamina propria cDC analogous to what happens with lung cDC during respiratory Sendai virus infection. Furthermore, a single oral exposure to ovalbumin during the intestinal infection could result in detectable ovalbumin-specific IgE in the serum [74]. In a different mouse model that utilizes reovirus (a double-stranded RNA virus of the family *Reoviridae*), the administration of peanut extract with the viral inoculation increased peanut-specific IgG2a, but did not alter the peanut-specific IgE level [75]. Unfortunately, neither of these models is robust because the viruses used caused only very mild gastrointestinal disease despite being natural rodent pathogens.

As a result, it appears that further insights into the possible role of viruses in food allergy will need to await further epidemiologic observations. One interesting intervention is the use of the rotavirus vaccine. If rotavirus (a double-stranded RNA virus of the family *Reoviridae*, like reovirus) infections could lead to increased food allergy, then (much like the anti-RSV treatments mentioned above) use of a rotavirus vaccine should markedly reduce the development of food allergies [76, 77]. Whether this is true or not awaits further study.

Conclusion

From animal models to validating observations in humans, the immune response to viral infections—especially those involving RNA viruses—has been demonstrated to play a significant role in the development and exacerbation of atopic diseases in childhood. We have outlined a pathway that may provide a mechanistic explanation of how an anti-viral immune response could be translated into atopic disease, and have presented preliminary clinical evidence that this antiviral IgE pathway could be a potential therapeutic target. Prophylaxis against RNA viruses, like RSV, also appears to have potential as a primary prevention, but candidate selection for other viruses remains a challenge. Finally, this review has tried to provide the current state of knowledge on viral infections and atopy. Clearly, additional mechanistic and epidemiologic studies are still needed to tease out the actual role

that viruses play in the development of clinical atopic disease, and we await these future studies with much anticipation.

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Figure. Potential mechanism for viral induced atopy: lessons from mouse studies

A respiratory RNA viral infection (blue arrows) leads to production of IgE against the virus. Crosslinking FcεRI on dendritic cells (cDC) by anti-viral IgE and virus leads to recruitment of Th2 cells in an antigen non-specific fashion (red arrow). If a non-viral antigen (brown arrows) is inhaled during the anti-viral immune response, it can be processed by a cDC and presented to the appropriate Th2 cell, which instructs antigen-specific B cells to produce IgE against the antigen. This IgE can load onto mast cells, basophils, and cDC in the respiratory mucosa. A subsequent exposure (i.e., challenge) to the non-viral antigen (green arrows) can crosslink the antigen specific IgE on mast cells and basophils, leading to allergic disease. If the IgE is crosslinked on a cDC there could be recruitment of additional Th2 cells, and potentially spreading of allergic sensitivity as outlined above.