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Postviral atopic airway disease: pathogenesis and potential avenues for intervention

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Abstract

Introduction: In early childhood, wheezing due to lower respiratory tract illness is often associated with infection by commonly known respiratory viruses such as respiratory syncytial virus (RSV) and human rhinovirus (RV). How respiratory viral infections lead to wheeze and/or asthma is an area of active research.

Areas covered: This review provides an updated summary of the published information on the development of post-viral induced atopy and asthma and the mechanisms involved. We focus on the contribution of animal models in identifying pathways that may contribute to atopy and asthma following respiratory virus infection, different polymorphisms that have been associated with asthma development, and current options for disease management and potential future interventions.

Expert commentary: Currently there are no prophylactic therapies that prevent infants infected with respiratory viruses from developing asthma or atopy. Neither are there curative therapies for patients with asthma. Therefore, a better understanding of genetic factors and other associated biomarkers in respiratory viral induced pathogenesis is important for developing effective personalized therapies.

Keywords

respiratory syncytial virus (RSV); Rhinovirus (RV); Sendai virus; pharmacogenetics; asthma; atopy; microRNA; epigenetics; machine learning

1. Introduction

Accumulating evidence indicates that respiratory viral infections early in life are associated with an increased risk for developing wheeze and asthma [1–3]. Primarily this risk has been identified with respiratory syncytial virus (RSV), and human rhinovirus (RV), although other respiratory viruses also have been associated with an increased risk of developing allergic diseases [4–6]. Further, studies are being conducted to understand the interactions between these viral infections, allergic sensitization, and genetics in the development of atopic disease.

This review aims to summarize recent data regarding the association between respiratory viral infections and the development of atopy, and potential mechanisms, current treatment options, and the role of pharmacogenetics in developing potential targeted therapeutics.

2. Viral illness and atopic disease

Viral lower respiratory tract infections (LRTI) represent the leading cause of hospitalization in young infants worldwide. Of all respiratory viruses associated with bronchiolitis/LRTI in early life, RSV and RV represent the most common etiologic agents.

RV is a member of the enterovirus genus in the *Picornaviridae* family of small, non-enveloped positive strand RNA viruses [7]. RV has three species, RV-A, RV-B and RV-C, each with many different genotypes (77, 25 and 49 types, respectively). Among the RV species, RV-C is most often associated with lower respiratory tract infections in infants and children, atopy and asthma. Wheeze with RV infection before the age of 3 years was demonstrated to increase the risk of atopic asthma at 7 and 13 years of age [8,9]. However, in these studies atopy predating the viral infection appears to be important for development of RV-induced atopic asthma.

RSV is an enveloped negative strand RNA virus in the *Pneumoviridae* family [10]. RSV has two subgroups, A and B, which are similar enough to be neutralized by antibodies raised against the other subtype [11].

By 2 years of age almost all children have been infected with RSV at least once. The clinical manifestations of the disease are variable and range from mild upper respiratory tract symptoms, to LRTI requiring hospitalization or even death [12,13]. The latter occurs mostly in countries with limited resources and in young infants. Shi et al. found that 45% of hospital admissions and deaths due to RSV-LRTI occurred in infants less than 6 months of age, emphasizing the acute burden associated with the disease [14].

Studies conducted in different parts of the world and with different study designs, have shown that RSV LRTI/bronchiolitis in early life is associated with up to a 5 fold increase in risk of developing recurrent wheezing and asthma later in childhood [1,6]. Further, hereditary factors are considered additional predictors for developing atopy (allergy) and asthma after severe RSV LRTI [15,16].

3. Aeroallergens and viral infection

Several studies have identified a temporal association in which atopy develops following a respiratory viral infection. An early study by Frick et al. followed a birth cohort ($n = 13$) during their first 4 years of life, and demonstrated that children born to allergic parents had a high prevalence (85%) of atopic disease, which is not surprising; however, allergic disease in the children was noted to develop 1–2 months following after the children had symptoms of an upper respiratory viral infection [17]. This pivotal study suggested that a viral infection might be the event precipitating atopy. Further evidence that respiratory viral infections may drive the risk of atopy came from the seminal study by Sigurs et al in 1995 [18]. In that study, which first noted the association between severe RSV infection early in infancy and the development of asthma, the authors found that 32% of infants hospitalized with RSV had developed allergen sensitization (i.e., atopy) by 3 years of age, while only 9% of controls (age and sex matched from the same geographic area as the hospitalized infants, but without current or history of hospitalization with RSV) had become atopic. This increased risk of atopy (and asthma) continued as children aged, and at 18 years of age those hospitalized as an infant with severe RSV LRTI were more likely to have developed allergic sensitization to perennial allergens (41% versus 14%, hospitalized versus controls, $p=0.001$), allergic rhinoconjunctivitis (OR 3.6; $p=0.003$), and asthma (OR 7.2; $p<0.001$) [5]. In addition to the Sigurs study, others have also suggested that there is an increasing risk of asthma/wheeze with increased severity of RSV and/or an association between timing of birth, the peak of RSV infection, and the subsequent risk of asthma [15,19].

Epidemiologic studies conducted over the past 30 years suggest that there is a causal link between early life viral wheezing, allergic sensitization and potential risk of developing asthma in childhood, [9]. The Childhood Origins of ASThma (COAST) study, which included a selected population of children born at high risk of developing asthma and allergic diseases, identified a strong association between RV illness in infancy and subsequent development of wheeze and asthma. However, in the COAST study, statistical modeling suggested that atopy pre-dated the viral illness and that RV induced wheezing occurred in children who were atopic by 1 year of age. In comparison, those who were sensitized at or after 5 years of age were less likely to develop viral wheezing and/or asthma by age 13 (17%) compared to children who were sensitized by 1 year of age (65%) [9]. Moreover, the strong risk of developing asthma at age 13 in this selected, high risk population was observed with RV infection early in life and dissipated with RSV infection. Interestingly, the COAST investigators found that only RV-induced wheeze in the first 3 years of life, but not RSV, was associated with increased risk of asthma at 13 years of age. It is possible, however, that early wheeze with RSV does not predict asthma at 13 years of age [1], since, as the Sigurs data would suggest, severity (i.e., hospitalization) in the first 6 months of life also would play a role. Unlike severe RSV disease, which appears to drive the development of atopy and asthma, wheezing with RV appears more likely to uncover those individuals who have an atopic predisposition to asthma. Together, these studies support the idea that initial atopic sensitization occurs early in life and may result from or be exacerbated by clinically significant respiratory viral infections in infancy.

How respiratory viral infections lead to wheeze and/or asthma is an area of active research. A better understanding of the mechanism(s) that can lead from viral infection into atopic disease is important in identifying potential therapeutic targets to prevent development of atopy and asthma in these children.

4. Mouse model for translating respiratory viral infection into atopic disease

Sendai virus (SeV) is a single strand negative sense RNA paramyxovirus, similar to human para-influenza viruses and RSV, and a natural rodent pathogen. Using SeV, a mechanistic pathway was discovered that leads from viral infection of the airway epithelium to the development of airway hyper-reactivity and mucous cell metaplasia [20,21] (reviewed in [22]). Development of post-viral airway disease required cysteinyl leukotriene (CysLT) mediated recruitment and survival of CD49d expressing neutrophils in the airways [23,24]. This unique neutrophil subset induced expression of the high affinity receptor for IgE, FcεRI, on lung conventional dendritic cells (cDC) through a cognate interaction [23]. As part of the antiviral immune response, IgE specific for SeV was produced, the viral antigens then crosslinked antiviral IgE bound to FcεRI on lung cDC, which led to the release of CCL28, a chemokine that attracted IL-13 producing *Gata3*⁺ lymphocytes (Th2 or ILC2) to the airway. These cells drove persistent post-viral airway disease long after the viral infection had resolved [20]. Another interesting aspect of the SeV model is that exposure to innocuous antigens during the peak of the antiviral immune response led to atopy, with production of IgE against the antigen [25]. Thus, the SeV model provides insight into how a respiratory viral infection could lead to both atopy and an asthma-like phenotype.

Studies have demonstrated that several components of our mouse model are present in humans, including CD49d expressing neutrophils and cDC FcεRI-CCL28 signaling [26]. However, and as expected, other components of the mouse model are not identical to human, for example in the human there is baseline expression of FcεRI on peripheral blood cDC, whereas murine cDC only express the receptor after a viral infection (and only in the lung) [27]. Nonetheless FcεRI expression on cDC does increase, as does IgE, in humans during a RV respiratory infection [28]. Crosslinking IgE (or FcεRI) on human peripheral blood cDC leads to increased production of CCL28 [26]. Further, crosslinking FcεRI on PBMC significantly reduced type I IFN production, which might suggest an increased susceptibility to RV infection and possibly explain viral induced exacerbation of asthma [29].

Our mouse data strongly suggest a role for CysLT mediated neutrophil survival as the origin of the association between a respiratory viral infection and atopy. Similar to the mouse model, we have shown that atopic humans have a higher frequency of CD49d expressing neutrophils in their nasal lavage and peripheral blood. Recently we demonstrated that CysLTR1, the receptor for CysLT, was expressed on CD49d⁺ but not CD49d⁻ human neutrophils [24]. The role that CysLT might play in this mechanism has not been studied in humans, but is clearly worth exploring.

Our model predicts that respiratory viral infections will drive the production of specific IgE against environmental allergens. As previously mentioned, exposure to an innocuous antigen

(ovalbumin) during the viral respiratory infection in mice led to production of ovalbumin specific IgE (sIgE), and the levels of sIgE were similar to those observed in mice inoculated with the traditional intraperitoneal ovalbumin plus alum sensitization schema. Furthermore, the anti-ovalbumin sIgE was functional, as mice exhibited increased airway disease with airway exposure to ovalbumin [25]. The idea that allergic sensitization is a result of the antiviral immune response is supported in humans by several studies [5,6,9,18]. All of these studies showed an increased prevalence of allergic sensitization (and in most cases, allergic disease) in children after they have had a severe respiratory viral infection (Figure 1). Thus, together these studies and those above provide strong relevance for using the SeV mouse model to understand mechanism(s) of viral induced atopy in humans.

5. Role of the developing immune system

One possible explanation for why respiratory viral infections early in life might drive atopic disease, including asthma, is that the antiviral immune response in infants is markedly different from that in older children, and also because infants have not been previously exposed to viral antigens. We showed that the immune transcriptional profiles of infants less than 6 months of age compared with those 6–24 months old were significantly different in response to RSV infection, adjusted for disease severity and other demographic characteristics [30]. Overall, the immune profile of infants less than 6 months of age hospitalized with RSV infection was contracted and dominated by a greater proportion of underexpressed transcripts as compared to those older in age (6–24 months) who were also hospitalized with RSV infection. Using a number of analytic strategies, including modular analyses (a data driven tool designed to group transcripts based on their biological function [31]) we found that despite these infants being equally ill as reflected by their similar clinical disease severity scores, those of younger age displayed significantly less overexpression of interferon, inflammation and neutrophil transcripts, lack of activation of plasma cell related genes, and greater underexpression of B-cell, NK-cell and T-cell related genes (Figure 2A) [30].

Further, when comparing modular fingerprints from children hospitalized with LRTI due to RV, also stratified by age (less than 6 months versus 6–24 months of age), we found significant differences in the type and breadth of the immune responses to these viral infections. Particularly, children with RV infection, independent of age, demonstrated mild activation of immune response related pathways, with more subtle differences according to age (Figure 2B). While younger infants with RV infection showed less activation of interferon related genes, there were no differences in the degree of overexpression of neutrophil, monocyte or inflammatory genes. On the other hand, and similar to that from infants with RSV LRTI, adaptive immune response pathways were greatly suppressed in younger versus older children with RV LRTI. These data suggest that although there are pathways that are commonly activated upon infection with different respiratory viruses, the types and breadth of these responses are greatly influenced by age. Nevertheless, whether age at the time of the infection and/or the observed age-related changes in immune responses influence the subsequent development of asthma or atopy awaits further study.

6. RSV genotype and disease severity in young children

It is important to note that the virus type may be an important component in driving the development of atopy/asthma. For example, different RSV strains may not have an equal likelihood of initiating atopy in individuals with a genetic predisposition. Within the two subtypes (A and B) are multiple genotypes: 11 for A and 23 for B. Genotypes are identified by the variations in the RSV attachment (G) glycoprotein. Furthermore, RSV continues to evolve. The most dramatic recent examples have been two strains with different duplications in the C-terminal region of the G protein. One of these viruses, subtype B, genotype BA, with a 60-nucleotide (20 amino acid) duplication was first isolated in Buenos Aires, Argentina in 1999 [32]. The other, subtype A, genotype ON1, with a 72-nucleotide (24 amino acid) duplication was first isolated in Ontario, Canada in 2010 [33]. Both of these strains have become among the most frequent genotypes identified around the world in the intervening time, suggesting that both have an advantage in virus replication or spread [34–37].

RSV disease severity has been linked to the development of atopy, but it is not clear if any particular virus subtype or genotype, or group of genotypes, is linked to disease severity. It would seem logical that a virus capable of enhanced replication or spread might correlate with disease severity. Nevertheless, different epidemiologic studies conducted globally, have estimated the prevalence of RSV genotypes mainly based on samples obtained per standard care. Large multicenter studies comparing disease severity caused by various RSV genotype(s) will be necessary to address this question. Initial, smaller studies have attempted to decipher this association. Our group conducted a prospective study to characterize the genetic variability and circulating RSV genotypes from 253 infants (median age 2.1 months) hospitalized with RSV LRTI during five respiratory seasons. We found that there were three main circulating genotypes during the study period: RSV A/GA2 and A/GA5 and RSV B/BA, and that infants infected with the GA5 genotype had higher viral loads and longer duration of hospitalization. The blood immunoprofiles analyzed in these children according to the most prevalent genotypes (RSV A/GA2 and A/GA5 and RSV B/BA), showed that infants infected with GA5 had lower systemic expression of interferon genes and greater overexpression of neutrophil genes compared with children with GA2 or BA infection. [38]. Future studies in populations infected with other genotypes will be necessary to confirm and extend these findings.

7. Cysteinyl leukotrienes (CysLTs) and atopy

A hallmark of human RSV infection, as well as our SeV mouse model, is an initial influx of neutrophils into the airway [24,39,40]. In addition, concentrations of cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄) are elevated in the airways during natural RSV infection in infants, just as they are in our SeV mouse model [39,41]. We have demonstrated that human CD49d⁺ neutrophils are increased in the nasal lavage of humans during a viral URI or with specific allergen challenge [24,42]. Similar to mice, human CD49d⁺ neutrophils express CysLTR1 – the cysteinyl leukotriene receptor for LTC₄, LTD₄, and LTE₄ [24]. These ligands are pro-inflammatory and powerful bronchoconstrictors, stimulate mucus secretion and, thus, mediators of atopic asthma [43].

Leukotriene C4 (LTC₄) was detected in upper respiratory samples of 57 of 78 infants with RSV bronchiolitis [41]. The role of CysLTR1 in respiratory viral infections can be inferred from studies with leukotriene blocking drugs. Initial studies using montelukast, an inhibitor of CysLTR1, given after RSV infection to children aged 3 to 36 months showed that treatment increased the days free of respiratory symptoms, although the effect was lost once children were older than 5 years of age [44].

Leukotriene C4 synthase (*LTC4S*) is an enzyme that conjugates LTA₄ and glutathione to form LTC₄, which subsequently is converted to LTD₄ and LTE₄ [45]. Polymorphism in the *LTC4S* gene (−444A>C SNP) promoter causes dysregulation of CysLT levels and may be associated with severe asthma in Caucasian populations based on meta-analyses [46,47]. Further studies are needed to validate this potential link between asthma severity and the *LTC4S* polymorphism.

8. Epigenetics: MicroRNAs in virus induced atopy

An emerging area of research is focused on the role of microRNAs in disease processes, including the development of atopy and asthma, since miRNAs are epigenetic regulators that may serve as prognostic biomarkers for asthma, severity of disease, and remission or treatment response [48]. MicroRNAs (miRNA) are highly conserved short non-coding RNAs that bind multiple target messenger RNAs to inversely regulate protein encoding genes in response to environmental stressors and other stimuli. miRNAs have been implicated in the fine tuning of pulmonary innate immune responses and inflammatory sequelae following respiratory viral infections and asthma [49,50]. In vitro studies have identified different miRNAs with antiviral activity against several viruses including influenza and RSV. Part of the antiviral activity was attributed to miRNAs targeting the P38 MAPK signaling pathway; however, it is clear that further studies in animal models are required to investigate this further [51].

Literature regarding the role of miRNAs in children with respiratory viral infections is limited. A recent study included 10 children (less than or equal to 3 years of age) with confirmed RV infection as well as age-matched controls, and showed that RV infection was associated with specific miRNA profiles in the nasal airway epithelium [52]. Further miR-155, that has a role in regulating inflammatory responses due to asthma, was identified as one of the dysregulated miRNA during RV infection [52]. RV infection is known to activate the NFκB pathway and has been associated with airway hyperactivity, and a recent study investigated nasal miRNA profiles from 16 infants with RV or RSV bronchiolitis. Investigators showed that miRNA profiles targeting the NFκB signaling pathway were upregulated only during RV infection but not RSV LRTI [53]. Further longitudinal studies integrating miRNA profiles (“miRNAome”) with clinical observations are required to utilize the true potential of miRNAs and determine the role of miRNA profiles during viral infection in infants and their association with the development of asthma and atopy.

A Bayesian Network Analysis and atopic disease

Atopy is a very complex disease involving multiple environmental, pharmacogenetic, physiologic, biochemical, and microbiological factors that result in asthma and other atopic

diseases. Advanced statistical modeling, such as Bayesian Network Analysis, a machine learning statistical analysis process, can serve as a tool to identify risk factors that may contribute to the development of the asthma phenotype. Through correlations, Bayesian Network Analysis determines a hierarchical network that specifies which variables associated with the outcome are actually contributing to the disease phenotype. For example, GWAS or RNAseq coupled with Bayesian network based multilevel analysis of relevance (BN-BMLA) can identify genes that may be used as targets for personalized therapy. There are few studies that have used BN-BMLA for evaluation of asthma coupled with genome screening. One such study identified a SNP (*rs3751464*) in the *FRMD6* gene that was associated with asthma. Further, a BN-BMLA approach identified an additional 5 SNPs in four genes on Chr 11 (*PRPF19*) and Chr 14 (*FRMD6*, *PTGER2* and *PTGDR*) that were linked to asthma phenotypes [54]. A more recent study found an association between a SNP in *FRMD6* and exercise induced asthma [55]. Further, machine learning processes have been shown to predict acute asthma exacerbations with high sensitivity and accuracy using a 7-day observation window to predict the patient outcome on day 8 [56]. However, it is important to note that there are no studies that have yet used this statistical tool to examine post viral atopic diseases. The strength of including BN-BMLA in postviral atopic disease research is that it seeks to model causal relationships between multiple variables and can have a dynamic state analysis at given time points. Perhaps in the future, BN-BMLA will be used clinically to predict those at risk for developing viral induced asthma/atopy, as well as providing insights into the most important pathways driving disease.

9. Pharmacogenomics in atopy

The concept of pharmacogenetics dates back 510 BC when Pythagoras recognized the dangers of fava bean ingestion in some individuals – the first notice of Glucose-6-phosphate dehydrogenase (G6PD) deficiency [57]. Asthma involves complex environmental risk factors and genetic interactions in the development of a persistent disease state [58]. As a result of multiple pathways to disease development, it is not surprising that studies have shown heterogeneity in asthma treatment responses [59]. There is wide individual variability in both responders and non-responders. The variation in drug response may be associated with point mutations or single nucleotide polymorphisms (SNPs) in the genome. For example, as mentioned, the *LTC4S* variant –444A may have pharmacodynamic significance as one CysLTR1 antagonist, zafirlukast, when tested in adult patients, was less effective in improving lung function in those with the AA genotype compared to the CC or CA genotype; however, the difference was not significant, likely due to small numbers (n=23 p=0.1) [46]. The presence of SNPs in both the cysteinyl leukotriene 1 (*CYSLTR1*) and 2 (*CYSLTR2*) genes may increase the risk for atopic asthma [60]. Further, polymorphisms may influence the efficacy of drugs that act at CysLTR1, such as high-affinity antagonist ligands (e.g., montelukast, pranlukast, and zafirlukast). Similarly, although inhaled corticosteroids (ICS) are effective in controlling asthma both in children and adults, there are patients that do not respond to ICS. Previous studies have identified SNPs in the *IL4* allele (589 CT) that may be associated with ICS-resistant asthma. Further, it was found that in caucasian children a heterozygous mutation in *TBX21* resulting in a T-bet protein that with a His33Gln polymorphism had a better response to ICS therapy compared to those with

homozygous His/His alleles at this position [61]. These studies emphasize the important associations between SNPs and treatment responses, and support the need for a comprehensive data bank of pharmacogenetics and epigenetic changes in atopic and non-atopic individuals so that personalized therapies for viral induced atopy/asthma can be developed.

10. Treatment Options

There is currently no established therapy for the prevention of RSV or RV virus induced asthma/atopy; however, therapies targeting the canonical type 2 cytokines IL-4, IL-5, and IL-13 generally have shown consistent efficacy as treatments against asthma, as have therapies directed at blocking IgE (i.e., omalizumab) [62–64].

IL-13 and blockade of molecular pathway

Molecular fingerprinting could help in selecting the target population that may benefit from therapeutic interventions. There is considerable evidence to suggest that the Th2 cytokine IL-13 plays a key role in the development of allergic asthma [65,66], and blocking of IL-13 signaling with monoclonal antibodies has shown some effectiveness in a population of asthmatic patients [67,68].

Because of the heterogeneity within asthma patients, the use of precision medicine/therapy will require a clear characterization of the different sub-phenotypes, with the specific molecular Th2 pathways activated or suppressed serving as biomarkers. Woodruff, et al [69] phenotyped asthmatic patients based on the levels of IL-13 gene inducibility and correlated these molecular based phenotypes with clinical heterogeneity. Lebrikizumab, a humanized monoclonal antibody directed against IL-13, was shown to selectively improve lung function in patients with high serum periostin levels. Periostin, is a matrix cellular protein involved in several aspects of allergic inflammation, and secreted by bronchial epithelial cells upon IL-13 stimulation [67]. Thus periostin levels could be used to predict responsiveness to specific anti-Th2 therapies such as IL-13 blockade, and appears to be a marker of the overall IL-13 burden in the individual.

The role of periostin in viral bronchiolitis is not well understood. A recent study that included a small cohort of children under 36 months of age with bronchiolitis due to RSV showed that serum periostin was upregulated during the acute phase of the disease [70]. Another study in children under 24 months of age hospitalized with RV (N= 18) or RSV (N=116) bronchiolitis also found increased periostin mRNA expression along with thymic stromal lymphopoietin (TSLP) and IL-33 in nasopharyngeal aspirates [71]. Whether anti-TSLP or anti-IL-33 treatments would be beneficial for infants with RV and/or RSV infection has not yet been determined.

Group 2 innate lymphoid cells (ILC2s) are lineage negative, early innate effector cells that are a significant source of IL-13 and IL-5 in several respiratory diseases [72,73]. Recent studies in murine models have looked at the functional significance of TSLP and IL-33 in the proliferation and activation of ILC2s following RSV infection. One study using an adult mouse model found TSLP dependent and IL-33 independent ILC2 cells following RSV

infection, and suggested that TSLP induced ILC2s are involved in inducing a type 2 inflammatory phenotype [73]. A murine study with neonatal RSV infection showed that IL-33 was necessary to induce ILC2s and Th2 biased immunopathophysiology [74]. These studies support age biased regulation of ILC2s in RSV which may have broader implication in developing targeted therapies against TSLP or IL-33.

Although heredity appears to play an important role in atopy and asthma, the contribution of genetic and epigenetic changes in the antiviral response to this risk is just beginning to be assessed. A study by Forton et al. analyzed 113 SNPs in infants with RSV bronchiolitis by performing haplotype tagging at 5q31 across 11 genes including the Th2-cytokine cluster. The authors found that in infants (less than 6 months) the high risk haplotype was across *IL13* CNS-1 and *IL4* (odds ratio 1.69, $p < 0.0001$) which correlated with increased IL-13 expression, something previously identified for the same risk haplotype [75]. Although these results have further advanced our understanding of atopic asthma from a genetic perspective, further studies are still required to evaluate the relationship between the gene expression and production of various cytokines such as IL-13.

Current RSV treatment options

Currently, the treatment options for the management of acute RSV infection remain supportive and vaccines are not available. There are, however, several antivirals, monoclonal antibodies, and vaccines in the preclinical stage or phase II-III clinical trials. As these interventions become available we will have the opportunity to evaluate both their impact at reducing the acute burden of RSV disease, but also the development of long term sequelae, such as asthma and atopy.

Preventive strategies

Monoclonal antibodies—Palivizumab, is a humanized monoclonal antibody targeting the RSV surface F glycoprotein, and has been approved by the US Federal Drug Administration for the prevention of severe RSV infection (i.e hospitalization) in high risk populations -- namely premature infants and children with chronic lung or congenital heart disease. In addition, a randomized clinical trial in healthy premature infants born at 33–35 weeks gestation, showed that palivizumab prophylaxis resulted in a 61% reduction of recurrent wheezing during the first year of life [76].

A new generation mAb, nismivab (MEDI-8897), derived from D25, a human antibody targeting the prefusion form of the F protein that has greater neutralizing potency than palivizumab, has been developed and is currently entering phase III clinical trials ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02878330) Identifier: NCT02878330) [77]. MEDI-8897 has been modified to significantly extend its half-life in vivo, and offers the opportunity to provide passive immunization for the prevention of RSV LRTI using a once per season, fixed dose administration.

Vaccines—Different vaccine strategies are being explored for the prevention of severe RSV infection in the main target populations of infants and the elderly. These strategies comprise live vaccines including attenuated RSV strains, or RSV genes expressed using

another vector virus, and protein vaccines that use stabilized prefusion F protein subunits or virus-like particles. Of all of these vaccines, the maternal RSV F protein subunit “nanoparticle” vaccine candidate is farthest along in clinical development [78]. A combined strategy using passive immunization to protect young infants via either maternal vaccination or administration of mAbs at birth, followed by pediatric active immunization may be the most effective way to prevent severe RSV infection in young children.

Therapeutic strategies—There also are multiple antivirals under development and in different phases of clinical trials for the treatment of acute RSV infection. These drugs belong to four main therapeutic classes: small interfering siRNAs (i.e ALN-RSV01), small molecules (lumicitabine, a polymerase inhibitor), nanobodies (ALX-0171) and fusion inhibitors (i.e presatovir) ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT03418571; NCT03332459; NCT01909843; NCT02135614) [79,80]. These drugs have been shown in animal models or experimental human studies to ameliorate disease severity by reducing viral load, and are complementary to vaccine development. Including long-term follow-up in these ongoing clinical trials will help elucidate whether the treatment of acute RSV infection will have an impact on the wheezing phenotype, and/or development of asthma and atopy [80].

In conclusion, over the past several years there have been many advances in understanding the risk of developing post-viral atopic disease and/or asthma. These include mechanistic studies in animal models, broader understanding of the relevance of human genetics, as well as potential effectiveness of therapeutic treatment options (Figure 1).

11. Expert commentary

We have understood for many years that a severe respiratory viral infection early in life imparts a great risk for the development of asthma and atopy. However, being able to mechanistically tie an antiviral immune response (a traditionally Th1 response) to atopic disease (Th2 response) has been a challenge. Animal models have been useful to identify potential mechanistic pathways that may play a role in the translation of a viral respiratory infection into asthma and atopic disease. However, what is less clear is whether the pathways identified in mouse models are actually relevant or present in humans. In the near future, we predict that there will be more studies exploring whether these components are present in the human infant. Once these pathways are verified in the main target populations, then therapeutic interventional studies can be undertaken. This is important, because as pointed out in our review, currently the major thrust of exploration is on preventing specific respiratory viral infections (i.e., RSV) or on treating asthma and atopy after the diseases have become established. What is lacking is an approach for treating an infant before or at the time of the symptomatic infection that will prevent the viral infection from translating into atopic disease. This is the importance of the mouse model studies, where these potential pathways have been identified.

12. Five-year view

Looking in our crystal ball, we predict that the future will involve a three-tiered approach to the prevention and treatment of atopic diseases, including asthma (figure 1). The first

component will be to identify infants (or their parents) who are at-risk of developing post-viral atopic disease. These individuals will then be treated to prevent them from being infected in the first place. However, for this approach to be implemented, we need better genetic and other biomarkers to determine the best candidates for vaccination. Alternatively, if the cost of therapeutics were to be low enough, we could envision a situation where all infants (and/or their parents) are immunized. The second tier is to treat those infants who end up with a clinically significant respiratory viral infection early in life. The exact timing of these infections is not clear, but it does appear to be a greater risk if the child is 6 months of age or less. We do not know the exact interventions needed, but this is where work on the developing infant immune response, and mouse models are important. The final tier is to treat those individuals who still develop atopic disease. In this arena we are making significant progress as many new biologic therapies are being developed that have significant efficacy. The only downside is that most of these treatments appear right now to need life-long administration.

As we have discussed, the future is bright for the development of multiple interventions to prevent or treat post-viral atopic disease. Multiple pathways have been implicated and we now await the appropriate clinical trials to determine how effective these interventions are in preventing the development of atopic disease.

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Key issues

- Severe respiratory viral infection in infancy is linked to the development of atopy/asthma/wheeze.
- Development of post-viral atopy and asthma involves genetic and immunological pathways; however, more studies are needed to understand what triggers the translation from viral infection to asthma development.
- Currently there are no conclusive genetic, epigenetic or biomarkers that serve as predictors for the development of post-viral asthma and/or atopy.
- Treatment options currently include blocking Th2 cytokines and IgE, although these options are only effective for existing disease.
- Future therapeutics are being developed (antiviral antibodies and vaccines), which will constitute a primary strategy to prevent respiratory viral infections and thereby, post-viral disease.

Figure 1. Proposed schema of post-viral asthma/atopy development and potential interventions.

The development of post-viral asthma and atopic disease depends upon the genetic composition of the infant. Infection with respiratory syncytial virus (RSV) or rhinovirus (RV) during the early development of the infant's immune system (probably before 6 months of age), can lead to an altered antiviral immune response. This response, in the proper genetic context, can lead to the development of post-viral asthma and/or atopy (red arrows). However, a more mature immune system and/or certain genetic predisposition will prevent the development of asthma/atopy and the infant will recover without these diseases (green arrows). There are two primary intervention points to prevent the development of post-viral disease (dotted box). The first involves primary prevention strategies of immunizing the mother and infant, which has the potential to prevent the respiratory viral infection in the first place (blue lines; the dotted blue line represents the unclear value of immunizing the mother). The other intervention point is to prevent translation of the antiviral immune response into post-viral atopic disease (purple lines). These interventions will be new therapeutics developed from studies in mouse models where specific mechanistic pathways are identified. Before these pathways are targeted in the infants, they need to be validated in humans, and then will be prime targets chosen for intervention to prevent the development of post-viral atopy and asthma.

A. Respiratory syncytial virus

B. Rhinovirus

Figure 2. Age at the time of infection influences the host immune response to respiratory syncytial virus (RSV) and rhinovirus (RV) infection.

(A) RSV immune response according to age. The upper panel shows the modular analyses performed and compared between 20 infants less than 6 months of age with RSV lower respiratory tract infection (LRTI), and 17 children with RSV LRTI 6–24 months of age. Both groups had similar clinical disease severity scores (CDSS). Healthy, age-matched controls, 9 per group, were used as a reference. Colored spots represent the percentage of significantly over-expressed (red) or under-expressed (blue) transcripts within a module in patients with RSV infection compared to controls, and the number included in the dots are the percentage of over or underexpressed transcripts. Blank modules demonstrate no significant differences between patients and controls. The two age groups revealed a similar trend in the overexpression of neutrophils (M5.15) and suppression of T-cells (M4.1, M4.15), lymphoid lineage (M6.19) and genes related to antimicrobial response (M2.1). On the other hand, the overall activation of the innate immunity, interferon and inflammatory response was lower in infants less than 6 months, and the adaptive immune response (B-cells (M4.10); plasma cells (M4.11) and cytotoxic/NK (M3.6)) was even further suppressed compared with children 6–24 months of age. The middle panel summarizes the percentage of over and underexpressed transcripts according to the two age groups and in relation to the

overall RSV signature. Infants less than 6 months of age with RSV LRTI displayed a greater number of underexpressed transcripts (64%) as compared with those 6–24 months of age (29%). The lower panel further illustrated in a spider graph format representing the per-module median expression values of the significant different modules between the two age groups. **(B)** Modular analysis in children with RV LRTI (less than 6 months; n=12 and 8 matched controls and 6–24 months: n=8 and 6 controls) revealed fewer differences in host responses according to age. Horizontal bars illustrate the proportion of over- and under-expressed modules in infants (less than 6 months) and children 6–24 months of age in relation to the global influenza and RV signature. These differences are further illustrated in a spider graph format representing the per-module median expression values of the significant different modules between the two age groups.