

REVIEW

Viral respiratory tract infections and asthma in early life: cause and effect?

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Summary

Interactions between viral respiratory tract infections in infancy and childhood, and asthma development and exacerbation, are complex and intriguing. This review aims to unravel some of these complexities. Does severe respiratory viral infection early in life predispose to later asthma development, or is it indicative of a predisposition to allergic respiratory disease? How could variables such as age and severity of viral infection affect the interaction between respiratory viral infections and asthma? How could respiratory viral infection drive allergic sensitization? Here, we review the evidence surrounding these questions, and discuss current and future research and therapeutic approaches targeting the interplay between viral respiratory tract infection and asthma.

Introduction

Many patients say that their asthma can be triggered by viral respiratory tract infections [1]. Anecdotal disparities between people with and without asthma are often apparent; loss of asthma control, sometimes severe enough to require hospitalization, can be a consequence of the 'cold' that a person without asthma shrugs off after a few coryzal days. A recent systematic review found that using current sensitive molecular techniques, respiratory viruses are detected in around 80% of asthma exacerbations, with prevalence highest in children [2]. Despite this conspicuous association, there remains uncertainty as to the exact interplay between respiratory viral infections and asthma [3]. In this review, we address whether severe respiratory viral infection early in life predisposes to asthma development in later life, or is simply indicative of a predisposition to allergic respiratory disease. We consider the potential influence of factors such as age and severity of viral infection, discuss the complex mechanistic associations being uncovered between

allergic sensitization and respiratory viral infections, and consider the implications for future research and preventive and therapeutic strategies.

The association between respiratory viral infections and asthma exacerbations

Around 5.6 million people in England have received a diagnosis of asthma [4]. In the United Kingdom, the cost to the National Health Service (NHS) of managing asthma has been estimated at £63m for inpatient care and £96m for primary care [5]. Furthermore, over 1100 people per year reportedly die from asthma in the United Kingdom [1].

Allergic asthma, is the commonest form of asthma (reviewed in [6]), and is particularly prevalent in children. Debate surrounds asthma classification, an issue which is particularly relevant to paediatric medicine since a wheezy infant will not necessarily go on to develop asthma [7]. This can present difficulties when assessing the contribution of respiratory viral infections to asthma exacerbations. Yet, there is substantial

evidence to support an association between respiratory viral infection and exacerbations of asthma. Peaks in the incidence of asthma exacerbations in children often coincide with peaks in respiratory viral infections [8], in particular at the start of the school year [9]. Furthermore, respiratory viral infection is associated with loss of asthma control [8, 10]. In a study of children aged 9–11 years with asthma exacerbations, 80–85% were found to have respiratory viruses in nasal aspirates [11]. Over half of the viruses in that study were picornaviruses (the majority being rhinoviruses), followed by respiratory syncytial virus (RSV) [11]. A study of children less than 3 years old directly shows an increased frequency of respiratory viral infections in those hospitalized with wheeze, compared to controls without wheeze [12]. Similar observations have been made in some studies of older asthmatic children admitted to hospital (reviewed in [2]). It also appears that allergen sensitization can act in synergy with respiratory viral infection to promote asthma exacerbations. Children experiencing the combination of a respiratory viral infection, allergen sensitization and high exposure to relevant allergens, were at significantly increased risk of hospitalization due to an acute asthma exacerbation [13]. Evidence supporting such synergism has also been found in adults [14].

Respiratory viral infection is thus associated with both community-managed and inpatient cases of asthma exacerbations in children and adults. Furthermore, the combination of allergic sensitization, exposure to relevant allergens, together with respiratory viral infection seems more likely to lead to severe asthma exacerbations requiring hospital care. But can respiratory viral infection actually promote allergic sensitization and the development of asthma?

Associations between respiratory viral infections and asthma development

It is probable that key events in early life can have an impact upon allergic sensitization and allergic asthma (reviewed in [15, 16]). Evidence suggests an association between RSV bronchiolitis and RSV-induced wheeze, and the development of allergic sensitization and asthma in later childhood. A Swedish study followed a cohort of children admitted to hospital as infants for RSV bronchiolitis. These children had increased frequencies of asthma, recurrent wheeze, allergic rhinitis and allergic sensitization throughout childhood up to the age of 18 years, compared to controls [17, 18]. In another study, infants with severe RSV infection had an increased likelihood of recurrent wheezing and allergic sensitization 6–9 months later

[19]. A large population-based birth cohort, found significant associations between RSV bronchiolitis requiring hospitalization and later wheezing and asthma, but not with allergen sensitization, at the age of 7 years [20]. A potent effect of age at respiratory viral infection upon later asthma development was shown in a cohort of 95 000 children followed over 5 years; infants aged 4 months at the peak of the winter viral season were most likely to suffer from bronchiolitis and to have asthma at the follow-up [21]. But, although age at infection is clearly important, the pre-existing immunological context in which a respiratory viral infection occurs will differ widely between individuals, and dissecting the variables, including genetic predisposition, which may contribute to asthma development, is challenging. For instance, a twin study found that genetic predisposition, rather than severe RSV infection, may be a more influential factor for later asthma development [22], although importantly these conclusions were determined by mathematical modelling, and not validated by prospective study.

One or more lower respiratory tract infections (LRTI) associated with wheezing in infancy (but not requiring hospital admission) has been found to increase the likelihood of asthma in childhood [23]. The Childhood Origins of ASThma (COAST) study, a birth cohort of children with increased risk of developing asthma, as determined by parental histories of asthma and allergic sensitization, found that rhinovirus-LRTI in infancy, which was more common than RSV-LRTI, was the strongest risk factor for preschool wheeze at 3 years [24], and that rhinovirus wheezing illness in preschool children was associated with a markedly increased asthma risk at 6 years [25]. Interestingly, in this cohort, mathematical modelling indicated that allergic sensitization preceded rhinovirus-induced wheezing illness [26] suggesting it might be a prerequisite. A limitation of this study is the assumption of continuous monitoring, which was not possible (sensitization was assessed annually), and that a transition from absence of viral wheeze and sensitization to presence of both of these could not happen simultaneously. In a different Australian cohort of children at high risk of developing atopic disease, allergic sensitization prior to the age of 2 years and a history of viral LRTI in infancy was associated with asthma at 5 years [27].

Clinical studies, therefore, tend to support a link between viral LRTI and the development of allergic sensitization and asthma, particularly in predisposed individuals. But, does respiratory viral infection promote the development of asthma, or is the association between viral LRTI and asthma simply a reflection of aberrant immunity underlying both conditions?

Does respiratory viral infection promote the development of asthma?

The influence of age at infection and concurrent allergen exposure

Allergen-reactive CD4⁺ T cells of the Th2 subset play a crucial role in driving allergic lung inflammation. These cells produce Th2-associated cytokines such as IL-4, IL-5 and IL-13 in response to allergen, drawing additional inflammatory cells into the lungs, and inducing effects such as goblet cell metaplasia and the production of allergen-specific IgE (reviewed in [28]). T cell responses are skewed towards a Th2 phenotype *in utero* and in early life [15]; hence, this skew could be influential in the association between viral LRTI in infancy and allergic asthma. Indeed, rhinovirus infection of neonatal, but not of adult, mice induces features associated with allergic asthma [29], and allergen exposure following recovery from neonatal infection with pneumonia virus of mice heightens Th2 responses and leads to the development of allergen-specific IgE [30]. House dust mite exposure during influenza infection of neonatal mice results in allergic airway inflammation (AAI) and airways remodelling that persist, causing reduced lung function in adulthood [31]. Furthermore, inhibition of Th2 responses during primary neonatal RSV infection of mice, reduces Th2 skewed inflammation, with allergic features found upon RSV re-infection [32]. Studies in young adult mice also demonstrate that allergen exposure during respiratory viral infection, can promote allergic sensitization and AAI [33, 34]. Furthermore, administration of dsRNA [a potent inducer of antiviral responses, recognized by Toll-like Receptor 3 (TLR-3)] to allergen sensitized mice during the first, but not the second, of two allergen airway challenges, increases the severity of AAI, perhaps implying that the initial development of AAI may be more susceptible to modulation by viral infection than established AAI [35].

Airway epithelial cells and effects upon T cells and dendritic cells

Respiratory viral infections have a predilection to infect airway epithelial cells (AECs), and AEC responses to viral infections can powerfully influence resultant immune responses. AECs have potent inhibitory effects on T cell proliferation and cytokine production [36], which may be important for maintaining tolerance to inhaled particles, such as allergens. Upon RSV infection of AECs, their inhibitory capacity is substantially reduced [36], possibly facilitating the onset of pro-inflammatory T cell responses. Dendritic cells (DCs) are professional antigen presenting cells (APCs), capable of presenting antigen and driving differentiation of

naïve T cells. DCs are strongly implicated in the initiation and maintenance of AAI ([37], reviewed in [38]). In the lung, DCs are found in close proximity to AECs [35] which, in homeostasis, inhibit their activation [39]. Engagement of TLR-3 on AECs by dsRNA increases DC recruitment to the lungs via the secretion of multiple chemokines [35]. The release of cytokines by AECs such as thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 can also exert important effects on immune cells in the airways.

Thymic stromal lymphopoietin

Specific expression of TSLP by AECs in mouse lungs induces changes consistent with AAI [40], and rat AECs exposed to RSV produce TSLP [41], as do human primary epithelial cells following dsRNA stimulation [42]. TSLP-producing AECs can promote the maturation, and hence the costimulatory abilities, of both human and mouse DCs [43]. These DCs are particularly good at inducing differentiation of naïve CD4⁺ T cells into allergy-promoting Th2 cells, by exerting effects such as upregulation of the costimulatory molecule OX40L [43]. TSLP stimulated DCs demonstrate increased production of the chemokine CCL17 which attracts Th2 T cells into the lungs [43]. TSLP can also have direct effects on T cells since the TSLP receptor is expressed on murine CD4⁺ T cells, and on activated human CD4⁺ T cells [44], and its stimulation can increase T cell proliferation [44].

IL-25, IL-33 and innate lymphoid cells

IL-25 mRNA is increased in lung tissue following neonatal infection with pneumonia virus of mice [30], and is also produced from human primary epithelial cells after dsRNA stimulation [42]. IL-25 is increased in lung biopsies from patients with asthma [45]. Importantly, IL-25 can augment TSLP production from epithelial cells [42], and has been shown to potentiate the expansion and cytokine production from Th2 memory cells driven by TSLP exposed DCs [45].

In vitro infection of human AECs with influenza virus also increases production of IL-33 [46]. IL-33 has been shown to selectively attract human and mouse Th2 cells [47], and mice that over-express IL-33 develop spontaneous pulmonary inflammation with allergic features [48]. IL-33 production from AECs in mice with influenza virus infection correlates with IFN- β production (a cytokine released early in antiviral responses) [46]. Other sources of IL-33 following viral infection include alveolar macrophages [49].

There is increasing interest in innate lymphoid cells (ILCs; reviewed in [50, 51]). In response to IL-33 and IL-25, such cells can produce Th2 associated cytokines,

particularly IL-13 and IL-5, thereby potentiating allergic responses. In mice, IL-33 produced during influenza infection can act directly upon ILCs in the lung and induce IL-5 and IL-13 [52]. This response seems to be required to limit morbidity following influenza infection, and is implicated in epithelial integrity [52]. The expansion of ILCs in the lungs has also been found to be sufficient to induce airway hyperreactivity during influenza infection [49]. In humans, a population of CD34⁺ cells, with similarities to ILCs, responsive to IL-33 and TSLP, was found in sputum samples from patients with asthma [53], and more recently, ILCs expressing the chemoattractant receptor CRTH2, and producing IL-13 in response to IL-2, IL-25 and IL-33, have been identified [54]. It is thus feasible in humans that the release of cytokines from AECs such as IL-25 and IL-33 in response to respiratory viral infection could stimulate ILCs to produce Th2-associated cytokines (ILC2) and drive allergic responses.

Virus-induced modulation of antigen presenting cells

Some studies suggest that severe viral LRTI could predispose to the development of allergic asthma by inducing persistent alterations in APC function. Exposure to IL-4 and IL-13 promotes differentiation of alternatively activated macrophages (AAM) (reviewed in [55]), which can drive naïve CD4⁺ T cells towards a Th2 phenotype [56]. Increased percentages of AAM have been found in biopsy specimens from asthmatic patients, compared to controls [57], and bone-marrow derived macrophages can develop an AAM phenotype *in vivo* and enhance AAI in mice driven by allergen-reactive Th2 cells [58]. Furthermore, IL-13 production by macrophages themselves, which may be promoted by innate immune cells known as natural killer T cells, has been found to be important for driving chronic airway inflammation in a post-viral mouse model [59].

Intriguingly, although RSV infection can also promote the differentiation of AAM (thought to be important for the resolution of disease) [60], depleting alveolar macrophages in the lungs during RSV infection does not affect T cell recruitment to the lungs, or the anti-RSV T cell response [61]. This raises the question of what effects respiratory viral infections can exert upon the professional APC, the DC. In a post-viral model of chronic airway inflammation, lung DCs were important for the recruitment of IL-13 producing T cells to the lungs [62]. Mechanistically, this involved type 1 interferon-dependent expression of the IgE receptor FcεR1 by lung DCs, and their subsequent release of the chemokine CCL28 [62]. In that scenario, a subset of polymorphonuclear neutrophils were important for inducing this DC phenotype [63]. In another study,

1 month following resolution of AAI, pulmonary DCs exhibited an enhanced capacity to stimulate naïve T cells to Th2 cytokine production. Importantly, Ym1 and Ym2, markers associated with AAMs, were expressed in these DCs, together with increased levels of OX40L [64]. These persistently activated DCs favoured 'neosensitization' [64]; the development of sensitization to additional allergens [65]. In addition, IL-13 induces the expression of Ym1 and Ym2 in pulmonary DCs, which then have an increased ability to stimulate Th2 cytokine production from CD4⁺ T cells [66]. Since respiratory viral infection can predispose to the release of IL-13 via the mechanisms described above, respiratory viral infection may similarly lead to persistent Th2-promoting APC populations in the lungs. Dendritic cells have been found at increased numbers in the lungs of mice long after the clearance of virus [67], and DCs obtained from murine lungs 30 days after influenza infection have an increased capacity to drive AAI [68]. Hence, an altered DC phenotype could be another mechanism which favours sensitization to aeroallergens following respiratory viral infection.

Is the association between respiratory viral infection and asthma a reflection of deficient lung growth or aberrant immunity?

It is possible that the associations between respiratory viral infection and asthma development reflect an underlying respiratory or immunological state predisposing to both conditions [69]. Individuals with asthma are more susceptible to certain respiratory viral infections. During the 2009 H1N1 influenza outbreak, double the percentage of children with asthma developed symptomatic H1N1 infection, compared to children without asthma [70]. Furthermore, a study of asthmatic individuals found that rhinovirus infections were of longer duration and more likely to cause a LRTI [71]. Studies have tried to address whether such associations could result from inherent structural differences in the lungs, and/or of deficiencies in the immune response to viral infection.

A study of infants born prematurely and followed up during their first RSV season, found that those requiring hospitalization for RSV infection already had significantly poorer lung function tests prior to infection, compared to those that did not require hospitalization [72]. So, severe RSV infection can be a reflection of pre-existing respiratory compromise. Another study found that lung function tests were significantly reduced, indicating airways obstruction, in 18 year olds that had been hospitalized with RSV as infants, regardless of whether they were asthmatic, when compared to non-RSV controls [17]. This suggests that severe RSV as an infant may affect lung remodelling at a particular

stage of early lung development and, indeed, airway remodelling (e.g. reticular basement membrane thickening) has been demonstrated in infants and young children prior to asthma diagnosis [73], and has been linked to an increased risk of asthma development [74, 75]. In mice, RSV infection can promote airway remodelling induced by repeated allergen challenges [76]. Thus, severe RSV infection occurring on the background of existing airway deficiencies associated with reduced lung function, might further affect lung development and potentially lead to susceptibility to future respiratory disease.

The immune response to respiratory viral infection may differ in asthma. In one study, people with asthma had increased skewing towards Th2 responses upon rhinovirus infection of peripheral blood mononuclear cells, compared to non-asthmatic controls [77]. This could make the antiviral response less effective and perhaps promote allergic sensitization. Differences in the antiviral responses of AECs from asthmatic patients have also been reported; AECs cultured *in vitro* from people with asthma seem less well differentiated and produced increased pro-inflammatory cytokines in response to RSV infection, compared to AECs from non-asthmatic individuals [78]. Furthermore, AECs from asthmatic patients were found to have deficient type I interferon (IFN) (e.g. IFN- α and IFN- β) and type III IFN (the IFN- λ 's) responses, leading to increased viral replication and cell lysis [79–81]. Addition of exogenous IFN- β to *in vitro* cultures significantly improved the antiviral response to rhinovirus of primary bronchial epithelial cells from asthmatic patients [82]. Recent data also suggest that IL-13 can inhibit the IFN- λ responses of AECs and alveolar macrophages in response to dsRNA, so a Th2 biased environment could potentiate any existing deficiencies in IFN- λ response [83]. That said, increased viral replication in AECs from asthmatics is not universally found in all studies [84].

Altered antiviral activity of a particular subset of DCs known as plasmacytoid dendritic cells (pDCs) in allergic patients is another area of interest. A reduced IFN- α response by pDCs from allergic patients has been found [85, 86]. There is also evidence to suggest that pDCs from allergic patients have increased expression of the IgE receptor Fc ϵ R1 [85], and that IgE cross-linking on pDCs may further reduce the IFN- α response [86], which could further impair antiviral responses in allergic patients. Overall, antiviral responses may differ in line with the heterogeneous nature of asthma and further research into antiviral responses in different asthma phenotypes is required.

Figure 1 depicts the immunological mechanisms which could promote allergic responses in the context of respiratory viral infection.

Is it the interplay between predisposition, timing of viral LRTI and subsequently enhanced allergic sensitization that determines asthma risk?

It is interesting to speculate how predisposition, the timing of viral infection and the exposure to allergen may have important ramifications for asthma development. Considering the evidence already discussed, it is possible that for an individual with a genetic or mechanical predisposition (perhaps increased susceptibility to viral infection [79], a strong family history of atopy [22] or reduced lung function secondary to complications of prematurity [72]), multiple viral LRTIs [12] or severe viral bronchiolitis at an early age [17] might be sufficient to induce changes within the lungs favouring sensitization to aeroallergens [31, 33, 43, 46], thus increasing allergic asthma risk. Once sensitized, exposure to allergen together with any additional respiratory viral infections may then promote further episodes of wheeze and asthma exacerbation [13, 87]. If consequently, chronic allergic lung inflammation became established, this could increase the likelihood of neosensitization to additional allergens during childhood, as has been found in experimental models [64]. As the frequency of respiratory viral infection falls during later childhood and beyond, established memory Th2 responses to particular allergens could sustain allergic responses and the clinical manifestation of asthma [28]. Figure 2 depicts this hypothesis of asthma risk enhancement by respiratory viral infection in early life.

How can we best target the interplay between respiratory viral infection and asthma?

Reducing the severity of viral LRTI in early life

The association between early life respiratory viral infections and asthma, and their potential to promote allergic responses, suggests that limiting the frequency, duration and/or severity of respiratory viral infections in infancy could help reduce the risk of asthma development. This has been tried with glucocorticoids, but these have not been shown to be effective at reducing hospitalization for viral bronchiolitis [88]. There is also insufficient evidence to recommend antivirals such as ribavirin for treatment of RSV bronchiolitis. However, one study found that infants under 2 years of age hospitalized with RSV bronchiolitis who received ribavirin were less likely to have subsequent allergic sensitization or recurrent wheeze [89]. Interestingly, a study examining the effects of prophylaxis with the anti-RSV monoclonal antibody palivizumab in preterm infants, found that the subsequent relative risk of recurrent wheeze in childhood was reduced by 80% in children lacking a family history of atopy [90]. Larger prospective trials

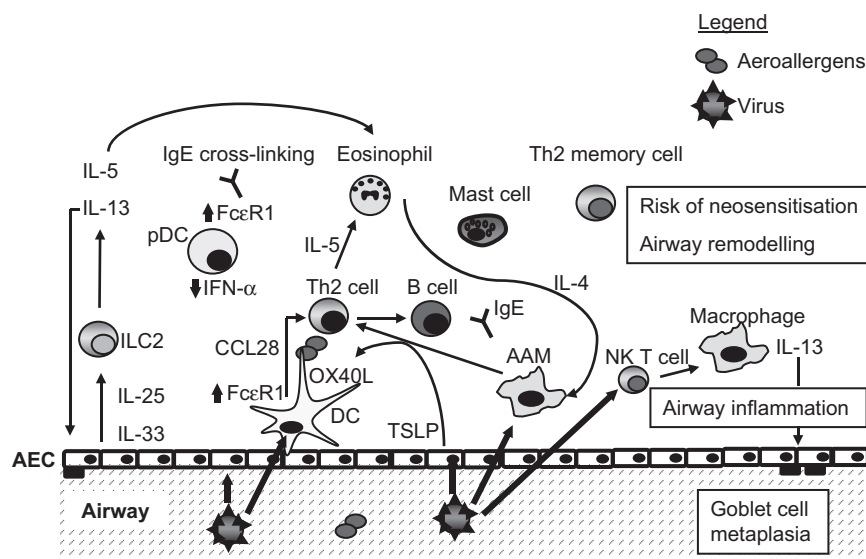


Fig. 1. Respiratory virus-induced immune mechanisms implicated in the development of allergic asthma. Respiratory viral infections exert a multitude of effects in the lung, especially through their actions on airway epithelial cells (AEC) and antigen presenting cells such as macrophages and dendritic cells (DCs). In susceptible individuals, severe, or multiple, respiratory viral infections in infancy may promote allergen sensitization and increase the risk of later allergic asthma development. Recognition of viral infection by the innate immune system can lead to the production of cytokines such as IL-25, IL-33 and TSLP from AEC. These cytokines induce group 2 innate lymphoid cells (ILC2), alternatively activated macrophages (AAM), and DCs with increased OX40L expression, which favours the generation of Th2 cell responses to aeroallergens encountered in the lung. The production of cytokines such as IL-4, IL-5 and IL-13 from Th2 cells enhances recruitment of eosinophils and mast cells to the lung and induces features of asthma including airway inflammation, goblet cell metaplasia and bronchoconstriction. Viral infection can exert effects upon natural killer T cells (NK T cells) to promote IL-13 production by macrophages, and can increase FcεR1 expression on DCs resulting in increased CCL28 production and Th2 cell recruitment. In individuals with allergy, increased FcεR1 expression and IgE cross-linking on plasmacytoid DCs (pDCs) can reduce their IFN-α production, hampering antiviral responses. The generation of allergen-specific Th2 memory responses and allergen specific-IgE can lead to chronic allergic airway inflammation, airway remodelling and neosensitization.

are required to confirm this observation and it will be interesting to see whether an effect on children with atopic family history will also become apparent. Those results do, however, suggest that finding ways of disrupting, limiting or redirecting inflammatory and immune responses to respiratory viral infection may indeed hold benefits for the prevention of asthma.

Reducing viral LRTIs and asthma exacerbations in young children

Recurrent virus-induced wheezing illnesses in preschool children are associated with an increased asthma risk [25] and, if the hypothesis we outlined in Fig. 2 is correct, these LRTIs will contribute to asthma development in predisposed children. So, it may be beneficial to find means of limiting the frequency, duration and/or severity of viral LRTIs and asthma exacerbations beyond infancy. This has traditionally been tried by doubling the dose of preventative inhaled corticosteroids during viral infections, but this does not reliably reduce the severity of exacerbations and current guidelines do not recommend this approach [91]. However, although some *in vitro* data suggests that corticosteroid treatment

can impair type I IFN responses [92], there is also evidence that patients on daily inhaled corticosteroids are less likely to have acute asthma exacerbations in response to viral upper respiratory tract infections (URTIs) [9]. Furthermore, combinations of inhaled corticosteroids with long-acting β₂ agonists may also reduce the likelihood of virus-induced asthma exacerbations [93], and this could be related to reduced release of lymphocyte-attracting chemokines from AECs seen *in vitro* using these combination therapies [94]. The leukotriene receptor antagonist montelukast has also been used in children during URTIs, and may induce small reductions in the severity of acute asthma exacerbations [95], although other studies have not found beneficial effects [96]. It is encouraging that treatment with the anti-IgE monoclonal antibody omalizumab reduced seasonal asthma exacerbations in 6–20 year olds [97]. Such exacerbations are often triggered by respiratory viral infection, but the frequency of respiratory viral infection was not affected by omalizumab treatment [97]. This points to the possibility that omalizumab may inhibit interactions between allergic and virus-induced immune responses; as raised by the previously discussed studies surrounding the link to FcεR1

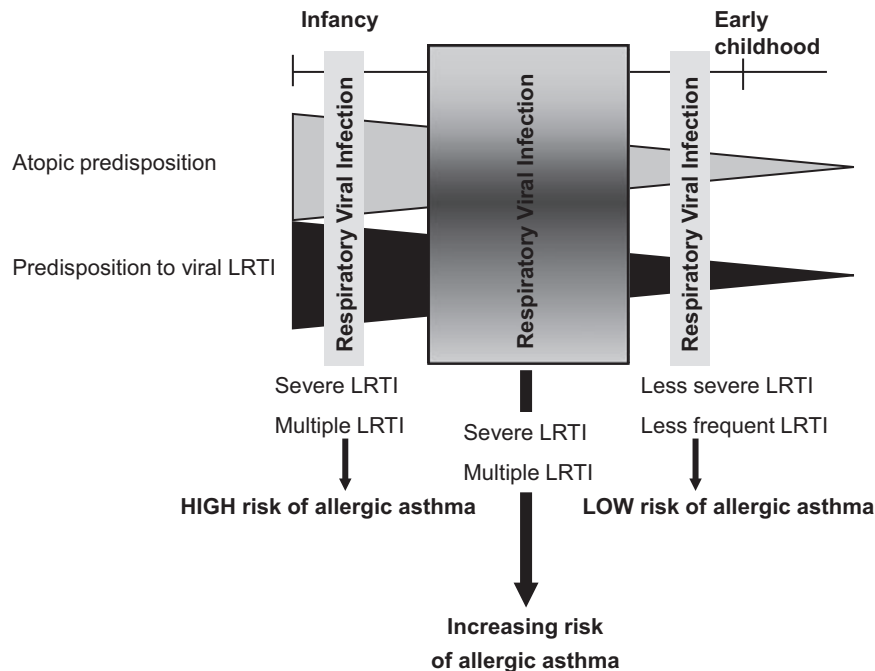


Fig. 2. Timing and severity of respiratory viral infections may be sufficient to increase the risk of allergic asthma development in moderate risk individuals. Individuals with predispositions to allergic disease and viral infection (e.g. genetic factors, reduced lung function, prematurity) are at increased risk of severe respiratory viral infection and/or multiple viral lower respiratory tract infections (LRTI) infections in infancy and hence a high risk of later development of allergic asthma. Individuals at the other end of the spectrum may experience milder respiratory viral infections, perhaps at an older age and thus have a low risk of allergic asthma development. For individuals with moderate predisposition to respiratory viral infection and/or allergic sensitization, multiple or severe respiratory viral infections in infancy and early childhood may be sufficient to promote enhanced allergic sensitization and increase the risk of allergic asthma development.

expression upon lung DCs, recruitment of IL-13 producing T cells post-viral infection [62], and reduced IFN- α production by pDCs after IgE cross-linking [86]. In addition, virus-specific IgE antibodies, that arise during respiratory viral infection in infants [98, 99] and have been implicated in virus-induced lung function changes [100], may have also been reduced by omalizumab treatment. This area thus holds interest for future study.

Novel therapeutic approaches include antivirals, but only a few of these have been demonstrated to shorten the duration of respiratory viral infections, and the effects on asthma exacerbations have not been sufficiently studied (reviewed in [101]). An alternative approach is to boost type I and III IFN responses to augment antiviral responses. Type I IFNs have previously been examined in the context of viral URTI, but these studies were hampered by mixed results and a high frequency of side-effects (reviewed in [101]). Boosting the type III IFN response remains an interesting prospect for the future, whether this is through therapeutic administration of type III IFNs, or via augmenting the host IFN (both type I and III) response pharmacologically, as has been demonstrated recently following administration of the macrolide antibiotic azithromycin [102]. Such novel approaches will need to

be carefully studied in very well-defined populations of children stratified based on detailed disease phenotyping.

Conclusions

Research into associations between respiratory viral infection and asthma is often approached from either the 'cause' or the 'effect' perspective. Yet, a comprehensive approach encompassing both aspects, which are not mutually exclusive, could prove beneficial. For, although the associations between respiratory viral infection and asthma are evident, they are also complex. Such complexities may prove favourable since there is the possibility that interventions developed to modify the immune response to respiratory viral infection may also have the potential, if given early in life, to modify allergic sensitization and asthma development. Optimal therapeutic approaches need to be founded on a strong scientific basis, necessitating further detailed unravelling of the interplay between respiratory viral infection and asthma. A comprehensive understanding of these issues should lead to novel therapeutic targets primed to disrupt the interplay between respiratory viral infection and asthma.

Conflicts of interest

The authors have no conflicts of interest to declare.

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