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Evolving Concepts in how Viruses Impact Asthma

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Abstract

Over the last decade, there have been substantial advances in our understanding about how viral infections regulate asthma (Table 1). Important lessons have been learned from birth cohort studies examining viral infections and subsequent asthma, understanding the relationships between host genetics and viral infections, the contributions of respiratory viral infections to patterns of immune development, the impact of environmental exposure on severity of viral infections, and how the viral genome influences host immune responses to viral infections. Further, there has been major progress in our knowledge about how bacteria regulate host immune responses in asthma pathogenesis. In this article, we also examine the dynamics of respiratory tract bacterial colonization during viral upper respiratory tract infection, in addition to the relationship of the gut and respiratory microbiomes with respiratory viral infections. Finally, we focus on potential interventions that could decrease virus-induced wheezing and asthma. There are emerging therapeutic options to decrease severity of wheezing exacerbations caused by respiratory viral infections. Primary prevention is a major goal and a strategy toward this end is considered.

Keywords

virus; asthma; genetics; immune; microbiome

Introduction

Over the last decade, there have been substantial advances in our understanding about how viral infections regulate asthma (Table 1). Important lessons have been learned from birth cohort studies examining viral infections and subsequent asthma, understanding the relationships between host genetics and viral infections, the contributions of respiratory viral infections to patterns of immune development, the impact of environmental exposure on severity of viral infections, and how the viral genome influences host immune responses to viral infections. Further, there has been major progress in our knowledge about how bacteria regulate host immune responses in asthma pathogenesis. In this article, we also examine the dynamics of respiratory tract bacterial colonization during viral upper respiratory tract infection, in addition to the relationship of the gut and respiratory microbiomes with respiratory viral infections. Finally, we focus on potential interventions that could decrease virus-induced wheezing and asthma. There are emerging therapeutic options to decrease severity of wheezing exacerbations caused by respiratory viral infections. Primary prevention is a major goal and a strategy toward this end is considered.

The viral genome and how it influences host immune responses to viral infections

Respiratory syncytial virus (RSV) and rhinovirus (RV) are important causes of wheezing in early life and wheezing illness with these viruses have been associated with increased asthma risk later in childhood. At age 6, there is an increased risk of asthma if children had wheezing illness with RSV (odds ratio 2.6), RV (odds ratio 9.8), or both RSV and RV (odds ratio 10.0) in the first 3 years of life. RSV is a negative-sense, single stranded RNA virus that is a member of the Paramyxoviridae family and is the leading cause of hospitalization each year in the United States in children under 1 year of age.[1] There are three species of RV in the enterovirus genus, and all are positive-sense, single-stranded RNA viruses that have protein capsids. RV are the most frequently detected viruses in wheezing children over the age of 1 year, and from children and adults with acute exacerbations of asthma.

The clinical manifestations of a viral infection in the respiratory tract result from a complex interplay of the host, environment, and virus. To make comparisons between different immune responses elicited by diverse viruses, host and the environmental conditions must be held constant in order to prevent the introduction of confounding factors. This requires artificial conditions, such as the use of human cell lines for *in vitro* infection studies, the infection of genetically identical animals, such as mice, housed in the same environment, and the use of a standard viral inoculum. Determining the effect of specific genes within a virus requires that all other viral genes are identical. Such studies have begun but are still relatively new.

Experiments in models of RSV genomes have provided important insights into how the viral genome influences host immune responses to infection. Three RSV strains commonly used in pathogenesis studies are A2, line 19, and Long. RSV A2 infection in BALB/c mice resulted in a predominant IFN-γ immune response, no production of the Th2 cytokine IL-13 in the lung, an absence of airway mucus, and no airway responsiveness (AR) to methacholine.[2] Infection with RSV Long similarly did not result in host IL-13 production in the lung nor was there airway mucus.[3] However, line 19 infection in genetically identical mice in the same environment caused the host immune response to produce IL-13, decreased IFN-γ compared to A2 infection, airway mucus, and heightened AR.[2] Sequencing of the A2, line 19, RSV Long strains revealed six amino acid differences between line 19 and the A2 and Long strains, of which 5 amino acid differences were in the fusion (F) protein.[3] To determine the contribution of the F gene of each virus to disease pathogenesis, a reverse genetics approach was undertaken by creating chimeric viruses whereby an A2 virus was manipulated to replace the A2 F gene with either the F gene of either line 19 or Long. Infection with the chimeric virus containing the line 19 F gene caused decreased host IFN-α lung levels, higher viral load in the lungs, greater lung IL-13 protein, augmented airway mucus, and increased AR, compared to the chimeric viruses containing either A2 or Long F proteins.[3] Therefore, this reverse genetic approach provided the opportunity to not only discover which genes in RSV line 19 strain were responsible for the lung IL-13, airway mucus, and AR, but also the identification of the specific amino acids that caused airway remodeling. These techniques not only provide the knowledge of unique components of the

viral genome that contribute to specific pathogenic features but may also assist in vaccine and therapeutic strategies aimed at the proteins responsible for specific disease characteristics.

Future perspectives:

To date, there have not been studies that reveal a relationship between RSV genotypes and the presence of wheezing in hospitalized children with bronchiolitis or bronchopneumonia; however, this may be a function of the lack of application of technology to sequence strains because of cost. Studies relating viral genetics to severity of illness in mice have demonstrated the intricate interactions between viral genome, viral proteins, host cell function and metabolism and immune response. Developing a greater understanding of this chain of events could highlight several therapeutic opportunities, including identification of high-priority pathogens, inhibition of viral or host proteins that are critical for replication, and strategies to inhibit virus-induced skewing of immune responses that favors viral replication over host defense.

Host genetics and viral respiratory infections

A number of studies have begun to shed light on the relationships among host genetics, viral infections and acute and long-term respiratory outcomes. Candidate gene approaches have been utilized to identify associations between genetic polymorphisms and viral respiratory illness outcomes. Polymorphisms in several antiviral and innate immune genes have been linked to susceptibility to respiratory viruses, infection severity, and virus-induced asthma exacerbations, and have been replicated across multiple cohorts (Table 2). These genes include *STAT4, JAK2, MX1, VDR, DDX58, and EIF2AK2*.[4] Additionally, whole exome sequencing has been utilized to identify rare variants in innate immune responses linked to severe respiratory viral infections. Autosomal recessive *IRF7* deficiency has been observed in one patient in association with severe influenza infection and acts through impairment of interferon amplification.[5] Dominant negative loss-of-function variants in *IFIH1*, critical to viral RNA sensing, have been shown to be a risk for intensive care unit hospitalization due to viral infections in previously healthy children.[6]

A number of polymorphisms have been specifically associated with increased severity of illnesses associated with hospitalization from RSV infection. A candidate gene approach identified SNPs in the innate immune genes *VDR, IFNA5, and NOS2* as risk factors for RSV bronchiolitis.[7] In order to further elucidate associations of host genetics with RSV illness severity and asthma risk, a recent review examined overlap amongst genes associated with both outcomes. This approach identified a number of genes involved with both innate immunity and type 2 (Th2) inflammatory responses (*ADAM33, IL4R, CD14, TNF, IL13 and IL1RL1)* that are highly relevant to these outcomes.[8]

The most replicated association between host genetics and asthma risk is the 17q21 locus. In two birth cohort studies, variants in this locus, including ORMDL3 and GSDMB, were also associated with increased risk of wheezing with RV infections in early life.[9] Interestingly, these variants were only associated with increased risk of subsequent asthma in children who developed RV wheezing in the first 3 years of life. In contrast, early life RSV wheezing

was not linked to 17q21 variants in these cohorts. In addition, farm exposures[10] and pets[11] in the home lessen the risk of asthma for children with high-risk 17q21 genotypes. In each case, the genetic risk associated with 17q21 was buffered by protective environmental exposures.

RV virulence varies by species; RV-A and RV-C are more likely to cause illnesses, wheezing and lower respiratory tract infection compared to RV-B,[12] which has a slower rate of replication and induces muted cytokine and chemokine responses.[13] Whether there are individual types within RV species that are more virulent is unknown, and difficult to study given the genetic diversity of these viruses and high mutation rate. A functional polymorphism in cadherin-related family member 3 (*CDHR3*) has been associated by genome wide association study (GWAS) with early childhood asthma and severe wheezing episodes.[14] Interestingly, CDHR3 is a receptor that enables binding and replication of RV-C, suggesting that this link between *CDHR3* and asthma risk may be mediated by RV-C infections.[15] In support of this hypothesis, children with the risk polymorphism in *CDHR3* were recently found to have greater risk of RV-C illnesses, but not illnesses associated with other viruses.[16]

Future perspectives:

These genetic associations among respiratory virus susceptibility, infection severity and subsequent asthma risk may prove to be important to risk stratify populations, and potentially provide new therapeutic targets for reducing illness severity and subsequent risk. Further, unbiased approaches have been employed recently to identify pathways of gene expression in the upper airway that differentiate a viral cold that resolves from one that leads to an asthma exacerbation.[1] Efforts are ongoing to understand how these gene expression patterns are regulated in hopes of identifying new personalized therapeutic strategies to prevent asthma exacerbation. The integration of multiple “omics” approaches holds promise to provide the ability to unravel these complex relationships.

Environmental factors affecting the inception and severity of asthma exacerbations

The exposome, defined as the measure of all exposures that influence the health of an individual, is an important determinant of asthma risk during the lifespan of an individual.[17] Early exposures can set in motion pathways that will ultimately define illnesses and symptom exacerbations, which is especially true when considering the ontogeny of asthma. From birth through school years, children are frequently exposed to a variety of respiratory pathogens, allergens, microbes and airway irritants. The pathogenic or beneficial effects of these exposures and their interactions remain the focus of research to develop new interventions and preventive therapies.

Most of the initial research devoted to the ontogeny of asthma focused on RSV infections which are frequently detected by culture and tests for RSV antigen in nasal washes from wheezing infants during the mid-winter months. Studies in the past reported that flares of wheezing caused by RSV leading to hospitalization during infancy increased the risk for

developing asthma and allergy.[18, 19] However, recent studies indicate that the more severe episodes (i.e., those requiring hospitalization) of infantile wheezing caused by RSV increase the risk for subsequent wheeze in infants and toddlers, but it is less certain whether RSV-induced wheeze influences the development of atopy or asthma as children grow older.[20]

In contrast, flares of wheezing caused by RV are more strongly linked to persistent wheezing and the development of asthma, especially in children who are sensitized to allergens at an early age.[21–23] In keeping with this, the dominant risk factors for asthma attacks that require hospital care among children after 3 years of age is the combination of allergic airway inflammation and RV infection.[24–26] As a result, several host factors should be considered in efforts to treat asthma exacerbations more effectively and to reduce the risk for asthma development, For example:

1. There may be phenotypes of asthmatic children who would benefit from development of vaccines to RV or RSV. For example, genetic variations at the 17q21 locus and a coding SNP in *CDHR3* (the receptor for RV-C genotypes) increase the risk for wheezing with RV during childhood.[9, 14]
2. There is current interest in whether the administration of a biologic such as omalizumab (anti-IgE antibody) during early childhood will have a disease modifying effect after this intervention is discontinued (i.e., the Preventing Asthma in High Risk Kids (PARK) trial; NCT02570984).
3. There is evidence that the asthmatic airway, especially epithelial cells and innate lymphoid cells, has a Type 2 bias with enhanced production of TSLP, IL-13, and IL-25 in parallel with decreased type I and III IFN responses that are needed for effective antiviral killing and clearance.[27–34] This bias may increase the susceptibility of allergic asthmatics to RV infections. Once infected, however, *in vivo* studies have shown that during RV infections viral loads and clearance are similar among children and young adults with asthma compared to non-allergic individuals without asthma.[31] At present, mechanisms to explain these differences are poorly understood. A better understanding is likely to come from research focused on the cascade of early, innate cellular and molecular events that follow RV infection of epithelial cells.

Future perspectives:

Airway inflammation caused by recurrent infections (predominantly with RV) in the allergic host will continue to be the focus of research designed to develop new therapies to help children and young adults with asthma. Whether treatments targeting allergic inflammation will be sufficient to reduce the frequency and severity of exacerbations (e.g., using new monoclonal antibody-based biologics), or whether additional therapeutics will be needed to decrease the frequency of RV infections, or enhance viral killing, remains to be determined. Looking to the future, the evaluation of other interventions such as the administration of antibiotics to treat secondary bacterial pathogens, or azithromycin to reduce wheezing following virus infection also deserve further study, along with investigations to determine whether the administration of vitamin D, probiotics, and dietary modifications (e.g., fish oil) will have benefits. In contrast, the adverse effects of airway irritants such as environmental

tobacco smoke (ETS) and air pollution (e.g., diesel fuel) on the severity and persistence of RV-induced asthma remain poorly understood.

Effects of respiratory viral infections on patterns of immune development

Acute wheezing illnesses with respiratory tract viruses in infancy and early childhood represent an important risk factor for childhood recurrent wheezing and later asthma development. This link is particularly well-established with RV and RSV, suggesting that these viruses may have a causative role, and significant research is directed towards understanding how these viruses can alter immune development to contribute to asthma pathogenesis. That said, causation remains unproven and asthma prevention strategies targeting viral illnesses do not currently exist.

RV-associated wheezing, in particular, is associated with a higher asthma risk than other viruses; this has been consistently demonstrated across multiple studies.[21, 23, 35–38] Many of these studies have linked RV-induced wheezing with other asthma risk factors, in particular markers of atopy including allergic sensitization, increased eosinophils, and atopic eczema, suggesting possible additive or synergistic effects in increasing asthma risk. Experimental models have demonstrated alterations in type-2 immune responses to RV that may account for this risk (Figure 1). Mouse models have demonstrated that neonatal RV (RV1B) infection results in persistent airway hyperresponsiveness, mucous cell metaplasia, and IL-13 production that does not occur in adult mice. Furthermore, knockout of IL4R prevents this response, consistent with an IL13-dependent process.[39] Subsequent work demonstrated that RV infection leads to expression of epithelial derived cytokines IL-25, IL-33, and TSLP and an increase in ILC2s as an important source of airway IL-13; blocking these pathways with anti-IL-25 attenuates neonatal RV-induced AHR and mucous cell metaplasia.[40, 41] While there is no equivalent human evidence regarding the immune effects of RV in early life, these same pathways are known to play a key role in the response to RV leading to exacerbations in established asthma.[29]

A key question however, is whether underlying Th2 inflammation or RV associated wheezing comes first. A prospective birth cohort analysis has shown that allergic sensitization generally precedes RV wheezing but not the other way around, suggesting allergic sensitization may lead to more severe RV illnesses and the development of asthma.[42] Supporting this observation, *in vitro* studies have shown that Th2 inflammation can inhibit type I and III interferon antiviral responses to RV infections,[43, 44] which may increase susceptibility to more severe RV infections. However in contrast, several human studies have demonstrated increased IFN signatures in asthmatic children with virus infections, as well as in severe asthma in adults;[45–47] these might represent different disease states, as a recent report found that early life exacerbation-prone asthma was correlated with low IFN signatures, while the highest IFN signatures were associated with later-onset asthma.[48]

Allergy is a major risk factor for the progression from wheezing illnesses to asthma, and this has been a very consistent finding across multiple cohorts.[21, 49, 50] Allergic sensitization precedes wheezing illnesses in most young children,[42] and allergic inflammation can impair antiviral responses *in vitro*[51] and *in vivo*.[52] This suggests that allergic airway inflammation

can increase susceptibility to and severity of viral respiratory illnesses. Allergic sensitization in early childhood may also modify the relationship between microbial colonization and respiratory outcomes. In preschool children whose airways were colonized with pathogen-dominated microbiomes, sensitized children were at increased risk for chronic asthma while non-sensitized children were likely to have transient wheeze that resolved by age 4 years.[53]

It is well established that hospitalization for RSV bronchiolitis in the first year of life is associated with later development of asthma.[38, 54–56] RSV induces a broad innate immune response in infants including systemic interferon, neutrophil, and inflammatory pathways, and distinct RSV strains and concomitant airway bacteria can influence the severity of infection.[57, 58] The risk for more severe RSV-illnesses has also been linked to polymorphisms in several immune regulatory genes,[59] many of which also can influence asthma risk. However, whether RSV is causal remains a subject of debate with two large cohort studies showing different conclusions,[59, 60] one suggesting causation and the other an underlying genetic predisposition. Notably, two prevention studies using palivizumab (a monoclonal antibody directed against RSV) in high-risk infants found that prevention of more severe RSV-illnesses decreased the risk of childhood recurrent wheezing but not asthma development.[61, 62] Ultimately RSV infection appears to have the greatest impact on asthma risk during a critical window of lung development for infants born during the fall (in the Northern hemisphere) who are at ~4 months of age during the peak of the winter RSV season. It has been well-established that RSV infection can induce pathologic Th2 immune responses, especially within the context of formalin-inactivated RSV vaccination.[63–65] More recently, studies in mice have demonstrated the ability for RSV-related Pneumonia Virus of Mice as well as human RSV infection to break tolerance to allergens in neonatal mice.[66] Furthermore, it is now appreciated that RSV triggers release of epithelial-derived cytokines that promote Th2 responses and can induce ILC2 responses following infection.[67, 68] These same epithelial cytokines have also been implicated in RV infection, perhaps suggesting a shared innate Th2-skewing mechanism during viral infection.[27, 40]

Future perspectives:

Fully understanding the patterns of immune development that lead to asthma inception, and how such patterns are affected by exogeneous exposures including viral infections, will direct asthma prevention research. Ongoing studies are focused on altering Th2-skewing in early life including through blocking IgE and through altering microbial exposures. If effective, decreasing Th2-inflammation in early life may function in part through enhancing antiviral responses.[51, 69] However, antiviral specific therapies including RV and RSV vaccines, may also prove to be critical in asthma prevention.

Dynamics of respiratory tract bacterial colonization during viral upper respiratory tract infection

Detection of viruses in the upper airway during peak viral seasons can be as high as 90% in prospective studies.[70] However, rates of illness are significantly lower, leading researchers to question why some patients are more susceptible to increased morbidity when they have a

viral upper respiratory tract infection (URI). One factor that has been shown to increase upper and lower airway symptoms during viral infections are bacteria.[71]

These bacteria collectively constitute the microbiota. The upper airway microbiota develops over the first year of life with alterations in the natural development associated with increased risk for URIs during the first few years of life.[72, 73] The most abundant bacteria within the upper airway of infants and children are *Staphylococcus, Streptococcus, Moraxella, Haemophilus, Dolosigranulum*, and *Corynebacterium*.[71, 72, 74–78]

In several infant cross-sectional and cohort studies, the presence of *Streptococcus, Moraxella*, or *Haemophilus* during upper respiratory infection increases the likelihood that the infant will have lower airway symptoms.[72, 76] Studies examining airway bacteria during RSV bronchiolitis have reported links between an increased abundance of *Streptococcus*[9] and *Haemophilus*.[78] In contrast, RV-bronchiolitis is associated with an increased abundance of *Moraxella* and *Haemophilus*.[9] While these studies suggest that a bacteria-virus interaction occurs during infancy, only a few studies have examined the association between virus and bacteria in school-age children. One such study revealed that children with *Streptococcus* or *Moraxella* present in their airway are more likely to have cold and asthma symptoms during a naturally occurring RV infection.[71] Collectively, these studies demonstrate that an association exists between specific bacteria and illness severity.

While *Streptococcus, Moraxella* and *Haemophilus* are often associated with an increase in viral-associated symptoms, a higher abundance of *Corynebacterium, Staphylococcus* and *Dolosigranulum* is often present in the airway in the absence of viral detection and clinical symptoms.[75, 77, 78] In addition, when the latter three bacteria are enriched in the upper airway, infants are less likely to have an acute respiratory illness,[72] and school-age children are less likely to have a symptomatic illness during RV infection.[75] Furthermore, high abundance of *Lactobacillus* in the upper airway during RSV illness is associated with a decreased risk of childhood wheeze,[77] suggesting that bacteria present in the airway during viral illnesses may contribute to both illness severity and long term sequela.

Future perspectives:

Because most studies examining airway bacteria during viral infection have been cross-sectional, observational studies, it remains unclear how airway microbes affect the epithelium, and whether these interactions contribute to the causation of wheezing illnesses, asthma development in young children, and exacerbations of established asthma. Greater insight is needed into metabolic, immunologic and toxic effects of bacteria on epithelial cells that could contribute to acute illnesses and asthma risk. While many studies have examined changes in bacteria that occur during viral infection, few have examined how the airway microbiome influences susceptibility vs. resilience to viral infection. Some bacteria could promote a “pro-inflammatory” environment thereby making the airway susceptible to viral infection. The presence of *H. influenzae* in the infant airway prior to viral infection is associated with increased expression of local inflammatory cytokines suggesting a link between bacteria and airway inflammation.[79] In contrast, mice receiving intranasal administration of *Lactobacillus rhamnosus* prior to viral infection have enhanced antiviral immune responses,[80] suggesting that some bacteria protect the airway and reduce the risk of

symptomatic viral infection. Greater understanding of these relationships may lead to new preventive approaches to acute viral-bacterial illnesses and perhaps the development of childhood asthma.

The influence of the gut microbiome on viral infections of the respiratory tract

The gut microbiome represents the most abundant and diverse microbial environment in the human body, comprised of approximately 40 trillion bacteria.[81] These bacteria have coevolved with humans over millennia to contribute to a symbiosis in which humans consume prebiotic fiber which is metabolized by resident microbes in the gut to create short chain fatty acids (SCFA) which in turn regulate immune responses.[82, 83] Alterations in this relationship are occurring in modern times due to practices such as the frequent use of antibiotics, and the consumption of a high-sugar, low fiber diet. As a consequence, a state of microbial dysbiosis, or an ecological imbalance, may result, which leads to the loss of metabolic capabilities and predisposes infants to both the development of atopic diseases as well as an increased susceptibility to viral infections.[84]

Although epidemiologic evidence strongly supports a role of the gut microbiome in the development of asthma, the mechanisms remain unclear.[85, 86] The most popular theory to explain these observations is that colonization with certain gut bacteria have a direct anti-inflammatory effect on the respiratory tract decreasing the likelihood of airway hyperreactivity.[87] However, there is evidence that certain species of microbiota in the gastrointestinal tract prime the respiratory immune system to effectively fight viral pathogens. Immunologic factors in early life such as low blood cell interferon responses[88–91] and attenuated cytokine production[92] have been associated with increased risk for wheezing in infancy. Furthermore, patterns of metabolites (which can regulate immune responses[93]) at birth are associated with the risk for wheezing illnesses.[94] The idea that delayed immune maturation might contribute to wheezing is supported by studies showing that early life exposures to dogs,[95, 96] farm life,[10, 97] and increased microbes and allergens[98] are inversely related to the risk of wheezing illnesses. Furthermore, exposure to these microbes and allergens during the prenatal period or infancy may be immunostimulatory.[99, 100] A loss, therefore, of these resident microbes may then lead to a predisposition to viral infections and in turn, the development of asthma.

Several studies have proposed mechanisms for the influence of the gut microbiota on both local and distant immune functions. SCFA have been shown to have a local effect on immune responses through their influence on mucosal barrier function, and a loss of SCFA-producing bacteria has been implicated in the development of food allergy.[101] Recent advances have also shown that this symbiosis also influences vital immune responses in other systemic tissues. For example, in the absence of SCFA, mucosal barrier function can break down and allow for translocation of gut pathobionts, bacteria that are symbiotic under normal conditions but pathogenic when removed from their normal environment, which, in turn, can drive autoimmunity.[102] Similarly, in a murine model intact commensal bacteria in the gut were required for adaptive immune responses to respiratory influenza virus infection.

Specifically, when mice were treated with antibiotics, they had reduced virus-specific antibody titers, CD4+ T-cell responses, and cytokine secretion which consequently resulted in elevated viral titers post infection. This impairment, however, was rescued by local or distal injection of Toll-like receptor ligands.[103] Further, exposure to house dust from homes with dogs enriched the cecal microbiome in a murine model with *L. johnsonii*, which protected them against infection with RSV.[104]

Future Perspectives:

Although the pathways remain incomplete, evidence continues to mount that the gut microbiome can influence the maturation of the immune system in viral defense and therefore the development of asthma.[105] Future therapies look to a role of probiotics for the prevention and treatment of allergic disorders, with recent evidence that atopy risk may be associated with a dysbiosis of the gut microbiome. Studies have shown that in asthma, MMP9 (members of a family of enzymes that cleave extracellular matrix proteins) levels were significantly increased and treatment with the probiotic, *L. rhamnosus* GG (LCC), decreased MMP9 expression in lung tissue and inhibited inflammatory cell infiltration, as well as reducing exhaled nitric oxide among 4- to 7-year olds in pediatric asthma.[106]

In early childhood, total fecal IgE levels appear to be specifically correlated with house dust mite-specific IgE levels, indicating that fecal IgE levels represent markers of allergic response to aeroallergens. A significant correlation of fecal IgE levels with *Dorea spp*. and *Clostridium spp*. related to allergic rhinitis and asthma, respectively, suggest that modulation of particular subsets of gut microbial dysbiosis could contribute to the susceptibility to allergic airway diseases.[107] Future work is required for identification of specific species and functional studies to understand the strength and mechanism of these associations. In the future, it is critical to understand more precisely the microbiota composition. Optimized biomarker studies of the microbial taxa and the metabolites involved in asthma-associated dysbiosis could help identify infants at risk of asthma before symptoms. This would also provide a scientific rationale for future therapeutic strategies aimed at restoring an altered infant gut microbiome. Future studies need to revolve around state-of-the-art methods for the evaluation of the microflora to better define indications, the probiotic strains and the type of prebiotic to be used.

Potential for primary prevention: clinical trials aiming to prevent the development of the episodic wheeze phenotype

The inception of childhood asthma is tightly related to early life events such as respiratory infections and the development of aeroallergens sensitization. Other co-factors (e.g., vitamin D) may modulate asthma inception pathways. Previous and on-going clinical trials, geared for asthma prevention, have targeted these pathways and co-factors.

Early life respiratory infections are significant determinants of childhood asthma[108]. In young toddlers, prevention of severe RSV bronchiolitis may reduce the risk of episodic wheeze/asthma development[109, 110]. In preterm infants (33–35 wks), palivizumab treatment during the RSV season resulted in a 73% reduction in the number of wheezing days during

the first year of life, and outside of the RSV season[109]. A follow up study from the same cohort, revealed that at the age of 6 years the intervention resulted in a 41% relative risk reduction in parent-reported asthma, but the forced expiratory volume in 0.5 s ($FEV_{0.5}$) percentage predicted values, which was an additional primary outcome, were similar between the palivizumab and placebo treated infants[110].

Since early life respiratory infections cannot be completely prevented, attenuation of the immune/inflammatory processes during these infections may be another pathway for asthma prevention. This concept is illustrated by the results of a proof-of concept clinical trial in 40 infants hospitalized with RSV bronchiolitis. In this trial, azithromycin treatment for 2 weeks, during acute RSV bronchiolitis, reduced the likelihood of developing recurrent wheeze during the subsequent year[111]. Azithromycin effects were attributed to anti-inflammatory properties and/or its effects on the airway microbiome[112]. A larger confirmatory trial is ongoing (APW-RSV II; NCT02911935; Table 3).

Based on observational studies that linked maternal vitamin D deficiency to childhood asthma, two clinical trials (VDAART[113], COPSAC2010[114]) investigated whether maternal vitamin D supplementation (2400 IU/day[113], 4000IU/day[114]) during pregnancy would prevent asthma/recurrent wheeze in their children. A recent meta-analysis that combined these two trials revealed that this intervention resulted in a 25% significant reduction in asthma/recurrent wheeze risk during the first 3 years of life[115]. The effect was most profound among women with sufficient serum vitamin D levels at randomization highlighting the importance of normal preconception vitamin D levels[115]. It was suggested that vitamin D beneficial effects may be related to enhancement of in-utero lung growth and development and promotion of antimicrobial effects, thereby reducing early life respiratory infections, and/or providing immune modulation effects[116].

Omega-3 fatty acids were suggested to have anti-inflammatory effects, potentially due to decreased production of arachidonic acid metabolites. In a recent clinical trial, high dose Omega-3 fatty acids supplementation (2.4 g daily) to pregnant women, beginning at 24 week of gestation, resulted in a 30% relative risk reduction of persistent wheeze or asthma at age 3 years[117]. These positive effects were driven by subgroups of children born to mothers with a variant of the gene encoding fatty acid desaturase, predisposing to low ability to produce omega-3 fatty acids, and by infants born to mothers with low omega-3 fatty acids baseline blood levels. These sub-group analyses suggest the plausibility of a precision-medicine approach of this potential future intervention. Nevertheless, it is important to assure that high dose omega-3 fatty acids does not possess any safety issues, before omega-3 fatty acids may be utilized for asthma prevention.

The ongoing ORBEX clinical trial (NCT02148796) is attempting to modulate the infant immune system by treating high-risk preschool children with Broncho-Vaxom® for 2 years to prevent/delay the development of wheezing lower respiratory tract illness (WLRI) during a third observation year. Broncho-Vaxom® contains bacterial lysates and was previously shown to reduce the rate of respiratory infections[118]. Hence, it is postulated that prevention of early life WLRI will prevent the development of the recurrent wheeze phenotype. Finally, the ongoing PARK clinical trial (NCT02570984) is targeting the association between

allergic sensitization and asthma inception. PARK investigates whether treatment of high-risk preschool children with Omalizumab for 2-years would prevent asthma development, and whether the treatment would decrease asthma severity among infants who will develop asthma, during an additional 2-year observation period.

Future perspectives:

This is an exciting time for all involved in childhood asthma prevention: recent clinical trials have shown the feasibility of asthma prevention, and multiple clinical trials are ongoing toward this goal. In addition to targeting type 2 immune responses, new interventions are needed to inhibit viral replication, either with specific inhibitors or strategies to boost the development of global antiviral responses in the airways. Finally, studies in farming environments strongly suggest that environmental exposure can lower the risk of viral respiratory illness in addition to reducing allergy.[10, 97] Identifying relevant mechanisms is likely to lead to new preventive approaches to virus-induced wheeze and asthma.

New therapeutic options to decrease severity of asthma exacerbations caused by respiratory viral infection

Recent studies have focused on short-term increases in standard asthma therapy, vitamin D supplementation, azithromycin and anti-IgE therapy. However, mixed efficacy results limit the widespread application of many of these therapies in clinical practice. Maintenance inhaled corticosteroids (ICS) are effective in reducing the risk of asthma exacerbations and, when combined with inhaled long acting beta agonists (LABA), this decreases the risk further. However, exacerbations continue to occur. Attempts to increase dosing of inhaled steroid with early signs of loss of asthma control with viral infection, termed the “yellow zone”, to decrease exacerbation risk, have yielded mixed results. GINA guidelines suggest increasing ICS at onset of symptoms as part of a self-management plan (http://www.ginasthma.org). A Cochrane database review (including five studies in adults and three studies in children) concluded that current evidence does not support increasing ICS in mild to moderate asthma patients as part of a self-management plan to treat exacerbations.[119]

A clinical trial examined this question further in 254 children aged 5–11 with history of mild to moderate persistent asthma with at least one previous exacerbation in the past year.[120] Children were treated for 48 weeks with low dose inhaled steroid and assigned to either continue this or quintuple the dose for 7 days at onset of loss of asthma control. There was no significant difference in the rate of severe exacerbations in the groups. The total corticosteroid exposure in the high dose group was 16% higher (including both inhaled corticosteroid use and prednisone) and there was an effect on linear growth velocity between the high dose and low dose group (−0.23 cm/year), suggesting potential risk without identifiable benefit of the therapy.

Vitamin D levels have been inversely associated with asthma severity, including hospitalization for severe infections.[121] A large study aimed at optimizing low Vitamin D levels through supplementation did not reduce rates of colds or treatment failures in adults with asthma.[122, 123] In contrast, a meta-analysis of seven randomized trials demonstrated a

significant reduction in asthma exacerbations, with the effect seen only in patients with low vitamin D at baseline.[124] There are ongoing studies in children with asthma examining the possible role of vitamin D supplementation in preventing asthma exacerbations (Table 3).

Current guidelines do not recommend the use of antibiotic treatment for episodes of asthma-like symptoms in children, yet they are commonly used. A randomized, double-blind, placebo-controlled trial conducted in the US, evaluated the role of early administration of azithromycin in prevention of progression to severe lower respiratory tract illness (LRTI) symptoms.[125] Preschool children, age 12–71 months, with history of recurrent severe wheezing in the setting of LRTI, were randomized to azithromycin 12 mg/kg for 5 days (307 patients) or placebo (300 patients). The medications were to be started as soon as the children developed signs or symptoms that typically preceded the development of a severe LRTI. The primary outcome measure was the number of respiratory tract infections not progressing to a severe LRTI. The azithromycin group experienced a lower risk of progression to a severe LRTI than the placebo group.

In the $COPSAC_{2010}$ (Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort), children (age 1–3) with recurrent asthma-like symptoms within this cohort were enrolled in a study to assess the duration of episodes when treated with azithromycin.[126] With each episode of 3 days of consecutive symptoms (wheeze, cough, dyspnea), children were randomized to receive 10 mg/kg azithromycin or placebo for 3 days. Seventy-two children from the recurrent asthma-like symptoms group had 158 episodes. The azithromycin treatment shortened the days of symptoms, 3.4 days compared with 7.7 days after placebo, corresponding to a calculated reduction in episode length of 63.3%. More improvement was seen when the treatment was started earlier in the episode; however, treatment did not significantly affect the time to next episode of troublesome lung symptoms in children.

With these episodes, a hypopharyngeal aspirate was collected and cultured for common bacterial pathogens and a nasopharyngeal aspirate was collected for viral PCR. Overall, the presence of any cultured pathogenic bacteria did not significantly alter the treatment effect compared to episodes without bacteria present; however, azithromycin was more effective in those whose culture grew *H. influenzae*. The treatment effect in these studies is promising; however, resistance to these antibiotics and eliminating commensal microbes along with pathogens are concerns with repeated treatment.

Birth cohort studies have shown allergic sensitization to be a risk factor for RV-induced wheeze.[42] Additionally, in one prospective cohort study, the severity of RV-triggered asthma exacerbation increased as the degree of allergen sensitization increased, with serum IgE levels (total IgE and allergen specific IgE) increasing from baseline during the exacerbation.[127] Persistence of asthma by age 13 was most strongly associated with wheezing illness with RV and aeroallergen sensitization in early life[37] suggesting a role for both viral infection and allergic sensitization in the development of asthma.

A possible mechanism for impaired response to viral infections in allergic asthmatics is a decreased secretion of IFN in response to viral infection. Purified plasmacytoid dendritic

cells (pDC) from patients with allergic asthma were shown to secrete less IFN-α in response to exposure with influenza A virus.[51] Increased FcεRIα expression and serum IgE levels were inversely associated with IFN- α secretion. The increased susceptibility to viral wheeze in atopic patients and impaired antiviral response in these patients suggests a role for possible therapeutic intervention to decrease allergic inflammation with the goal of decreasing asthma exacerbations in response to viral infection.

Omalizumab, a humanized monoclonal antibody that selectively binds to IgE, has recently been studied as an add-on therapy to prevent fall asthma exacerbations in atopic asthmatics in the Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations (PROSE) study.[128] The PROSE study included 478 children, age 6–17, with respiratory allergy and asthma, randomized to either inhaled corticosteroid boost, add on omalizumab or placebo. All patients had guidelines-based care in addition to the add-on treatment (ICS boost, omalizumab or placebo). Treatment was begun 4–6 weeks before the participant's school start day and ended 90 days after school start date. Omalizumab treatment significantly decreased the odds of having at least 1 exacerbation, whereas boosting ICS did not reduce risk. Omalizumab increased IFN-α responses to RV *ex vivo*. Within the omalizumab group, greater restoration of IFN-α responses were associated with fewer exacerbations. In this trial, omalizumab was associated with a decreased frequency of RV illnesses, decreased duration of RV infection as well as decreased frequency of overall respiratory illness, and reduced peak RV shedding.[52] Omalizumab reduced expression of FcεRIα on the surface of pDC and this reduction was associated with lower exacerbation rates and correlated with enhanced IFN-α production, suggestion a possible mechanism for the interaction between allergic sensitization and virus-induced asthma exacerbations.[69] However, the connection between the pDC type I IFN production and asthma exacerbation will benefit from further study.

In an observational study following children with asthma presenting with an acute asthma exacerbation triggered by RV, the use of omalizumab for at least 4 weeks prior to presentation was associated with reduced severity of exacerbation compared with patients primarily treated with ICS.[129] This suggests a benefit in not only frequency and duration of asthma exacerbation, but also severity of exacerbation.

Another possible mechanism for the interaction between allergic sensitization and virus-induced asthma exacerbations is the presence of anti-viral IgE in response to infection. In RSV infection in infants, RSV specific IgE was detected in nasopharyngeal secretions, with significantly higher titers in subjects with wheezing.[130, 131] Correlation of the peak titers with degree of hypoxia was also noted. Following known exposure to a specific laboratory strain, RV-specific IgE could be detected in human sera.[132] While the IgE response to RV and RSV are associated with infection, the role of IgE in the host response to these infections is not fully understood. Given the decreased exacerbations with use of omalizumab, further investigation into the role of anti-viral IgE is indicated.

Future perspectives:

Given the morbidity of RSV and RV infections in patients with asthma, a consistent and effective treatment approach is highly desirable. While studies have found possible benefits

to treatment with azithromycin and omalizumab, the widespread use of these treatment approaches is not currently justified. Further characterization of risk in this patient population and additional work to delineate the mechanisms by which these drugs are effective may lead to selection of patients most appropriate for these therapies.

Conclusion

There have been important advances in our knowledge of the relationship between viruses and asthma over the last decade. Advances in scientific methods have provided innovative opportunities to examine host, environment, and viral interactions that either protect against or increase vulnerability to asthma development and exacerbations. The exploration of the contribution of the respiratory and gut microbiome to virally-induced asthma is in its infancy and we suspect that over the next 5 years there will be major advances in this area. Finally, primary prevention is a major goal to diminish the morbidity of virally-mediated wheezing, asthma and exacerbations. Until primary prevention becomes a reality, clinical trials examining the impact of established medications, as well as novel therapies, will be critical to diminish the impact of viral infections on wheezing and asthma.

Abbreviations:

RSV	Respiratory syncytial virus
RV	Rhinovirus
AR	Airway responsiveness
F	Fusion
Th2	Type 2
CDHR3	Cadherin-related family member 3
GWAS	Genome wide association study
ETS	Environmental tobacco smoke
URI	Upper respiratory tract infection
SCFA	Short chain fatty acids
$FEV_{0.5}$	Forced expiratory volume in 0.5 s
WLRI	Wheezing lower respiratory tract illness
ICS	Inhaled corticosteroids
LABA	Long acting beta agonists
LRTI	Lower respiratory tract illness
pDC	Plasmacytoid dendritic cells

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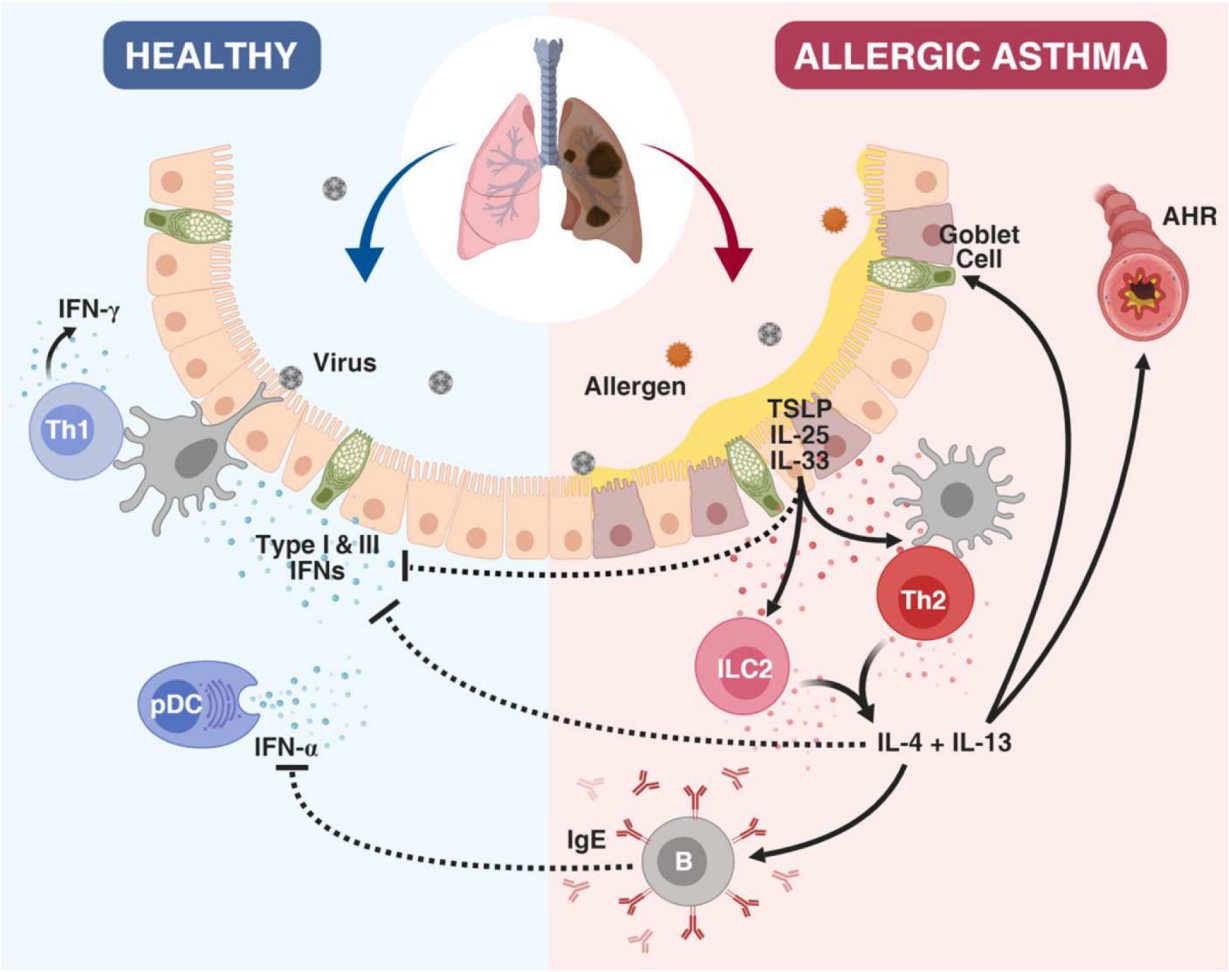

Figure 1.

Immune responses to virus in the allergic asthmatic host. In the healthy host, anti-viral IFN responses control and clear respiratory viral infections. In allergic asthmatics, the release of the type 2-skewing cytokines TSLP, IL-25, and IL-33 promote the induction of Th2 cytokines and the suppression of IFN responses, in addition to promoting airway hyperreactivity (AHR) and increased mucus and IgE production. Furthermore, IgE has the capacity to suppress IFN-α production by Plasmacytoid DCs (pDCs).

Table 1.

Review of most salient points

1	Polymorphisms in several antiviral and innate immune genes have been linked to susceptibility to respiratory viruses, infection severity, and virus-induced asthma exacerbations, and have been replicated across multiple cohorts; these genes include *STAT4, JAK2, MX1, VDR, DDX58, and EIF2AK2.*
2	Rhinovirus virulence varies by species; RV-A and RV-C are more likely to cause illnesses, wheezing and lower respiratory tract infection compared to RV-B.
3	RV infection leads to expression of epithelial derived cytokines IL-25, IL-33, and TSLP and an increase in ILC2s as an important source of airway IL-13; blocking these pathways with anti-IL-25 attenuates neonatal RV-induced AHR and mucous cell metaplasia in mice.
4	Two prevention studies using palivizumab (a monoclonal antibody directed against RSV) in high-risk infants found that prevention of more severe RSV-illnesses decreased the risk of childhood recurrent wheezing but not asthma development.
5	In several infant cross-sectional and cohort studies, the presence of *Streptococcus, Moraxella*, or *Haemophilus* during upper respiratory infection increases the likelihood that the infant will have lower airway symptoms; studies examining airway bacteria during RSV bronchiolitis have reported links between an increased abundance of *Streptococcus* and *Haemophilus*, while in contrast, RV-bronchiolitis is associated with an increased abundance of *Moraxella* and *Haemophilus*.
6	The presence of *H. influenzae* in the infant airway prior to viral infection is associated with increased expression of local inflammatory cytokines suggesting that a link exists between bacteria and airway inflammation; in contrast, mice receiving intranasal administration of *Lactobacillus rhamnosus* prior to viral infection have an enhanced antiviral immune response[80], suggesting that some bacteria may protect the airway and help prevent viral infection.
7	The gut microbiome also regulate pulmonary anti-viral immunity; in a murine model intact commensal bacteria in the gut were required for adaptive immune responses to respiratory influenza virus infection.
8	Unique components of the viral genome contribute to respiratory illness and knowledge of these factors may also assist in vaccine and therapeutic strategies aimed at the proteins responsible for specific disease characteristics.
9	Omalizumab, a humanized monoclonal antibody that selectively binds to IgE, decreased fall asthma exacerbations in atopic asthmatics and increased IFN-a responses to RV *ex vivo* in the Preventative Omalizumab or Step-Up Therapy for Fall Exacerbations (PROSE) study, whereas boosting ICS did not reduce risk.
10	A recent meta-analysis that combined two clinical trials (VDAART, COPSAC2010) investigated whether maternal vitamin D supplementation (2400 IU/day, 4000IU/day) during pregnancy revealed that this intervention resulted in a 25% significant reduction in asthma/recurrent wheeze risk during the first 3 years of life.

Table 2.

Polymorphisms in several antiviral and innate immune genes have been linked to susceptibility to respiratory viruses, infection severity, and virus-induced asthma exacerbations, and have been replicated across multiple cohorts.

Gene	Function
STAT4	Transcription factor required for IL-12 signaling in the development of Th1 cells from naïve CD4 T cells
JAK2	A non-receptor tyrosine kinase critical for signaling of the GM-CSF, gp130, and single chain receptor families.
MX1	Responsible for the antiviral state against influenza infection
VDR	Vitamin D receptor
DDX58	Involved in antiviral signaling in response to viruses containing a dsDNA genome
EIF2AK2	Innate antiviral immune response to viral infection that can trigger apoptosis via FADD-mediated caspase 8
IRF7	Critical role in the innate immune response against DNA and RNA viruses
IFIH1	Provides instructions for making the MDA5 protein that has a critical role in innate antiviral immunity
IFNA5	One of the type I IFN-α isoforms that has antiviral activities
NOS2	Nitric oxide synthase gene that mediates the antiviral activity of IFN-γ
ADAM33	Member of the ADAM (a disintegrin and metalloprotease domain) family identified as a major susceptibility gene in asthma
IL4R	Interleukin 4 receptor through which IL-4 and IL-13 signal to induce IgE class switching and airway mucus metaplasia
CD14	Multiple functions, one of which is critical for TLR signaling in host defense
TNF	Tumor necrosis factor that is produced in abundance by mast cells and has roles in cell survival and proliferation
IL13	Important in airway mucous cell metaplasia, airways responsiveness, VCAM expression
IL1RL1	One subunit of the receptor for IL-33, which can activate ILC2 and promote CD4 T cell differentiation toward Th2 phenotype
CDHR3	Cadherin that is the receptor for rhinovirus

Table 3.

Future/ongoing interventional studies examining treatments for viral triggered asthma

Study Title	Study Population	Intervention	Primary Outcome Measurement	Estimated Completion Date
Vitamin D In the Prevention of Viral-Induced Asthma in preschoolers	children age 1-<6 with recurrent cold triggered asthma attacks, expected enrollment 865 subjects	Baseline and 3.5 month high dose vitamin D 100,000 IU and daily Vitamin D dose 400 IU OR placebo	Number of courses of rescue oral steroids (OCS) over 7 months	December 2022 *enrolling*
Azithromycin to Prevent Wheezing Following Severe RSV Bronchiolitis II	children 1–18 months of age, hospitalized due to RSV bronchiolitis, expected enrollment 200 subjects	Azithromycin (10 mg/kg × 7 days followed by 5 mg/kg × 7days) OR placebo	Time to occurrence of a 3rd episode of post-RSV wheezing, observation over 48 months	December 2021 *not yet enrolling*