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Interactions between innate and adaptive immunity in asthma pathogenesis: New perspectives from studies on acute exacerbations

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Asthma is a complex multigenic disease. The most frequently encountered form is atopic asthma, which is at its highest prevalence during childhood/young adulthood, and this represents the main focus of this review. The primary risk factor for atopic asthma is sensitization to perennial aeroallergens resulting from a failure to generate protective immunologic tolerance. This tolerance process is orchestrated by airway mucosal dendritic cells and normally results in programming of regulatory T cells, which inhibit activation of the T_H2 memory cells that, among other activities, drive IgE production and prime the effector populations responsible for IgE-mediated tissue damage. Emerging evidence highlights the complexity of this process, in particular the iterative nature of the underlying interactions between innate and adaptive immune mechanisms in which virtually every signal emanating from one cellular compartment provokes an answering response from the other. To further complicate this picture, the local mesenchyme can also interpose signals to fine tune immune responses to optimally meet local microenvironmental needs. Perturbation of the balance between these interlinked innate and adaptive immune pathways is increasingly believed to be the basis for disease expression, and in the specific case of atopic asthma, the prototypic example of this (discussed below) is acute exacerbations triggered by viral infections.

Key words: Asthma, atopy, innate immunity, viral infection, dendritic cells, regulatory T cells

Abbreviations used: AAM, Alternatively activated macrophage, AEC, Airway epithelial cell, AM, Airway mucosal, DC, Dendritic cell, FoxP3, Forkhead box protein 3, iNKT, Invariant natural killer T, iTreg, Adaptive/inducible regulatory T, LPR, Late-phase reaction, PRR, Pathogen-recognition receptor, TLR, Toll-like receptor, TSLP, Thymic stromal lymphopoietin

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List of Design Committee Members: *Authors:* Patrick G. Holt, DSc, FAA, and Deborah H. Strickland, PhD

Activity Objectives

1. To recognize the complexities of interactions between innate and adaptive immune mechanisms in asthma.

2. To identify the key cells and immunologic milieu in IgE-mediated tissue damage.

3. To describe how viral infection perturbs the balance between the innate and adaptive immune pathways.

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Glossary

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CCL17

CCL17 is also known as thymus and activation-regulated chemokine, which is important in the trafficking of $CCR4^+$ T cells to the skin in patients with atopic dermatitis and can be induced by allergens, such as dust mites.

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CCL22

The *CCL22* gene is located in a cluster of chemokines genes, including *CCL17*. Like CCL17, CCL22 is important for $CCR4^+$ T-cell trafficking, and its levels are increased in patients with atopic dermatitis.

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CCR2

CCR2 is the monocyte chemoattractant 1 receptor that is important for the trafficking of monocytes into target tissues.

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CD80/CD86

Interactions between T cells and B cells or antigen-presenting cells that are required for T-cell activation can occur through CD80/CD86:CD28 or CD40:CD40 ligand. T cells that do not get a second (or costimulatory) signal become anergic. Abatacept (cytotoxic T lymphocyte–associated antigen 4 IgG) blocks costimulation by interfering with CD80/CD86:CD28 interactions and is approved for the treatment of rheumatoid arthritis.

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GM-CSF

GM-CSF can promote the differentiation of dendritic cells, as well as Treg cells

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IL-6

IL-6 is released by dendritic cells, primes for T_H2 effector cells, and inhibits the suppressive functions of $CD4^+CD25^+$ Treg cells.

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IL-25

IL-25 is also known as IL-17E and is produced by mast cells and T_H2 cells. Its levels are increased after airway challenge, and this results in airway eosinophilia.

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IL-33

IL-33 is an IL-1 family member that is produced by epithelial cells, smooth

muscle cells, and fibroblasts that increase IL-5 and IL-13 production.
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Pattern-recognition receptors

Pattern-recognition receptors (PRRs) bind to pathogen-associated molecular patterns, such as flagellin, RNA, and LPS. PRRs, such as Toll and NOD receptors, can be membrane bound or intracellular.
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Plasmacytoid dendritic cells

Plasmacytoid dendritic cells express Toll receptors 7 and 9 and express IFN-α.
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T regulatory cells

Regulatory T (Treg) cells function to dampen the immune response and express FoxP3 and/or TGF-β, CD25, and IL-10. Congenital absence of FoxP3 Treg cells causes immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, an immunodeficiency associated with polyorgan autoimmunity. Therapies that successfully treat autoimmunity or allergy can be associated with increased numbers of Treg cells. Naturally occurring Treg cells come from the thymus, whereas adaptive Treg cells (also known as T_R1 or T_H3 cells) arise in the periphery, are CD80/CD86 independent, are specific for tissue-specific antigens, and require antigen-presenting cells and cytokines for suppressive actions.
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T_H2-inducing adjuvants

The most commonly used T_H2-inducing adjuvant is alum, which is used in vaccines, as well as in animal models of allergy. A number of naturally occurring adjuvants that activate the innate immune system occur in vaccines, such as double- and single-stranded RNA, LPS, CpG, and flagellin.
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T_H17

T_H17 cells are $CD4^+$ T cells defined by production of IL-17A, IL-17F, IL-6, IL-21, IL-22, and TNF-α and are involved in autoimmunity. T_H17 $CD4^+$ T-cell production of IL-17 is increased by IL-23 secreted by dendritic cells. IL-23 activation of the transcription factor signal transducer and activator of transcription 3 maintains the T_H17 phenotype of the $CD4^+$ T cells.
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Thymic stromal lymphopoeitin

Thymic stromal lymphopoeitin promotes antigen presentation, is expressed in activated epithelial cells, and induces the expression of second signal molecules, such as OX40, CD40, and CD80.
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Type I interferon

Type 1 interferons (α, β, and ω) are made principally by myeloid cells, as well as by activated epithelium, and are secreted in large amounts in response to viral infections to inhibit viral replication and increase MHC class I expression. IFN-α and IFN-β have clinical utility in treating hypereosinophilic syndrome and multiple sclerosis.

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The normal response of the adaptive immune system to *de novo* exposure to environmental allergens is the generation of 1 or more forms of immunologic tolerance. This process, first described by us in immunologically naive experimental animals,[1] also operates in human subjects during early life[2] and confers long-term protection against inhalant allergy. Failure of this process unleashes T_H2 memory cells, which in the presence of their respective

sensitizing allergens can recruit IgE-producing B cells and prime IgE receptor–bearing mast cell and basophil populations, as well as myeloid cells, which separately and (in particular) in concert can inflict major damage in airway tissues at sites of aeroallergen exposure.

However, human epidemiologic data exemplified by a large-scale community cohort study published here recently[3] clearly demonstrate that clinically significant airways inflammation is the exception as opposed to the rule among atopic subjects sensitized to perennial aeroallergens. This indicates the operation of additional control mechanisms downstream of those that control T_H2 memory priming. The cellular players in these pathways include dendritic cells (DCs), which are also centrally involved in the success or failure of tolerance induction to the aeroallergen; populations of innate and inducible ***regulatory T (Treg) cells***, which interact with them; and airway epithelial cells (AECs), which modulate many of the functions of transiting immune cells.

The first half of this review will focus on recent information regarding the functions of these cell populations related to the crucial tolerance/immunity decisions that determine sensitization status and on functions related to how the reactivation of primed T_H2 memory cells is controlled under steady-state conditions. However, it is also now firmly established that a crucial additional factor in the initial development of the atopic asthma phenotype[2], [4] and its continued expression in later life[5], [6] is acute lower respiratory tract viral infection, which appears to act in synergy with atopy. The most compelling data on the role of viruses in asthma relates to their role in triggering acute severe exacerbations. Accordingly, we have included in the second half of this review a separate section on interactions between innate and adaptive immune pathways during severe virus-associated asthma exacerbations in atopic subjects, in particular how viruses can exploit innate immune mechanisms to recruit and amplify IgE-dependent immunity in the airway mucosa as a means to evade local T_H1 ("sterilizing") immunity.

Induction and expression of immunity to airborne antigens: Cellular participants in the ongoing maintenance of immunologic homeostasis in the airway muco

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As the primary interface between the environment and the immune system, the airway mucosa exists in a state of perpetual danger from pathogens and potentially inflammatory components of biological dusts. Ongoing survival in the absence of chronic inflammation requires both efficient local immune surveillance for incoming antigen and tight control of immune responses that are activated locally. The roll call of cellular players in this complex game continues to expand, and the summary below is restricted to 3 of the major participants that are most relevant in the context of the overall review theme.

DC populations

Immune surveillance of airway mucosal (AM) surfaces is controlled principally by local populations of DCs, which ramify throughout the surface epithelium and underlying lamina propria.[7], [8] They are able to sample the airway luminal surface by means of endocytosis through dendrites, which they extend through epithelial tight junctions.[9], [10] The steady-state dynamics of these mucosal cells are unique among DCs, with the AMDC population being renewed every 24 to 36 hours as antigen-laden cells emigrate to the draining lymph nodes and are replaced by incoming (immature) bone marrow–derived precursors.[11] This rapic turnover further accelerates during local challenge with strong proinflammatory stimuli,[12] in particular microbial agents, including bacteria and viruses. An observation of particular relevance to the second part of this review is our earlier finding on the sequelae of viral infection in relation to the AMDC network. In particular, airway challenge with virtually all classes of antigens/irritants promotes rapid recruitment of immature DCs into the airway epithelium,[8], [12] and the response resolves equally rapidly after clearance of the stimulating agent. The single notable exception to this is live virus infection in

the airways, as demonstrated in a parainfluenza model in rats (Fig 1)[13] and recently in a murine influenza model (unpublished data) in which the AMDC population remains increased for many weeks after viral clearance. As discussed in the second half of this review, this poses significant potential dangers to the host in relation to loss of local immunologic control.

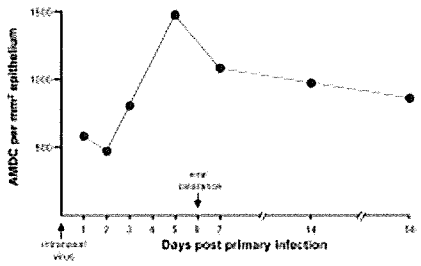

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Fig 1. Persistent upregulation of the AMDC network in the wake of parainfluenza infection. Rats were infected intranasally with live parainfluenza virus, and AMDC numbers were determined by means of immunostaining of frozen sections of tracheal epithelium at the time points shown. Viral clearance occurred by day 5, but the AMDC network remained significantly increased above baseline until day 14,[13] and this increase persisted until at least day 56 (unpublished data).

AMDC surveillance for microbial pathogens uses ***pattern-recognition receptors*** (PRRs), and a large repertoire of these are expressed by these cells.[14] Signaling through PRRs induces the expression of innate response genes, such as *IL1* and *TNFA*, and activation of DC function/migration, culminating in linkage of the innate and adaptive arms of the respiratory immune response. An additional function of AMDCs is discrimination between pathogenic and nonpathogenic antigens, the later being continuously sampled from the environment during respiration. At sites of aeroallergen exposure in healthy airways, local AMDCs play a central role in the induction of responses to these agents.[1] In the steady state the normal outcome of aeroallergen exposure is initiation of tolerance, and experimental animals repeatedly exposed through this route cannot be induced to mount an immunologic response on later exposure to antigen, even in the presence of ***T_H2-inducing adjuvants***.[1] This form of "inhalation tolerance" is mediated in some circumstances by T-cell deletion but more commonly by Treg cells.[1], [9], [15]

In the steady state AMDCs are functionally immature and specialized for antigen capture and transport to airway draining lymph nodes. It should be emphasized that the overall antigen-presenting cell function of this network is normally strictly compartmentalized, and resident AMDCs lack the capacity to effectively present antigen to T cells, principally because of poor expression of costimulators, such as CD86. Acquisition of this capacity normally does not occur until they "mature" in a microenvironment rich in inductive signals, such as ***GM-CSF***/CD40 ligand, which in the steady state equates to the airway draining lymph nodes.[14] This functional compartmentalization has the effect of screening AM tissues from the consequences of continuous T-cell activation in response to ubiquitous nonpathogenic environmental antigens.

The signals given by these migratory AMDCs to T cells are therefore crucial in determining the nature of the ensuing immune response. Direct evidence for the induction of Treg cells by DCs expressing an immature phenotype comparable with that of resident AMDCs has been provided in studies in which injection of antigens linked to DEC-205 lectin, which is preferentially expressed on DCs, resulted in antigen loading of lymph node DCs and ensuing tolerance.[20] It has also been shown that ***plasmacytoid dendritic cell*** populations might function through various mechanisms to induce tolerance in the respiratory tract.[21], [22], [23] Although tolerance represents the usual outcome

of repeated aeroallergen exposure, the initial response of the immune system is to prime low-level T_H2-polarized immunity.[16] These responses are normally transient in both animals and human subjects, but in genetically predisposed individuals this response can be exaggerated, dysregulated, or both and result in priming of allergen-specific T_H2 memory.

AMDCs also play an important role in the effector phase of atopic asthma. In sensitized experimental animals AMDCs are rapidly activated *in situ* after aeroallergen exposure through initial interactions with transiting T_H memory cells, resulting in CD86 upregulation and expression of potent antigen-presenting cell activity,[17], [18], [19] providing a plausible mechanism for the triggering of aeroallergen-induced triggering of memory T_H2 cells during the asthma late-phase reaction (LPR; Fig 2).[13] Other T-cell types, including T_H1 effectors[24] and in particular cells of the ***T_H17*** lineage,[25] might also participate ir this response, but direct data regarding their contributions remain sparse.

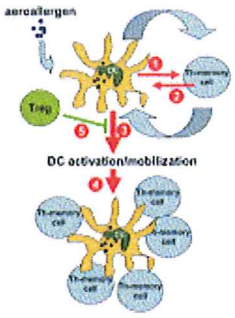

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Fig 2. Bidirectional interactions between resident AMDCs and transiting aeroallergen-specific T_H memory cells after aeroallergy exposure.
Aeroallergen exposure of sensitized animals triggers a multistage response involving short-term clustering of $CD86^{low}$ AMDCs with T_H memory cells (step 1) and CD40 ligand signaling back from T_H memory cells to AMDCs (step 2). This stimulates DC activation (CD86 upregulation and chemokine secretion) and mobilization (step 3), and migrating AMDCs form stable clusters with T_H memory cells as they transit the epithelium and submucosa and in the process present activation signals that trigger T_H2 cytokine secretion (step 4).[16], [17], [18] Attenuation of this process occurs through the progressive accumulation of Treg cells in the airway mucosa (step 5), which inhibit T_H cell–mediated upregulation of CD86 on AMDCs.[19]

Regulation of the immunologic milieu in the airway mucosa through local signals derived from AECs

The high efficiency and tight control that are the hallmarks of the respiratory immune system are highlighted by the response of healthy subjects to viral infections, which are usually self-limiting and in most cases involve minimal local and systemic inflammation. The initial point of entry of incoming respiratory viruses is through the epithelial layer of the airway mucosa, and earlier notions that AECs function only as a passive barrier in this and other local immune responses have been revised in light of the demonstration that they can directly influence local DC functions. This includes both the steady state[26] and during inflammatory episodes (see below). AECs express multiple PRRs that facilitate their recognition of different types of luminal antigens. Early detection of incoming virus in the airways has been demonstrated to involve signaling through PRRs expressed on AECs, an important consequence of which is upregulation of ***type I interferon*** production, which appears to be attenuated in asthmatic subjects.[27] We have recently demonstrated the

potential of type 1 interferon produced by AECs to modulate the maturation of incoming monocytic precursors of AMDCs, resulting in optimization of their T_H1-associated antimicrobial functions and at the same time attenuating their T_H2-trophic functions.[26]

It is also noteworthy in this context that one clinically important allergen, house dust mite, has the potential through various mechanisms, including PRR signaling, to modulate AECs and hence AMDCs and as a consequence to promote local induction of T_H2 immunity.[28], [29], [30], [31] For example, it has been shown that DCs from allergic donors exposed to Der p 1 induced T_H2 differentiation, whereas DCs from nonallergic subjects induced T_H1 responses.[7], [9]

A variety of studies have now shown that AECs are able to produce a broad range of cytokines, including the key DC survival factor GM-CSF, and also a range of others that are believed to play important roles in the regulation of local innate and adaptive immunity, particularly ***IL-25***, ***IL-33***, and ***thymic stromal lymphopoietin*** (TSLP). IL-25 is induced by a range of hematopoetic and stromal cells that are involved in innate and adaptive immunity and can influence the activities of multiple cell types.[32], [33], [34] In the mouse IL-25 acts on recruited and resident airway cells to promote IL-4–dependent differentiatior of T_H2 cells,[35] eosinophilia,[36] and airway hyperresponsiveness development.[37], [38] Allergen-activated AECs have recently been shown to have increased levels of IL-25, which augments T_H2 cytokine production.[39] Corresponding data in human subjects is, however, limited, but there is support for a role for this mediator in human disease.[32]

There is also growing interest in the role of AEC-derived IL-33 in the augmentation of T_H2 responses by effects on T_H2 cells and innate effectors. IL-33 has also been shown to amplify alternatively activated macrophage (AAM) polarization and chemokine production and thus contribute to innate and antigen-induced airways inflammation.[40] IL-33 levels are reportedly increased in human asthmatic subjects[31] and thus potentially play a role in activation of alveolar macrophages toward an AAM phenotype, which bears relevance to virally induced asthma exacerbations, as described below.

TSLP has been associated with allergic inflammation both in the airways and ir the skin, and increased expression of TSLP has been observed in both patients with allergic dermatitis and those with allergic asthma.[41] The major target of TSLP in this context appears to be DCs,[42] and its effects include upregulation of ***CD80***, ***CD86***, HLA-DR, and particularly OX40 ligand, which strongly promotes inflammatory T_H2 responses.[43] IL-25 produced by AECs[35] has been suggested to enhance the activity of TSLP.[44] TSLP-activated DCs also show enhanced production of the chemoattractants ***CCL17*** and CCL22.[45] In experimental animals TSLP $^{-/-}$ mice are resistant to the development of antigen-specific T_H2 inflammation,[46] and conversely, overexpression of TSLP ir the skin and airways leads to expression of allergic dermatitis and allergic asthma phenotypes.[47] It is noteworthy that ligands that activate Toll-like receptor (TLR) 2, TLR3, TLR8, and TLR9 can induce TSLP production.[48]

Negative control of adaptive immunity in the airways: Treg cells to center stage?

Aside from their role discussed above in relation to development of tolerance tc inhaled allergen, Treg cells appear to play an important role in events that follow the failure of tolerance mechanisms. In particular, it is clear that sensitization to aeroallergens *per se* is insufficient to guarantee subsequent expression of airway symptoms,[3] which are restricted to only a small subset of sensitized atopic subjects in whom (presumably) control of airways inflammation is defective. It is increasingly believed that a key risk factor in this regard is an imbalance between Treg cells and T_H2 effector populations, with symptomatic subjects displaying numeric deficiencies, functional deficiencies, or

both in the Treg cell compartment.[49], [50], [51] It has also been suggested that Treg cells play an essential role in the control of host-antimicrobial defense to limit tissue damage resulting from excessively intense immune responses during pathogen clearance. Conversely, the capacity to trigger effective responses to pathogens might also require initial bypassing of Treg cell–mediated immune suppression, a function that has been ascribed to the proinflammatory cytokine ***IL-6***.[52]

Several Treg cell populations have been described that might act to influence different aspects of immune function through a variety of mechanisms, such as cell–cell contact–dependent pathways and inhibitory cytokine secretion.[53], [54] Forkhead box protein 3 (FoxP3)–positive Treg cells are broadly divided into naturally occurring/innate and adaptive/inducible (iTreg) populations. Moreover, it has recently become evident that FoxP3$^+$ iTreg cells can develop extrathymically from naive T cells[55] and also from T effectors,[53], [56], [57], [58] exemplifying the plasticity of the T-cell response. In subjects with atopic asthma, the relative importance of naturally occurring/innate Treg cells versus iTreg cells is unclear. A variety of animal model data support a role for iTreg cells in the control of allergic asthma,[55], [59] but to date, the few relevant studies in human allergic asthma have yielded conflicting results. The numbers of CD4$^+$CD25$^+$ Treg cells in the peripheral blood of asthmatic subjects versus nonatopic control subjects have been reported variously to be equivalent or higher[60], [61] or reduced[62] in subjects with allergic asthma. Many of the latter studies only evaluated CD4$^+$CD25$^+$ cells and are thus difficult to interpret; however, studies that in addition have examined FoxP3 expression suggest that this decrease in asthmatic subjects might be real.[62], [63], [64] Functional studies on Treg cells in atopic patients have also yielded conflicting data, with some studies reporting decreased suppressive capacity of CD4$^+$CD25$^+$ T cells from patients with active airway disease[64] and others reporting no differences between asthmatic and control subjects.[65] These human studies have focused almost exclusively on PBMCs, which is not ideal given the mounting evidence that microenvironmental factors exert dominant influences over local cellular functions. A notable exception is a recent study demonstrating reduced numbers of Treg cells in the bronchoalveolar lavage fluid of pediatric asthmatic subecjts.[63]

A key unifying theme that has emerged from the experimental literature is the role of Treg cells in re-establishing homeostasis in the respiratory tract after induction of antigen-induced airways inflammation in sensitized animals. Relevant studies include the demonstration that depletion of CD4$^+$CD25$^+$ cells enhances allergic airways inflammation[66], [67] while their systemic administration,[19], [66], [68], [69] intratracheal administration,[70] or both is protective. An important target for Treg cells in this context is T_H-mediated upregulation of CD86 expression on initially quiescent resident AMDCs (Fig 2). Importantly, Treg cell control of allergic inflammation CD4$^+$CD25$^+$ cells has also been shown to reverse established airway hyperresponsiveness and has been linked to prevention of airway wall remodeling and decreased mucus hypersecretion.[6

Virus-induced acute exacerbations: A paradigm for understanding innate/adaptive immune interactions in asthma pathogenesis?

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Initial development of the asthma phenotype

The role of viral infections in the pathogenesis of atopic asthma has been an area of ongoing controversy over the last 20 or more years. They have variously been invoked as direct causal agents through effects on lung function indirect stimulants through promotion of atopic sensitization to bystander allergens, or conversely as protective agents through promotion of functional maturation of immune defense mechanisms. However, increasing clarity has been brought to this debate through the unfolding results of long-term prospective birth cohort studies that have tracked individual subjects over many years. In particular, although it is clear that viral infection during early life can function as an independent risk factor for the development of persistent asthma

by the end of the preschool years, it is also evident that maximum risk is associated with concomitant early sensitization to aeroallergens.[71], [72] To explain these data, we have proposed a "2-hit" model for asthma development in childhood[2], [4] in which inflammation from atopy-dependent and virus-triggered pathways interacts to disturb lung growth and differentiation during infancy, precipitating changes in lung function that track into later life and creating susceptibility to the asthmatogenic effects of environmental irritants, especially aeroallergens. However, the nature of these interactions is incompletely understood.

Virus infection and asthma symptomatology: Experimental models

The importance of ongoing atopy in persistence of the asthmatic phenotype int the teen years and beyond is now well established.[3], [73] It is also evident that viral infections continue to play a central role, and this is clearest with respect to expression of symptoms characteristic of the most severe grades of asthma, which are most common in virally infected atopic subjects.[6], [74], [75], [76], [77], [78] This again suggests underlying interactions between virus-associated and atopic inflammatory pathways.

Some hints as to the mechanistic basis for these interactions are available in the experimental literature. First, a series of studies on respiratory viral challenge of human atopic subjects (reviewed in Friedlander and Busse[5]) has provided indirect evidence that viruses might act to enhance asthma LPRs through augmentation of underlying allergen-specific responses. Recent studies with selective cytokine receptor antagonists strongly suggest a central role for T_H2-associated IL-4/IL-13 pathways in the LPRs in human atopic asthmatic subjects,[79] which is similar to that observed in animal models. In addition, a recent study on experimental parainfluenza infection in the mouse[80] described a pathway in which enhancement of key AMDC functions by type 1 interferon production triggered in the lung by the infection could lead to amplification of local T_H2-associated responses by selective upregulation of the α chain of the high-affinity IgE receptor (IgE FcR1α). The authors pointed to earlier reports of the appearance of IgE specific for respiratory syncytial virus (RSV)[81] and parainfluenza[82] in postinfected children and its association with recurrence of wheeze and suggested arming of IgE receptors on AMDCs with virus-specific IgE as a potential pathway for recruitment of T_H2 immunity into the host antiviral response, thus contributing to the ensuing pathology.

Acute asthma exacerbations in children resulting in hospitalization: Insight from the extreme end of the severity spectrum

A recent study from our group provides a differing perspective on the antiviral response in the airways of human atopic subjects but one that nevertheless contains many of the elements of the murine model above. We focused on children at the most severe end of the asthma exacerbation spectrum, who were selected on the basis of their presentation at a hospital emergency department with symptoms of sufficient severity to require immediate hospitalization.[83] Viral infection was confirmed by means of culture, PCR, or both in approximately 85% of cases, and 96% were atopic, with the majority being in the upper quartile for atopy severity on the basis of age-related IgE values. PBMCs (and subsequently subsets thereof) were profiled by means of microarray and flow cytometry as paired samples from individual children, comparing cells collected at admission (ie, during exacerbation) versus those collected after 6 to 12 weeks' convalescence when all parameters had returned to baseline.

The key finding from this study was the presence in circulating myeloid cells (monocytes and DCs) of prominent exacerbation-associated gene signatures from members of the type 1 interferon and IL-4/IL-13 signaling pathways.[83] Moreover, they exhibited high-level expression of ***CCR2***, which has been identified as one of the major chemokine receptors involved in homing of inflammatory cells to inflamed airways,[84] and were also IL-13 receptor positive.

These cells would have been very recently released from the bone marrow, and it is highly likely that their gene expression programs, as detected, would have been preactivated before release. The latter includes FcεR1α, which is strongly upregulated *in vitro* in myeloid cells from atopic subjects by IL-4/IL-13.[83]

A consistent finding in these children was the lack of effector gene expression signatures in the circulating T-cell compartment during exacerbation, either T_H2 genes or those expected in the face of an antiviral response, such as those encoding IFN-γ and LTα. The majority of such genes were in fact downregulated relative to baseline values despite the presence of markers of activation, such as CD25 and CD69, which, as noted,[83] can indicate the presence of "exhausted" effector memory cells that have participated in the host response at an earlier stage of the infection cycle.

Our findings are thus suggestive of infection-triggered type 1 interferon and IL-4/IL-13 being released from the airway mucosa into the circulation during acute exacerbation and being sensed by receptor-bearing myeloid precursors in bone marrow. Is this plausible? In fact, the existence of a lung/bone marrow axis in which peripherally generated mediator signals recruit replacements for resident cell populations is a well-established phenomenon and is central to the process through which myeloid populations are renewed in airway tissues during inflammation.[11], [85] Additional precedents include signaling to eosinophil precursors in the bone marrow from inflamed airway mucosa.[86] It is additionally recognized that this signaling to bone marrow goes beyond simple chemotactic attraction and can involve selective functional programming of immature myeloid cells through upregulation of specific effector pathways, regulatory pathways, or both required to meet the specific challenge at the inflammatory site,[87] with the classic example being the IL-4/IL-13–dependent "alternative activation" signature observed here, which was first identified in models of helminth parasitism, in which host defenses are heavily T_H2 polarized.

Potential consequences at the infection site: Viral evasion of host defenses?

Two additional observations from these findings merit highlighting in this context. First, the intensity of respective gene expression signatures over a panel of 52 genes tested correlated strongly with exacerbation severity using a standardized clinical scale, and second, the average increase in the overall FcεR1α load within the circulating myeloid population during acute exacerbation was in the range of 10- to 12-fold over baseline levels, reflecting a combination of increased myeloid cell numbers, as well as increased expression per cell.[83] Taken together with the finding that the relevant cell populations express high levels of airway homing–associated CCR2, these findings suggest upregulated immigration at the peak of exacerbation of IgE FcR–bearing myeloid cells, including replacements for the AMDC, which, as described above, display markedly enhanced turnover during this period. This outcome mirrors that described in the murine model of parainfluenza infection[80]; however, in the latter case DC upregulation was envisaged as occurring exclusively within the lung itself in response to type 1 interferon, whereas our human findings suggest that an additional and possibly dominant (bone marrow) pathway might exist in human subjects to the same end point. Moreover, the murine model focused on the requirement for development of underlying T_H2 immunity to the virus, whereas in atopic children abundant supplies of specific IgE and associated T_H2 memory would be available before infection.

Viewed from the perspective of the virus, the creation of a T_H2-rich milieu at the infection site would potentially promote infection persistence by antagonizing local antiviral adaptive immune defenses, which are T_H1 polarized. Viral evasion of host defenses through strategies involving deviation of T_H1 immunity are well recognized in infections as diverse as dengue,[88] herpes,[89] and HIV[90] and are possibly the basis for the T_H2 immunity referred to above in relation to RSV and parainfluenza.[81], [82]

Consequences for the atopic host

Based on the findings discussed above in peripheral blood myeloid populations during exacerbations and recent studies in experimental models,[81], [82] we have proposed that the following stepwise process underlies the induction and persistence of asthma symptoms in virally infected atopic children (Fig 3).[83]

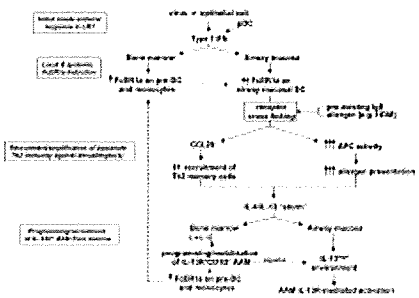

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Fig 3. Recruitment of bystander T_H2 immunity during virus-induced asthma exacerbations in atopic subjects. The schema proposed above is based on findings derived from expression profiling of paired PBMC samples from atopic children during acute severe asthma exacerbations associated with respiratory viral infection versus after exacerbation.[83] See the text for details. *APC*, Antigen-presenting cell.

Spread of viral infection to the lower respiratory tract

At the time of admission, exacerbating children manifest lower respiratory tract symptoms, inferring that infection has already escaped eradication in the upper airways. This might reflect intrinsic[27] or acquired[92], [93] defects in local front-line innate defenses, as postulated by others.

Initial innate response in the lower respiratory tract

Local infection initiates a cycle of type 1 interferon production by, among other things, infected epithelial cells and incoming plasmacytoid DCs. AMDC turnove accelerates and type 1 interferon upregulates their IgE FcR expression locally and as observed here on their bone marrow–derived replacements. It is noteworthy that upregulation of FcεR1α expression on DCs has previously been reported in airway biopsy samples from adult atopic asthmatic subjects.[92]

Initial recruitment of allergen-specific T_H2 immunity

Loading of IgE FcR on AMDCs with aeroallergen-specific IgE would occur rapidly in these atopic subjects, which, as demonstrated in studies on human Langerhans cells,[94] would arm them for optimal allergen surveillance. Subsequent binding of allergen to loaded IgE receptors on these cells would potentially activate their production of chemokines, which attract T_H2 memory cells,[80] and also markedly increase their allergen uptake/presentation functions optimizing their capacity to trigger T_H2 cell activation.[94] It should be emphasized that as discussed above, the activation state of resident AMDCs is normally set at a low level to prevent ongoing local T-cell activation.

IL-4/IL-13 signaling to bone marrow precursors

The presence of the strong alternative activation signature in recently released myeloid cells suggests cytokine signaling either directly to bone marrow or through migration of T_H2 memory cells activated in the airways. The high expression of CCR2 and FcεR1α on these immature cells indicates their availability for migration into inflamed airway tissues, thus providing an expanded source of replacements for rapidly turning over AMDCs at the infection site, which are preprogrammed for IgE FcR expression, thus optimizing local conditions for continuation of IgE-mediated T_H2 activation.

The specter of "alternative activation" of myeloid cells in the airways

In an additional publication on the murine parainfluenza model, the Holtzmann group recently documented a complex pathway triggered in the lungs of mice in the wake of viral clearance, in which invariant natural killer T (iNKT) cells can program and fully activate IL-13 receptor–positive AAMs.[91] In this system interactions between $CD1D^+$ AAMs in the postinfected lung and iNKT cells trigger high-level IL-13 secretion by the activated iNKT cells, thus activating the IL-13 receptor on adjacent AAMs, which in turn triggers their *IL13* gene expression. Once this occurs, the potential consequence is autocrine IL-13 production by the AAMs. Given the long lifespan of macrophages in the lung environment,[95] such an outcome might result in persistence of IL-13–mediated symptoms for prolonged periods after viral clearance. As shown in Fig 3, our data demonstrate that a similar outcome is theoretically possible during exacerbations and before viral elimination, without participation from iNKT cells; that is, preprogramming of the alternative activation phenotype can occur in immature myeloid cells in bone marrow in advance of their recruitment into the lung and airways, and on arrival, they might encounter IL-13 at sufficiently high levels to trigger their IL-13 receptor. However, it should be noted that, as shown in Fig 3, CD1D expression is a prominent feature of the expression signature on AAMs during exacerbation,[83] and hence the potential exists for the intervention of incoming iNKT cells as an additional late-stage amplification loop in this cascade.

In relation to the potential persistence of functionally activated macrophages in the lung and airways after viral infection, it is pertinent to draw attention again to the data in Fig 1 on the long-term sequelae of airway viral infection on the local (myeloid) AMDC population, which also remains expanded for a prolonged period after viral clearance.

Bidirectional effects of type 1 interferons in acute exacerbations?

A final example of innate/adaptive interactions in this cascade emerged from our recent *in vitro* studies on PBMCs from atopic subjects.[83] First, we demonstrated that type 1 interferon exposure upregulates FcεR1γ, which is known to stabilize the FcεR1α chain on the cell surface[96] and hence promote expression of functional IgE receptor dimer. However, we additionally demonstrated that type 1 interferon can inhibit IL-4/IL-13–mediated upregulation of genes in the alternative activation signature and in particular the *FCER1A* gene.[83] It is conceivable therefore that type 1 interferons might play a dual role in the proposed exacerbation-associated cascade in Fig 3: an initiator role by promotion of the first wave of IgE FcR upregulation on resident AMDCs through the FcεR1γ pathway and a later role in shutting down the cascade through inhibition of IL-4/IL-13 signaling. In this context it is noteworthy that AECs from symptomatic atopic asthmatic subjects appear to be deficient in capacity to produce type 1 interferons,[27] and it is tempting to speculate that their reduced capacity to achieve IL-4/IL-13 inhibitory levels *in vivo* might contribute to their susceptibility to virus-induced exacerbation.

The bone marrow axis and the "reflex" nature of allergic diseases

The model described in Fig 3 is also relevant to the longstanding debate on whether expression of allergic diseases at one site can trigger susceptibility at other sites, when additional data from epidermal studies are considered.

Notably, it has been demonstrated that in patients with active atopic dermatitis, FcεR1α expression is upregulated on DCs in lesions and also at distal nonlesional skin sites.[97] Similar observations followed for both atopic asthma and allergic rhinitis; that is, when these diseases were active as opposed to quiescent, FcεR1α expression was again increased on epidermal DCs, indicating the presence of a systemic element in the underlying atopic response,[97] and it is likely that this might be equivalent to the IL-4/IL-13 signal from the lesional site to the bone marrow reported here. It is interesting in this context to consider whether the link between allergic rhinitis and risk for asthma, which has been described in both adults[98] and schoolchildren,[3] might be related to this phenomenon (ie, whether active allergic rhinitis can increase the intensity of T_H2-associated responses to inhalants in distal tissues, such as the conducting airway mucosa) by contributing to preprogramming of IgE FcR expression in the bone marrow–derived pre-DC populations, which are constantly replenishing the AMDC network. This also begs the related question of whether in some circumstances viral infections in atopic subjects, which remain localized in the upper respiratory tract, might trigger this bone marrow–dependent pathway effectively enough to provoke flares of T_H2-mediated symptomatology in the lower airways, which are of sufficient intensity to be classified as asthma exacerbations.

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Terms in boldface and italics are defined in the glossary on page 964.

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