

ORIGINAL ARTICLE

Infection and the development of allergic disease

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Abstract

Persistent allergic diseases exemplified by atopic asthma frequently begin during very early life. Epidemiological findings indicate that progression from allergic sensitization to atopic asthma occurs most frequently when atopy is accompanied by early respiratory viral infections. The underlying mechanism appears to involve recruitment of atopy-associated effector mechanisms into the host response to the virus. This has the dual effect of antagonising anti-viral immunity and amplifying inflammation in the infected airway mucosa, driving asthma pathogenesis. Immune responses underlying the allergic state are uniquely plastic during childhood. Alleviating specific allergy during this period may reduce risk of subsequent asthma development.

Viral infections have an important role in allergic disease such as atopic asthma. We are investigating the functions of inflammation and respiratory viral infection in the generation and stabilisation of the allergic asthmatic phenotype (1, 2), focussing on the first years of life. Much of our data, including allergic asthmatic outcomes at age 5, come from a prospective Childhood Asthma Study (CAS) birth cohort study in Perth, Australia of 240 high-risk children (2, 3).

Computation of relative asthma risk for children in this cohort with no allergic sensitisation showed the contribution of severe respiratory infections as an independent factor in disease pathogenesis. The number of respiratory infections, particularly in the first 2 years, showed an almost linear relationship with risk for subsequent asthma development. Over the range examined, up to 9–10 infections in the first 2 years, we saw an almost eightfold increase in asthma risk (4). Allergic sensitisation was examined in parallel as IgE levels against aeroallergens. When this was included in logistic regression analysis, at every level of infection, additivity was observed with allergic sensitisation. The sensitisation level in the 2-year timeframe interacted positively with infection history to drive the later development of asthma. We also examined whether allergy had to manifest in the same timeframe as infection, or whether it could occur at a later stage in the study period. Risk was clearly associated with infection at the same time as allergy (3), suggesting direct interaction.

Data from this cohort and others show that these risk factors are also relevant for very long-term asthma. In a 10-year followup of the CAS cohort (in preparation), severe lower respiratory tract infections and concomitant sensitisation during infancy were again major predictors of current asthma. The odds ratios for asthma at age 10 after multiple respiratory

tract infections and early sensitisation were even higher than for asthma at age 5. Recent data from the Tucson cohort (5) and others show that asthma at age 10 is highly predictive of asthma in the 20s. Therefore, interactions we observe in early life are valid for outcomes over at least two decades.

Interaction mechanisms in allergic asthma: lessons from the emergency room

Epidemiological findings suggest that interactions between allergic sensitisation and viral infections are strongest in virally associated asthma exacerbations. International multi-centre data show that hospitalisation for acute asthma exacerbations spikes in the winter viral season. The phenotype of these children is almost invariably severely atopic. Beyond preschool years, the virus is predominantly rhinovirus.

We used a similar model to investigate mechanisms underlying interactions between allergic sensitisation and viral infections in children admitted for acute severe asthma (6). This population was 96% allergic, and in the top quartile for aeroallergen-specific IgE titre. Virus from these subjects was predominantly rhinovirus. The theoretical basis for the investigation originated from concepts known since the 1960s. All peripheral inflammatory sites produce mediators such as cytokines and chemokines that reach the bone marrow, where precursors of migrating myeloid cells are functionally programmed to respond to the signal responsible for generating the mediators. To examine acute virally induced exacerbation of asthma in the airways, we performed genomic analyses on cells from the peripheral circulation to identify effector gene pathways upregulated during viral induction of asthma.

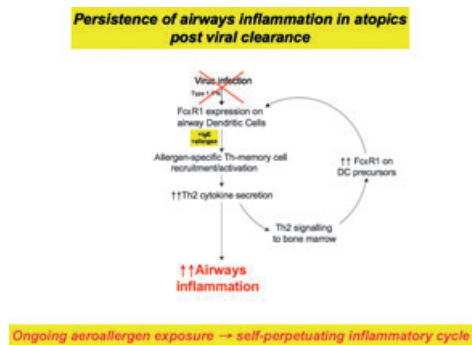


Figure 1 Persistence of airways inflammation in atopy post viral clearance. In atopic children, viral infection begins a cycle in which cytokines from the inflamed airway program bone marrow cells. Bone marrow-derived cells expressing high levels of FcεRI arrive in airway tissues and exacerbate the inflammatory milieu.

Blood was taken during the acute severe asthma stage and in convalescence. Comparative gene expression profiles identified gene expression signatures associated with acute asthma exacerbation. Bioinformatics identified involved pathways. We expected major signals in T-cells but by the time the subjects were hospitalised, the major Th2 signal had passed, and subjects were in a consolidation phase. Virtually all activation signals were in the myeloid compartment. The strongest signals were for the type 1 interferon (IFN) pathway and the interleukin (IL)-4/IL-13 pathways. This suggested that biologically active amounts of soluble or cell-associated cytokines were released from the inflamed airway, went to the bone marrow, and triggered programming of myeloid cells. The strongest signal was for the high-affinity IgE receptor FcεRI on myeloid cells. Total numbers of monocytes and dendritic cells (DCs) increased markedly during acute exacerbation, and the proportion of these cells expressing the high-affinity IgE receptor also increased.

This finding was reproducible *in vitro* with peripheral blood mononuclear cells from allergic individuals cultured with type 1 IFN to upregulate the γ chain of FcεRI and IL-4 and/or IL-13 to upregulate the α chain. Together, these upregulate the overall receptor. The α chain is constitutively hyperexpressed in the myeloid compartment of allergic individuals resulting from a constant IL-4 and IL-13 “drip feed” from inflammatory sites. Making more γ chain acts in synergy with the process already initiated in these individuals.

The implications of these findings are known from the atopic dermatitis literature (7). If FcεRI on DCs are crosslinked with IgE and allergen, the DCs become activated and secrete chemokines that attract Th2 memory cells. This also upregulates the processing and presentation of allergen to Th2 memory cells. This is the most efficient way known for a local microenvironment to activate a Th2 memory response and generate proinflammatory Th2 cytokines.

Our interest is in airways, which have a network of DCs that are almost identical to skin DCs, and function as the

gatekeepers of immune responses against viruses and allergens. From an animal parainfluenza model and from human data on RSV infections, we know that turnover rates of DCs at infection sites in the airway mucosa strongly increase during viral infection. During virally induced asthma exacerbations, replacements are required continuously for these DCs as they sample virus and transport it to the central immune system. Our data infer that during infection in atopic children the bone marrow-derived replacements for these rapidly cycling DCs arrive in airway tissues already fully “armed” via high levels of FcεRI expression, setting the scene for recruitment of underlying allergen specific Th2 immunity into the inflammatory milieu at the infection site.

We believe that this model for interaction between viral and IgE-induced signals in airway tissues, is another example of “immune evasion” that occurs with diverse viruses, including Herpes, HIV, and Dengue. Viruses tend to occupy niches where they can evade Th1 immunity attack, including by harnessing local Th2 immunity, and we propose this happens in allergic individuals infected by common respiratory viruses such as rhinovirus.

Interrupting the cytokine cascade may prevent acute asthma

In summary, the first step in this cascade is viral infection of target tissues in the airway mucosa. Locally, a type 1 IFN signal is generated, leading to upregulation of FcεRI on local airway DCs. If IgE and allergen are present to crosslink receptors, a cascade begins, leading to rapid upregulation of local aeroallergen-specific Th2 memory cells (Fig. 1). Children who are hospitalised for acute asthma have a ready supply of these constituents. This leads to an initial burst of airway cytokine secretion, blocking the local development of Th1 immunity, which is advantageous to the virus. In heavily allergic individuals, these signals reach the bone marrow, so precursors of airway DCs arrive prearmed with dimeric FcεRI, where they increase airway inflammation without requiring local type 1 IFN signals. Once the cycle is triggered, the virus is no longer needed. Once the bone marrow loop is in place, the cycle continues until another system such as T-regulatory cells, turns off the self-perpetuating inflammatory loop.

Thus, allergic and antiviral pathways interact to drive asthma pathogenesis through a lung-bone marrow axis involving DC and monocytes. The effects observed in airway mucosal target tissue are mediated directly by IgE through a circuit governed by FcεRI expression on cells that activate Th2 memory cells. These Th2 memory cells are the primary immunotherapy targets.

Ongoing studies on lower intensity infections suggest that children with severe viral induced asthma exacerbations may be an extreme example of what occurs in all allergic children with common colds. Most of these do not require hospitalisation, but we believe these interactions are happening in the background, albeit to a lesser degree. We are planning a large study to test this hypothesis. An implication of this model is that successful specific immunotherapy may lessen the severity and symptoms of respiratory infections in general,

especially in highly allergic individuals, as well as limiting progression towards chronic asthma.

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Conflict of interest

Patrick Holt has received research grants from Phadia, ALK-Abelló, Medimmune and Novartis, consultancy fees from

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