

Viral infections and allergies

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Abstract

Respiratory viral infections have been implicated in the origin of, protection from and exacerbation of allergy-related symptoms in a variety of ways. Viral infections are closely linked to infantile wheezing. Severe bronchiolitis in early infancy may predispose to chronic childhood asthma as well as allergic sensitization; alternatively it could represent a marker of susceptible individuals. In contrast, repeated mild infections in early life may have a protective role in the development of asthma or atopy by driving the immune system towards Th1 responses. However, evidence on this hypothesis is not consistent as far as respiratory viruses are concerned. Several factors, including the presence of an atopic environment, timing of exposure and severity of the infection, interactively contribute to the allergy–infection relationship. In the present report, recent data on the role of viral infections in the development and progression of allergy and asthma are reviewed.
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Introduction

There is substantial evidence that respiratory viral infections are associated with the development of allergic sensitization, asthma and other allergy-related illnesses (Lemanske, 2003). However, both an enhancing and a protective role have been proposed (Papadopoulos and Psarras, 2003). The respiratory tract and the immune system undergo rapid maturation during the first years of life and postnatal lung development is affected by and affects responses to viral infections. Several factors, including age, type of virus, severity, location and timing of the infection along with the interaction with allergens

and/or pollutants, have been implicated in the development of allergic diseases, particularly asthma, in relation to viral infections (Gern et al., 2005). There is still some controversy as to whether a severe bronchiolitis marks out individuals susceptible to develop asthma or some infections may actually initiate asthma and/or atopy (Martinez, 2003). These suggestions are not mutually exclusive: it is possible that a combination of predisposition and infection sequelae may affect the initiation and/or persistence of asthma and IgE-mediated allergy. This article reports the current status and recent data regarding the involvement of viral infections in the induction and progression of atopic diseases.

Can viral respiratory infections initiate allergy-related diseases?

Evidence supporting a role of respiratory viral infections in the onset of allergic diseases is certainly

Abbreviations: AHR, airway hyperresponsiveness; HAV, Hepatitis A virus; IFN, interferon; RSV, respiratory syncytial virus; RVs, rhinoviruses; Th, T helper; TNF α , tumor necrosis factor α

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not conclusive. Viruses induce inflammatory and antiviral responses by binding to specific receptors on the surface of airway epithelial cells, resulting in activation of innate immune responses, release of mediators such as cytokines and chemokines and recruitment of neutrophils and mononuclear cells to the area (Wark et al., 2002; Gern et al., 2005). Such events may be capable of reprogramming the immune and epithelial responses towards a hyperreactive state (Holtzman et al., 2002).

Traditionally, respiratory syncytial virus (RSV) has been considered as the most frequent cause of respiratory symptoms in infancy. However, more recent studies have shown that human rhinoviruses (RV) are in fact the most prevalent respiratory pathogen even in this age group (van Bente et al., 2003). Nevertheless, RSV remains the most prevalent cause of bronchiolitis, although there is evidence suggesting that RV-induced bronchiolitis may be equally, or even more, severe (Papadopoulos et al., 2002a). Epidemiological evidence suggests that RSV infections may not only trigger asthma-related symptoms but also contribute to allergic sensitization and the development of asthma. Prospective studies have shown that RSV infections are a significant independent risk factor for subsequent frequent wheezing within the first decade of life (Stein et al., 1999). RSV infections severe enough to require hospitalization may confer a high and long-term risk for both asthma and allergic sensitization (Sigurs et al., 2005). However, the aforementioned effect seems to wane with time: a meta-analysis of controlled studies indicated that RSV bronchiolitis did not differ from control group regarding wheezing episodes after the age of 5 years (Kneyber et al., 2000). On the other hand, these analyses have not always taken into account RV and other virus-induced bronchiolitis. Very importantly, an intervention study with anti-RSV immune globulin, reported significantly improved lung function and reduced atopy prevalence in the treated children comparing with controls at school-age, suggesting a causal relationship between the RSV disease and childhood allergy and asthma (Wenzel et al., 2002). Taking into account that all children are infected with RSV by the age of 2 years, it can be assumed that genetic, environmental (e.g. type of virus and concomitant allergen exposure) and additional immune factors must be contributing significantly to these outcomes (Arruda et al., 2005). The developmental stage of the infant when the infection occurs can be important. Infants with severe RSV bronchiolitis have large amounts of the Th2 (Th – T helper) cytokine IL-9 in their airways, produced mainly by neutrophils, which may be one of the mechanisms underlying persistence of allergy-related symptoms following RSV infection (McNamara et al., 2004). Similarly, in young infants, RSV and other viral infections, preferentially promote a Th2-like response in

the nose, along with infiltration and activation of eosinophils (Kristjansson et al., 2005). These responses may be partly explained by the poor IL-12, IL-18 and IFN- γ (IFN – interferon) production in this age group, resulting in a limited Th1 response, although other Th1 cytokines, such as tumor necrosis factor (TNF α) is up-regulated in order to stimulate Th1 immune maturation (Goriely et al., 2001; Openshaw et al., 2004; van Bente et al., 2005). In accordance to the above observations, studies in animal models were indicative of a possible protective role of delaying RSV infection beyond infancy in subsequent allergy-related symptoms in childhood (Culley et al., 2002). Persistence of RSV in the lungs can be another mechanism perpetuating airway inflammation, influencing immune responses to allergens and subsequently enhancing the occurrence of asthma and other atopic disease symptoms (Schwarze et al., 2004). Finally, studies in animal models indicate that elevated lung levels of IL-17 following RSV-infections, leading to increased mucus production and subsequently to more severe wheezing illnesses, are observed in the context of an atopic environment, suggesting that atopy may act synergistically with RSV-induced infection (Hashimoto et al., 2004). Such a hypothesis, in which viral infection acts as an amplifier of predisposition seems to be able to accommodate ‘contrasting’ findings (Papadopoulos and Johnston, 2001), and although the debate is still ongoing (Openshaw et al., 2003), most currently proposed models are more inclusive (Lemanske, 2004), suggesting that poor regulation of tissue inflammation could further increase the impact of viral infections on lung function (Gern et al., 2005).

Regarding other viruses, studies in animal models indicated that paramyxoviral infection could not only cause acute bronchiolitis, but also trigger a chronic response with AHR and goblet cell hyperplasia, leading to the development of more stable asthma phenotype later in life (Walter et al., 2002). Influenza A infections are able to induce increased airway responsiveness, goblet cell metaplasia and airway inflammation either through enhanced Th2 responses or by modulating airway dendritic cell function, leading to up-regulation of co-stimulatory molecule expression and enhanced recruitment of inflammatory cells (Dahl et al., 2004; Marsland et al., 2004; van Rij et al. 2005). However, depending on the time-point of infection, influenza A could also protect from allergen-induced airway eosinophilia due to induced Th1 responses (Wohlleben et al., 2003). Also, previous influenza virus infection in a mouse model, protected from subsequent RSV infection in mice pre-immunized with G-protein from RSV, by reducing cytokine secretion caused by RSV attachment protein, without affecting RSV clearance (Walzl et al., 2000). The ‘anti-allergic’ effects of influenza are probably associated with the timing of the infection and these

data may have important implications for the timing of vaccinations.

As mentioned above, RVs, although underestimated in the past, are currently recognized as the most prevalent respiratory viruses, able to induce a wide range of different clinical states (Tsolia et al., 2004; Xatzipsalti et al., 2005). Within the Childhood Origins of Asthma project, it was shown that first-year wheezing illnesses especially caused by RVs, was the strongest predictor of subsequent third year wheezing (Friedlander et al., 2005). RV-induced wheezing in infancy leading to hospitalization seems to be positively associated with the development of childhood asthma (Kotaniemi-Syrjanen et al., 2003). It has been suggested that persistence of RV-RNA in airway mucus after acute respiratory illness might lead to perpetuation of asymptomatic airway inflammation (Jartti et al., 2004).

Can viral infections protect from allergy-related diseases?

Consistent evidence of protection against allergies and asthma has been shown in large families, suggesting that infectious diseases, more likely to be transmitted in large families, could modulate the development of the immune system and allergy (Strachan, 1989). There is also evidence that repeated exposure to viral infections during early infancy in day-care centers may reduce the risk of allergen sensitization, on the basis of their ability to skew the immune system away from the Th2-type response (Ball et al., 2000). Low-grade RSV infection seem to protect mice from allergen-induced airway inflammation, suggesting that the effects of infections on the incidence of asthma and atopy depend on the severity or/and cumulative number as it was also suggested in prospective studies (Illi et al., 2001; Kondo et al., 2004). Neonatal IFN- γ responses were lower in infants with high frequency of respiratory infections; conversely, frequent infections were associated with a smaller decline in IFN- γ responses, indicating that pre-existing immunologic factors may influence the expression of viral infections in infancy (Copenhaver et al., 2004).

It has been suggested that infections with specific pathogens such as measles are associated with lower rates of allergen sensitization and asthma; however these results have not been verified (Paunio et al., 2000; Shaheen et al., 1996). Vaccination against Hepatitis B was associated with decreased risk of allergy-related outcomes, such as allergic rhinitis, but on the other hand, seropositivity to Hepatitis C antigen was significantly associated with high total serum IgE in a cohort of young adults (Uter et al., 2003). A positive titer of anti-Hepatitis-A (HAV) antibodies was inver-

sely correlated with asthma, atopy and hay fever prevalence compared with HAV-negative controls (Matricardi et al., 2000). Moreover, skin sensitization to peanut was less frequent among HAV seropositive subjects, suggesting that lower hygiene standards may prevent atopic sensitization not only to inhalants but also to food allergens. Contrasting evidence in respect to the effects of particular microorganisms has led to the proposal that it is the rate rather than the kind of infection affecting the development of allergic diseases (Matricardi and Ronchetti, 2001).

Interestingly, a single incidence of Salmonella gastroenteritis during childhood was capable of protecting from allergic sensitization in comparison to children that had suffered from viral gastroenteritis (Kalobatsou et al., 2005; Matricardi et al., 2003) suggesting that particular infections, possibly with highly IFN-inducing bacteria, could be enough to induce a protective effect.

In total, as far as any protective effects of viral infections on atopy and/or asthma are concerned, it seems that further prospective studies with laboratory confirmation of infections are required, in order to evaluate the individual and cumulative effects of different microorganisms and their products.

Interactions of viral infection with atopic host immune responses

Recent studies have emphasized the importance of atopy and allergic inflammation in the induction and perpetuation of virus-induced respiratory diseases (Heymann et al., 2005; Xepapadaki et al., 2005). Allergens and respiratory viruses may act synergistically in the expression of asthma symptoms (Green et al., 2002). The bronchial epithelium is a site of viral replication (Papadopoulos et al., 2000) and participates in the initiation of antiviral responses (Schroth et al., 1999; Papadopoulos et al., 2001). RVs are able to pass into the blood stream, causing viremia, more frequently during acute and severe asthma exacerbations (Xatzipsalti et al., 2005). In vitro studies have indicated that RV can induce epithelial cytotoxicity especially in already compromised epithelium, such as in the case of asthma, and may consequently contribute to the initiation and/or perpetuation of airway remodeling (Fig. 1) (Bossios et al., 2005). More recently, RV infection was shown to promote endothelial cell proliferation and differentiation though induction of vascular endothelial growth factor (VEGF); this response was further augmented in an atopic host environment (Psarras et al., 2006). When primary bronchial epithelial cells from atopic asthmatic individuals were exposed to RV, reduced early apoptosis in comparison to cells from normal individuals was

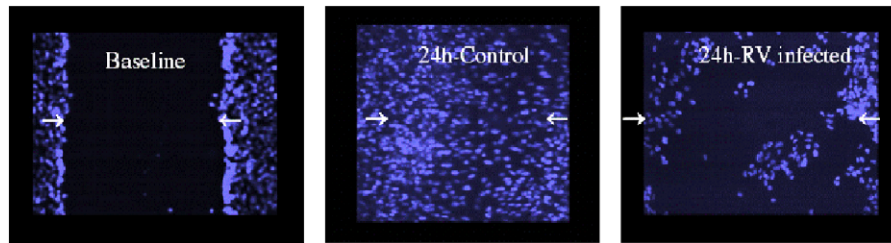


Fig. 1. In a simple model of epithelial wound healing, damaged epithelium ($t = 0$) is suboptimally repopulated after RV-infection in comparison to sham-infected control. DAPI-stained cells. First published in Respiratory Research (Bossios et al., 2005).

observed, leading to increased viral proliferation and subsequent cell cytotoxicity (Wark et al., 2005), an effect mediated through IFN- β . In accordance, we have also shown that the epithelial inflammatory response to RV infection is down-regulated in the presence of atopy, resulting in increased viral proliferation and augmented cell damage (Xatzipsalti et al., 2007). These data indicate a mechanism through which viral respiratory infections may promote airway remodeling and chronic asthma phenotype in atopic asthmatic individuals.

Several studies have shown that viral respiratory infections induce more symptoms in allergic patients than normal subjects. Segmental allergen challenge of the lung and experimental RV infection have illustrated that concurrent exposure to allergen and virus increase the risk of asthma exacerbation (Calhoun et al., 1994; Lemanske et al., 1989). Exposure to RV results in persistent upper and significantly increased lower respiratory symptoms in young asthmatic adults with atopic characteristics in contrast to non-atopic ones (Zambrano et al., 2003). Experimental inoculation with RV is more likely to increase airway responsiveness, in allergic than in non-allergic individuals (Gern et al., 1997). Clinical studies have shown that the risk of hospitalization among virus-infected adults is increased in patients who are both sensitized and exposed to respiratory allergens (Green et al., 2002). These findings have provided strong evidence that individuals with respiratory allergy are at increased risk for virus-induced wheezing. Nevertheless, other studies have shown that allergen exposure does not necessarily augment virus-mediated responses (Avila, 2000). Although this evidence seems contradictory to most previous findings, it indicates that allergen exposure and viral infection do not have a simple additive effect, and timing or dosage may be important.

Several investigators have focused on the altered immune response to RV infection in atopic asthmatic subjects. The defective epithelial repair cycle, characteristic of asthma and strongly correlating to AHR, is amplified by exposure to Th2 cytokines (Davies et al., 2003). Diminished IFN- γ production in response to RV stimulation of peripheral blood mononuclear cells has been described in asthmatic atopic individuals, charac-

terized by decreased levels of type-1 cytokines and more than a three-fold difference in the ratio of IFN- γ /IL-4 between normal and atopic individuals (Papadopoulos et al., 2002b). Th1Th2 imbalance correlates with airway hyperresponsiveness (AHR), supporting the concept that impaired antiviral responses may be associated with asthma severity (Brooks et al., 2003). Therefore, atopic asthmatic individuals seem to have a defective antiviral response that may be associated with incomplete viral clearance and persistent inflammation. AHR is a key feature in asthma and evidence from animal models and clinical studies, of mainly experimentally induced viral infections, suggest that viruses are able to induce AHR, in healthy but even more in patients with respiratory allergy (Folkerts et al., 1998; Gern, 2004). We have recently observed in a prospective study, that although the duration of AHR after a single cold does not differ in atopic and non-atopic asthmatic children, an increased number of symptomatic colds cumulatively lead to prolonged AHR in the atopic group (Xepapadaki et al., 2005). Taking into account that the degree of airway responsiveness is indicative of asthma severity and an indirect marker of airway inflammation, prolongation of virus-induced AHR may well reflect persistent airway inflammation after multiple viral insults. Perpetuation of sub-clinical airway inflammation could have a substantial impact on the risk of asthma persistence, providing a possible explanation for the well-established role of atopy as a major risk factor for the persistence of asthma and AHR from childhood to adulthood.

Conclusions

Viral infections may have multiple and contrasting effects on the development of allergy and asthma; under different circumstances infections may protect from or initiate allergic diseases (Kamradt et al., 2005). However, there is little doubt that a strong association exists between viral respiratory infections and induction of wheezing illnesses and asthma exacerbations. A number of factors such as the type of agent, the severity of the disease, the time of the infection and most importantly

host predisposition, play a crucial role. The presence of allergic inflammation seems to augment virus-induced inflammatory responses leading, especially after repetitive infections, to prolonged inflammation and AHR and possibly to a more persistent asthma phenotype.

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