



Virus infection and allergy in the development of asthma: what is the connection?

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Purpose of review

Information is accumulating which implicates airway inflammation resulting from respiratory viral infections, acting against a background of atopy, in both the cause and pathogenesis of atopic asthma. This review brings together the most recent publications relevant to this rapidly evolving area, particularly those focusing on underlying pathogenic mechanisms.

Recent findings

Salient findings from the recent literature include increased respiratory infection-associated symptom severity/duration and loss of asthma control in atopic relative to nonatopic children; up-regulation of FcεR1 expression on circulating monocytes/dendritic cells occurs during virus-associated atopic asthma exacerbations, providing a mechanism for transient amplification of underlying allergic airways inflammation; high potency of hRV-type C in induction of infection-associated wheeze; Th2-polarized immunity to mucosal dwelling bacteria and protection against asthma; a role for IL-15 in viral-associated airways inflammation; vitamin D and protection against infection-associated asthma exacerbations; strategies for reduction of infection-associated wheezing severity by boosting mucosal Treg cell activity via immunostimulation of the gut mucosa.

Summary

Research in this area is pointing towards new rationales for development of early intervention strategies for prevention of asthma initiation and progression in childhood, based on control of respiratory infections and/or sensitization to aeroallergens.

Keywords

atopic asthma, IgE receptor, IL-15, virus infection

INTRODUCTION

Over the past decade the original concept underlying the hygiene hypothesis, notably that infections protect against the development of allergic diseases, has been progressively refined in light of a growing body of data on how immune responses to microbial and allergenic antigens intersect and interact at multiple levels, and in particular how responses to one can influence resistance to the other. Knowledge in this area is still rapidly evolving. This brief review initially highlights some of the key conceptual 'milestones' that underpin research in this area, and then focuses on some of the most relevant recent findings from the past 12–18 months.

A CENTRAL ROLE FOR VIRAL INFECTION IN THE CAUSE OF ASTHMA: THE EPIDEMIOLOGICAL EVIDENCE

The current surge of interest in the contribution of respiratory viral infections to asthma development

derives in large part from the results of ongoing prospective birth cohort studies tracking community-based populations through the school years and beyond, especially those in which data collection on infection history was an integral part of the study design. These include in particular the Tucson cohort [1], the RAINE [2] and CAS [3] cohorts in Australia, and most recently the COAST [4] cohort in Wisconsin. Collectively these studies have identified lower respiratory tract infections (LRIs)

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KEY POINTS

- Intensity/duration of lower respiratory infection symptoms is highest in atopic children.
- Marked up-regulation of FcεR1 expression on circulating monocytes/dendritic cells occurs during and/or ensuing atopic asthma exacerbations.
- High potency of hRV-type C in induction of infection-associated wheeze is related to enhanced binding to epithelial target cells.
- 'Asthma sparing' effects of vitamin D may involve enhanced regulation of virus-associated airway inflammation.

occurring in the first few years of life as independent risk factors for the subsequent development of asthma (reviewed [5]). However, a series of additional observations point to another level of complexity in relation to the role of LRIs in asthma pathogenesis, notably that whereas early symptomatic infections *per se* increase risk of disease development, this risk is maximal in children expressing the atopic phenotype [5]. One explanation for this association is that the Th2 bias, which is intrinsic to immune responses against allergens in atopics, spills over into their host antimicrobial defences and thus attenuates them via immune deviation [6]. Such a mechanism does not require any direct contribution from allergen-specific immune responses, but instead is based on the notion that the immune responder phenotype characteristic of atopics is generalized, as opposed to compartmentalized and restricted only to nonreplicating antigens (allergens) encountered at mucosal surfaces. Several observations (see below) are consistent with the existence of such a pan-defect, but this does not alone provide a satisfactory explanation for all the relevant epidemiological findings. In particular, prospective analyses on the chronology of LRIs in relation to the onset of atopic sensitization in early childhood indicate that maximal risk for development of persistent asthma is only observed when sensitization to aeroallergens and LRIs occur concurrently [3,7], suggesting the possibility of direct interaction(s) between the underlying inflammatory pathways involved (see below).

VIRUSES AND ASTHMA ONSET: ARE ALL RESPIRATORY VIRUSES EQUIPOTENT?

This remains a 'hot button' issue in this field. Until comparatively recently, it was assumed that respiratory syncytial virus (RSV) was overwhelmingly the

most important trigger of severe (particularly wheezing) LRI in the first 2 years of life, and compelling data on the association between early RSV-induced LRI and subsequent development of persistent asthma have been published from independent prospective cohort studies [8[•],9]. However, more recent analyses in other populations have revealed that the contribution of rhinovirus (hRV) to LRI during infancy and the preschool years is considerably higher than previously believed and moreover that these infections link strongly with risk for subsequent asthma [3,4,10[•],11,12]. The association with the hRV-C subtype appears particularly strong, reflecting the high frequency with which it is isolated from young patients experiencing severe LRIs [13^{••},14]. Molecular modelling studies suggest that the potency of hRV-C in this regard may be related to its expression of unique attachment receptors for proteins expressed on the surface of nasal epithelial cells [15^{••}]. However, as pointed out in a recent review [16[•]], whereas the case for a major role for hRV as a causative factor in early-onset asthma is very strong, it would be premature at this stage to discount the importance of RSV, and the eventual resolution of the RSV vs. hRV debate must await relevant intervention trials. It is pertinent to note in this context that an anti-RSV antibody with a proven track record in high-risk infants is available [17].

VIRUS INFECTIONS AND ATOPY: UNRAVELLING THE INTERACTION(S)

As noted above, infection : atopy comorbidity has become a recurrent theme in the asthma literature, particularly in paediatrics, and information in support of this association continues to accumulate. Three informative recent additions to the literature are particularly worthy of note. Firstly in a unique study from the Wisconsin group [18^{••}], 58 school children were monitored weekly to cover the spring/fall virus seasons, to determine viral carriage and its relationship with asthma symptom severity. In addition to confirming the strong association with hRV, the study also confirmed that symptom severity/duration and susceptibility to loss of asthma control were much more frequent (more than twofold) amongst atopic children relative to their nonsensitized counterparts. In a similar vein, a study from Japan [19[•]] demonstrated that pandemic H1N1 influenza viral infection unmasked 'occult' asthma in significant numbers of children without any previous history of asthma attacks or treatment, and moreover that 85% of affected children were sensitized to common indoor allergens. In a third study [20^{••}], risk for a diagnosis of current asthma at

age 5 years associated with repeated severe LRI in the first 2 years of life was shown to increase as a function of concurrent aeroallergen-specific serum IgE titres, and this interaction occurred across the full spectrum of infection frequencies observed in the study population. The highly quantitative nature of these inter-relationships argues strongly that the underlying interactions may be direct and involve IgE antibody itself, as opposed to simply reflecting a generalized 'Th2 bias' of immune responses in atopic children.

In seeking more detailed information on the nature of these interactions our group is currently focusing on children experiencing severe asthma exacerbations resulting in hospitalization. In common with experience from other centres (reviewed [21]) the affected children involved are virtually all atopic and predominantly hRV-infected [22], implying the underlying operation of viral/atopy-initiated interactions comparable to those associated above with asthma initiation. The approach being followed involves genome-wide expression profiling of cell populations being exported from the bone marrow during the peak of the exacerbation, in particular myeloid populations (monocytes and dendritic cells) expressing high levels of surface CCR2, the major chemokine receptor associated with myeloid trafficking to inflamed lung. These studies have revealed the covert operation of a pathway involving translocation of exacerbation-associated cytokine signals (particularly IL-4/IL-13 and type1 IFN) to the bone marrow, which results in 'alternative activation' of myeloid populations including immature dendritic cells, together with large-scale up-regulation of surface expression of FcεR1 [22,23²²]. We posit that the replacement of airway mucosal dendritic cells (which are known to turn over rapidly during viral infection) with these 'FcεR1-armed' precursors from the bone marrow sets the scene for recruitment of underlying Th2-polarized immunity to aeroallergens into the inflammatory milieu of the virally infected airway mucosa [23²²]. This form of IgE-facilitated allergen presentation is recognized as a prime cause of intense Th2-mediated inflammation in atopic dermatitis lesions [24] and the accumulating evidence argues that a similar mechanism is triggered during virus-associated atopic asthma exacerbations and may be responsible for a major component of the underlying airways inflammation responsible for acute symptoms. An additional consequence of this may be attenuation of local Th1-associated antiviral defences via 'immune deviation' thus contributing to viral persistence; similar evasion strategies are recognized as part of the pathogenesis of a range of other virus-associated diseases (reviewed in

[23²²]). This bone marrow-mediated amplification loop may also operate (albeit at a lower level of intensity) during active flares of allergic diseases not involving viral triggers [23²²,25].

Consistently with the operation of this IgE-associated mechanism in childhood asthma, a study on sputum-derived cells from children collected during virus-associated exacerbations involving a similar genomics-based approach identified a range of expression signatures associated with disease severity, including up-regulation of FcεR1 and concomitant down-regulation of genes associated with antiviral immunity [26²²]. Also, a recent report from the US Inner City Asthma Consortium demonstrated that year-long treatment of high-risk children with anti-IgE reduced the frequency of exacerbations, particularly during winter [27²²].

An additional observation of interest in relation to this mechanism is that in both animal models [28] and human studies [29], the expansion of respiratory mucosal dendritic cell populations resulting from viral infection frequently persists beyond viral clearance. In this context a recent observation suggests that, particularly in the case of hRV, low-level viral persistence detectable as viral RNA after recovery from acute disease is a relatively frequent occurrence in asthmatic children [30²²], and this may have important implications in relation to overall asthma pathogenesis, especially in atopic children sensitized to perennial aeroallergens.

OPPORTUNISTIC BACTERIAL INFECTIONS ASSOCIATED WITH LRI: THE 'ELEPHANT IN THE ROOM'?

There is now compelling evidence (reviewed by Homer Boushey in Section 2 of this issue) that the lower airways are not sterile at baseline but instead contain significant populations of common mucosal dwelling bacteria. A theoretical implication of these findings is that the transient breakdown in epithelial barrier function that inevitably accompanies severe virus-induced asthma exacerbations may open a window for trans-mucosal incursion by such bacteria, and ensuing interaction between these and tissue phagocytes would further exacerbate local inflammation. Given that the intra-luminal presence of these organisms in the lower airways apparently represents the norm, it is reasonable to suspect that the mucosal immune system has evolved a strategy to deal with such challenges which may be relatively frequent occurrences. A recent study [31²²] from our group points to one possible (albeit unexpected) mechanism, notably the expression of Th2-polarized immunity against nonsuperantigen-producing

bacteria exemplified by *Haemophilus influenzae* and *Streptococcus pneumoniae*, the marker for which was relatively high titres of bacterial antigen-specific IgE. The relevant membrane-associated antigens on these organisms are released only in particulate form unsuitable for cross-linking IgE receptors on mast cells and as a consequence, unlike IgE against *Staphylococcal* superantigens which are secreted as soluble proteins, IgE against *Haemophilus* and *Streptococcus* is not associated with risk for airways inflammation but instead the converse, that is high titres are paradoxically associated with reduced risk for asthma [31²²]. In this regard it is known that IL-4 and IL-13, the primary Th2 cytokine that drive IgE class switching, are potent down-regulators of bacterial-induced macrophage activation, and we postulate that *Haemophilus* and *Streptococcus*-specific IgEs are simply surrogates for underlying IL-4/IL-13-producing bacterial-specific Th-memory cell populations that provide this anti-inflammatory cover against the effects of transmucosal bacterial incursion [31²²]. It is noteworthy that IgE titres against these *Haemophilus* and *Streptococcus* antigens are boosted in the wake of severe viral-associated asthma exacerbations [32] which may reflect one of the consequences of these transient bacterial incursions.

THE PARACETAMOL SAGA: MORE TWISTS AND TURNS

Over a decade since the 'paracetamol hypothesis' was first raised, controversy still surrounds this issue. In the past year further conflicting studies have been published concerning both prenatal and postnatal exposure and risk of allergy/asthma [33–38,39²³], and the debate appears destined to continue for some time to come. Despite the lack of any overall consensus, both sides have identified the issue of 'confounding by indication' as a key sticking point, the challenge being to tease out whether the indication for which paracetamol is prescribed (notably febrile respiratory illness) might be the relevant associate of asthma development, and not paracetamol itself [40]. A model for how to approach this is the recent study of Schnabel and Heinrich [39²⁴] on 3097 children involving careful prospective monitoring of symptoms and medication use during infancy, with follow-up targeting asthma and allergic disease 5–6 years later. A salient conclusion from this study, beyond the issue of paracetamol use *per se*, was that children who eventually developed asthma clearly experienced more days of febrile respiratory infection than children who did not.

In this regard we have recently completed analysis of the 10-year respiratory outcome data

from our high-risk CAS cohort in Perth, in whom every reported respiratory infection during their first 5 years triggered a visit by a clinical monitoring team. When these children were assessed at their 5th birthday a notable finding was that in relation to risk for current asthma at this age, febrile LRIs and wheezing LRIs during infancy were associated with comparably high risk [7]. Of particular interest, by the time of their 10th birthday the association with current asthma was much stronger for febrile LRIs, whereas the strength of the association with wheezing LRIs had waned [41²⁵]. This suggests to us the possibility that host responses to infections marked by fever and hence activation of the inflammasome may have uniquely potent asthma-promoting properties, that is the tissue damage they mediate may be more profound and long-lasting than that associated with infections marked by wheeze alone.

IL-15: A NEW LINK IN THE PATHWAY FROM VIRAL INFECTION TO ASTHMA?

IL-15 has previously been identified as a factor linking innate and adaptive immunity to viral infection via promotion of natural killer (NK) and CD8 T-memory cell responses. Earlier findings [42,43] have reported that a defect in production of type 1 interferons following infection of airway epithelial cells with hRV is a characteristic feature of the asthmatic phenotype, but the nature of the downstream effects of this defect is only partially understood. Recent studies from the Johnston group [44²⁶,45] implicate IL-15 in this process in the context of both RSV and hRV infections. They extend the observations on attenuated type 1 interferon in asthmatic children to include in-vitro production by their alveolar macrophages which is type 1 interferon-dependent, and also this alveolar macrophage response is reduced in asthmatic children relative to controls. Of note they additionally employ a human model of experimental hRV infection and demonstrate that BAL levels of IL-15 are deficient in asthmatic children and are related to airways hyper-responsiveness and virus load [44²⁶]. RSV exhibits similar IL-15-inducing activity in human airway epithelial cells [45], implying that this mechanism may be common to host responses to respiratory viral infections in general.

VITAMIN D AND SUSCEPTIBILITY TO RESPIRATORY INFECTION

The role of vitamin D in the pathogenesis of asthma is discussed in detail elsewhere in this issue. However, in the context of this review, it is pertinent to

note that protection against respiratory infections in children has recently joined the growing list of suggested mechanisms to explain the asthma-protective effects of this agent [46[■],47[■]]. Of particular relevance are the results of a small trial [47[■]] suggesting that vitamin D supplementation of atopic asthmatic school children has potential for prevention of virus-associated asthma exacerbations in this high-risk group. The underlying mechanism(s) are unknown, but an additional study linking vitamin D levels with T-regulatory cell activity in infants [48[■]] points towards a plausible candidate, and moreover suggests that these associations should be explored in more detail in the infant/preschool age group.

PREVENTION OF EARLY LRI IN CHILDREN TO FORESTALL ASTHMA DEVELOPMENT: THE COMMON MUCOSAL IMMUNE SYSTEM AS A THERAPEUTIC TARGET?

The growing evidence indicating a central role for early LRI in the development of persistent asthma in atopic children has served to elevate respiratory viral infections towards the head of the list of prospective therapeutic targets for primary prevention of asthma. The dilemma faced by researchers is the current lack of antiviral agents that are approved for use in children; in particular specific vaccines against the most important pathogens hRV and RSV are still not on the horizon. However, alternative approaches are being developed on the periphery of this field that are beginning to show promise.

One area of particular interest concerns attempts to boost endogenous anti-inflammatory mechanisms in the lung by oral administration of immunomodifying agents. The underlying scientific principles derive from the concept of the CMIS, notably that migratory cell populations (particularly T and B lymphocytes) that mature functionally in gut-associated lymphoid tissues (GALTs) develop homing receptors that control their subsequent recirculation behaviour, such that they subsequently preferentially traffic to mucosal tissues including those in the respiratory tract. These principles may explain the reported effects of live probiotics in reducing the intensity and duration of inflammatory symptoms associated with respiratory infections [49]. Interest in the use of available probiotics is increasing, and the search for more potent formulations to increase clinical effect size, which is currently modest at best, is being actively pursued.

Related possibilities exploiting similar principles also exist, notably involving the use of oral

extracts derived from bacteria as opposed to live organisms. One example of direct relevance to the topic of this review is the bacterial-derived therapeutic agent OM-85 which has been used extensively in Europe since the 1980s to treat immunocompromised adults and children who are susceptible to repeated LRIs. A recent study [50[■]] on the use of this bacterial extract on a double-blind, placebo-controlled basis in children with recurrent wheeze demonstrated an approximately 40% reduction in the attack rate over the treatment period. The most common trigger of wheeze in this context is tissue inflammation associated with viral infection, and the findings (which echo those from earlier open-label studies) which suggest attenuation via this agent are sufficient to justify further clinical studies.

Based on the results of recent studies in animal models [51[■],52[■]], the underlying mechanism(s) of action of this agent are likely to include generation of T-regulatory cells (Treg) in GALT which subsequently migrate to the airway mucosa, thus boosting capacity to control 'bystander' inflammation resulting from local expression of host-antiviral immunity. However, additional Treg-independent pathways may also be involved, in light of recent reports demonstrating that gut bacterial derived proteoglycans can up-regulate the innate immune functions of PMN in bone marrow [53[■]], and that other commensal-derived products can prime endogenous inflammasome functions in the lung, resulting in the boosting of local adaptive immunity to influenza virus [54[■]].

CONCLUSION

The general concept that interactions between inflammatory pathways triggered by exposure to respiratory viruses and aeroallergens play important roles in both the initiation and progression of asthma is now firmly embedded in the literature, and research into the underlying mechanisms is intensifying on a number of fronts. In particular, this work is providing new rationales for intervention in early-stage disease with the aim of halting progression to chronicity, several of which should be testable in the short-term future.

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Conflicts of interest

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