

Effects of Allergic Sensitization on Antiviral Immunity: Allergen, Virus, and Host Cell Mechanisms

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Abstract

Purpose of Review Multiple clinical and epidemiological studies demonstrate links between allergic sensitization and virus-induced atopic disease exacerbations. This review summarizes the recent findings regarding allergen, viral, and host cellular mechanisms relevant to these observations.

Recent Findings Recent studies have focused on the molecular pathways and genetic influences involved in allergen-mediated inhibition of innate antiviral immune responses. Multiple tissue and cell types from atopic individuals across the atopy spectrum exhibit deficient interferon responses to a variety of virus infections. Impairment in barrier function, viral RNA and DNA recognition by intracellular sensing molecules, and dysregulation of signaling components are broadly affected by allergic sensitization. Finally, genetic predisposition by numerous nucleotide polymorphisms also impacts immune pathways and potentially contributes to virus-associated atopic disease pathogenesis.

Summary Allergen-virus interactions in the setting of atopy involve complex tissue and cellular mechanisms. Future studies defining the pathways underlying these interactions could uncover potential therapeutic targets. Available data suggest that therapies tailored to restore specific components of

antiviral responses will likely lead to improved clinical outcomes in allergic disease.

Keywords Atopy · Viral infection · Allergic sensitization · Allergic asthma · Atopic dermatitis · Antiviral response

Introduction

The epidemiologic link between atopic disease and viral infections has long been appreciated. Coinciding peaks in asthma exacerbations and fall upper respiratory virus epidemics highlight one well-recognized aspect of this association. In the context of allergic asthma, the risk for respiratory virus-induced exacerbations is significantly increased by allergen exposure. This virus-allergen synergism is also evident in other atopic diseases. In atopic dermatitis, for example, a subset of patients is exquisitely susceptible to cutaneous herpes virus infection and reactivation. Questions regarding whether atopic individuals are more susceptible to viral infections and how viruses trigger disease exacerbations remain incompletely answered. In this review, we focus on how allergic sensitization and exposure impacts antiviral responses and how this interplay may lead to exacerbation of atopic diseases. The contributions of host genetics and potential therapeutic targets are also discussed.

Chicken or the Egg? Viral Infection and Atopic Diseases

Numerous studies have examined the role of viruses in the development and exacerbation of allergic asthma, which has been extensively reviewed [1–5] and is mentioned only briefly here. Large birth cohort studies uncovered the key genetic and environmental factors that predispose children to early wheezing and progression to asthma. In the Childhood Origins of

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Asthma Study (COAST) cohort, which focused on “high risk” children with a parental history of atopy, early life infection with rhinoviruses (RV) and respiratory syncytial virus (RSV) increased the risk of asthma development by tenfold and nearly threefold [6, 7], respectively. Additive effects of early allergen sensitization and RV infection ultimately increased the risk of asthma 20-fold at 13 years of age [8•]. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC), a similar high-risk birth cohort, also reported that early respiratory viral infection increases the risk for asthma development but did not detect virus-specific risks [9•]. Allergen sensitization also affects the severity of asthma exacerbations. A recent prospective study reported that baseline levels of serum IgE specific for mouse and dust mite antigens positively correlated with the severity of RV-triggered exacerbations. Concentrations of these allergen-specific IgE levels also increased during exacerbations, correlating with symptom severity [10•]. This study suggests that interactions between allergens and rhinoviruses may contribute to variations in the severity of atopic disease.

In addition to allergic asthma, viral infections also affect other atopic disease processes such as allergic rhinitis and atopic dermatitis. Children with early upper respiratory virus infections are at increased risk of allergic rhinitis later in life [11], and viruses are recovered more frequently in nasal samples from patients with allergic rhinitis compared to non-allergic controls [12]. Furthermore, a prospective study of children under 18 months of age found that allergic sensitization correlates with prolonged viral rhinitis symptoms [13]. A subset of atopic dermatitis (AD) patients is particularly susceptible to cutaneous herpes [14], poxvirus [15], and molluscum [16] infections, further highlighting the interplay between viruses and atopy. The mechanisms underlying these clinical correlations remain the subject of intense investigation.

The Antiviral Response Unraveled

Viruses encounter multiple cell types during infection. Respiratory viruses directly infect the respiratory epithelium, while cutaneous viral infections encounter epidermal barrier functions. Regardless of entry site, infection results in the recruitment of innate immune cells including dendritic cells (DCs), monocytes, and macrophages [17, 18]. These antigen-presenting cells (APCs) phagocytose viral particles and cellular debris. APC-specific antigen presentation and cytokine secretion connects the innate and adaptive immune responses by driving specific T cell differentiation and B cell immunoglobulin production and class switching. Interferons (IFN) are one class of cytokines secreted by APCs in response to virus infection and include type I (α , β), type II (γ), and type III (λ). IFNs represent a critical component of the antiviral response and are required for controlling viral infections [19].

Specifically, virus activation of intracellular RNA and DNA sensing molecules results in IFN β secretion, further enhancing the response via type I IFN receptor signaling and up regulation of IFN α and other interferon stimulated genes (ISGs) [19]. ISGs create an intracellular antiviral state to combat viral replication and make neighboring cells less permissive to new infection [20]. Downstream functions of type I IFN regulate adaptive responses by inhibiting Th2 cell differentiation and function [21, 22], which are critical to allergic responses [23]. Thus, virus infection could skew immune responses away from a Th2 “allergic” phenotype through induction of type I IFN. In the atopic environment, however, infections with viruses such as RV and herpes simplex virus (HSV) actually contribute to Th2 responses and atopic disease exacerbation.

At any point in the above process, allergic sensitization could impact antiviral responses (Fig. 1). It has been shown that multiple cell types from atopic individuals, including skin keratinocytes, airway epithelial cells, and innate immune cells, exhibit dysfunctional antiviral functions. Consequently, allergic inflammation disrupts specific host cellular immune mechanisms; examples of these and associations with atopic disease pathogenesis are discussed in detail below.

Allergic State and the Antiviral Response: Tissue and Cellular Mechanisms

Atopic Dermatitis and Skin Immune Responses

Atopic dermatitis (AD) is characterized by chronic allergic inflammation of the dermis and epidermis. Host factors, allergen, and exposure to viral and bacterial pathogens create a complex multifactorial environment contributing to life-long morbidity associated with recurrent exacerbations. Specific gene mutations are associated with AD and the development of severe cutaneous virus infections (Table 1 and Fig. 1). Mutations in filaggrin, a protein that regulates epidermal barrier function, are associated with specific AD-virus disease entities such as eczema herpeticum (associated with herpes simplex virus, HSV) [14] and eczema vaccinatum (associated with vaccinia virus, VV) [31•], where virus infection or vaccination, respectively, can result in disseminated viral disease. IL-25, a cytokine up regulated by allergen exposure and increased in the skin from AD patients, enhances replication of HSV and VV by inhibiting filaggrin expression, providing further evidence of allergen-mediated effects on viral infection [50•]. Similarly, other cytokines including IL-17 [31•], TSLP-1, and IL-33 [24•] also facilitate VV pathogenesis in a murine eczema vaccinatum model by promoting increased Th2 inflammation; deletion of these molecules protects mice from VV-induced cutaneous disease and dissemination. Pro-inflammatory cytokines secreted upon allergen exposure or

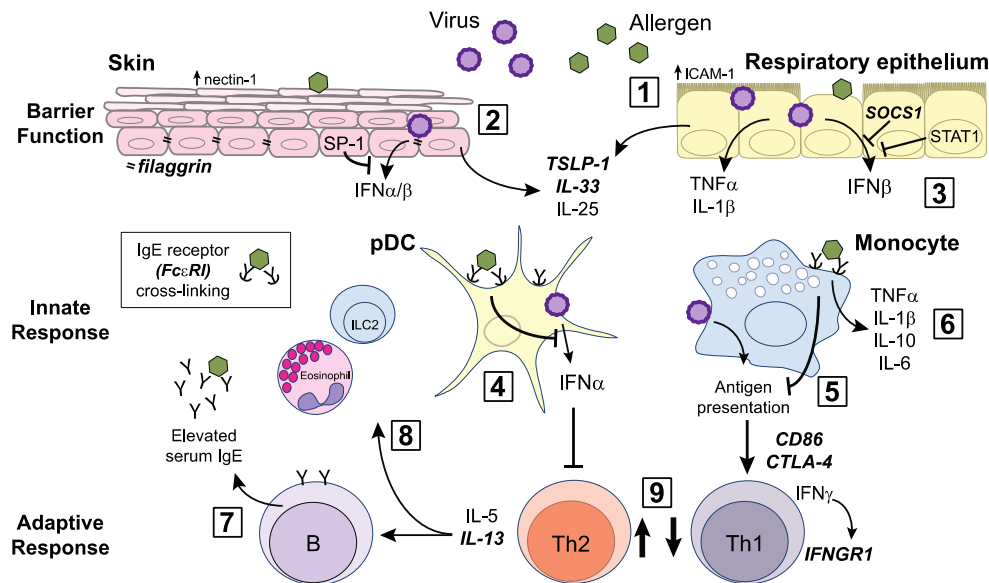


Fig. 1 Effects of allergic sensitization on antiviral responses—a complex interplay. Viruses and allergens first encounter barrier epidermis or respiratory epithelium. **1** Genetic predisposition (polymorphisms shown in *bold italics*) as well as allergen-induced impaired barrier function likely increases susceptibility to infection. **2** Virus infection of either the skin keratinocytes or respiratory epithelial cells results in secretion of pro-inflammatory cytokines and chemokines which recruit antigen presenting cells (DCs and monocytes) and have **3** impaired antiviral type I IFN responses. Allergen stimulation of antigen presenting cells

impairs anti-viral responses by **4** blocking type I IFN release from plasmacytoid DCs and **5** inhibiting virus-induced antigen presentation and Th1 differentiation by monocytes. **6** IgE receptor engagement also leads to additional pro-inflammatory cytokine release and impairs monocyte phagocytosis. **7** Th2 cytokines promote B cell class switching to produce more IgE, enhancing allergic effects. **8** This environment recruits additional allergic effector cells (ILC2, eosinophils, and basophils) further increasing Th2 mediated responses and inflammation. **9** Culminating in an increase in the Th2/Th1 balance

virus infection can promote additional dysregulation of epidermal tight junctions and keratinocyte turnover, further disrupting this important barrier and facilitating allergen and pathogen penetration [51].

Eczema herpeticum has also been associated with unmasking of the viral entry receptor nectin-1 and depletion of type I IFN-producing plasmacytoid DCs (pDCs) from the AD skin [18]. In addition, APC expression and activity of indoleamine 2/3-dioxygenase (IDO1), a tryptophan-catabolizing enzyme linked to atopic disorders, has been implicated in eczema herpeticum [52]. Down regulation of type I, II, and III IFN responses has also been reported [38, 53]. Similar studies in the human skin explants from AD patients demonstrate down regulation of innate immunity genes in VV infection [54]; these and other findings regarding viral infections in the AD skin have been comprehensively reviewed elsewhere [51].

Additional observations highlight a more direct connection between allergic sensitization and antiviral responses in AD pathogenesis. SP-1 (specificity protein 1), a transcription factor involved in skin antiviral responses, is down regulated in keratinocytes from AD patients and expressed at even lower levels in those with eczema herpeticum. SP-1 levels inversely correlated with VV replication in the AD skin, and SP-1 knockdown in normal keratinocytes recapitulated this phenotype. Further experiments linked this to abnormal interferon responses with impaired up regulation of the ISG OAS-1 [55].

In addition to keratinocytes, PBMCs isolated from eczema herpeticum patients also have deficient IFN responses following HSV exposure [38, 39]. In addition to effects on innate responses, cutaneous live virus vaccination studies in both AD patients [56] and mouse models of cutaneous allergy [57] reveal decreased generation viral-specific Th1 cells. In patients with AD, this inhibition correlated with serum IgE levels [56]. These data provide evidence supporting a direct link between allergic sensitization status and impaired antiviral adaptive immune responses in the skin.

Allergic Rhinitis, Asthma, and Respiratory Epithelial Cells

Similar to the epidermis, the airway epithelium provides the initial barrier to aeroallergens and respiratory pathogens. How epithelial cell antiviral responses are altered in the setting of atopy represents the focus of many studies. Even at baseline, there are significant differences in gene expression profiles and phenotypes of airway epithelial cells in atopic versus healthy individuals [58, 59]. Some of these differences could significantly alter responses to viral infections. For example, epithelial cells from asthmatics express higher levels of the RV receptor, ICAM-1 [59], potentially facilitating increased virus uptake and replication. Allergen and viruses synergistically impair barrier function by inhibiting expression of tight junction proteins further enhancing both allergen and virus

Table 1 Genetic polymorphisms in atopy linking allergic and anti-viral responses

Gene	Function	Allergen-virus link	Ref
IL-33	Induces a Th2 cytokines, regulates Treg cell development	SNPs associated with increased risk of asthma and hay fever. Produced by epithelial cells after RV and RSV exposure.	[24•, 25••, 26, 27]
TSLP-1	Induces a Th2 inflammatory response	Produced after allergen and virus exposure by respiratory epithelial cells and keratinocytes. Deletion protects mice from virus-allergen induced airway inflammation.	[24•, 28•, 29•]
FcεRI	Extracellular subunit of the high affinity IgE receptor	SNPs alter receptor surface expression. Engagement inhibits virus-induced type I IFN, downregulation of TLR7 in dendritic cells.	[30]
Filaggrin	Epidermal tight junctions	Deficiency results in increased risk of eczema herpeticum and eczema vaccinatum in AD patients. Also associated with increased risk of asthma development.	[14, 31•, 32•]
SOCS1	Transcriptional regulator of cytokine signaling/production, negatively regulates T cell differentiation, inhibits ISG expression	Increased expression in airway epithelium of asthmatics. Inhibits IFNβ secretion after in vitro RV exposure. Also involved in inhibition of Th1 differentiation.	[33••, 34]
IL-10	Negative regulator of pro-inflammatory cytokines, Th2 regulation	Polymorphism associated with RV-induced bronchiolitis and development of asthma.	[35–37]
IFNGRI	Adaptive antiviral responses, T cell differentiation	SNP results in loss of function mutation and is associated with eczema herpeticum in AD patients.	[38, 39•]
IL-1 receptor 2	Decoy receptor for IL-1, acting as inhibitor	Association with airway hyper-reactivity after picornavirus and RSV infections.	[40, 41]
IL-4Ra	Alpha subunit of IL-4 receptor. Binds IL-4 and IL-13. Regulates B cell IgE class switching and Th2 differentiation	Polymorphism associated with development of allergic asthma and also linked with RV-associated recurrent wheezing.	[42]
CTLA-4	T cell surface receptor, Regulator of T cell differentiation	Alterations in CTLA-4 function could influence T cell differentiation in the setting of allergen and/or virus responses.	[42–44]
CD86	APC expressed T cell co-stimulatory molecule, binds T cell CD28 and CTLA-4	Polymorphism increased risk for atopy. Stimulation of T cells in vitro had altered cytokine responses. Potential for altered T cell activation by APCs after allergen or virus exposure.	[44, 45]
TLR1	Heterodimer with TLR-2 to recognize bacterial lipoproteins	SNP was protective against virus-associated allergic asthma development.	[40]
TLR4	Innate receptor for bacterial LPS	Polymorphisms linked to severe bronchiolitis and wheezing, have defect in cytokine response to RSV in epithelial cells in vitro, and human PBMCs ex vivo.	[46]
ORMDL3	Sphingolipid biosynthesis	Upregulated after HRV exposure. Overexpression in mice results in elevated IgE, airway hyper-reactivity, airway remodeling.	[47••, 48•]
GSDMB	Unknown-associated with gastric and breast cancer development	Up regulated after HRV exposure. SNP homozygosity increases risk of asthma following RV infection.	[47••, 48•, 49]

exposure [60, 61•, 62•]. In an animal model of allergic sensitization, the combination of allergen (ovalbumin) and RV infection resulted in increased expression of pendrin, a negative regulator of air surface liquid thickness [63]. Elevated pendrin levels were confirmed in the nasal epithelium of asthmatics

with common colds, suggesting that atopic individuals have further decreased barrier protection due to thinner air surface liquid during viral infections. The above mechanisms all provide increased accessibility of allergen and viruses to both the airway epithelium and associated immune system components.

Epithelial cells from atopic individuals also exhibit defects in cellular antiviral immune responses. Multiple studies in subjects with allergic rhinitis and asthma demonstrate impaired interferon responses in the upper and lower respiratory epithelial cells after viral infection *in vivo* [64, 65] and *ex vivo* [64, 66, 67•, 68, 69]. Cellular mechanisms underlying these observations involve altered signaling upstream of interferon release. Inhibition of TLR3, MDA5, and RIG-I up regulation in epithelial cells from steroid-resistant asthmatic children results in decreased virus- and poly I:C-induced IFN β and λ production [65]. Another study reports diminished RV-induced TLR3 and MDA5 signaling in asthmatic airway epithelial cells despite normal expression of these dsRNA-sensing molecules [70], suggesting differences even within the spectrum of atopy. The complexity of epithelial responses is further highlighted by modulation of additional signaling mediators by allergic sensitization. Constitutive STAT1 activation, a transcription factor downstream of IFN receptors and critical to cellular antiviral responses, has been demonstrated in respiratory epithelial cells from asthmatics. Counter-intuitively, this persistent activation inhibits interferon release [71]. Additionally, up regulation of FOXA3 in goblet cells, both at baseline and in response to RV infection, drives mucus cell hyperplasia and inhibits antiviral pathway signaling via down regulated expression of MDA5 and decreased phosphorylation of STAT1, STAT2, and interferon regulatory factor 3. Finally, dysregulation of suppressor of cytokine signaling (SOCS) 1 has also been implicated in the inhibition of interferon responses in airway epithelial cells of asthmatics [33•, 34] and represents another signaling pathway potentially involved. Interestingly, some atopy-associated deficits, including control of viral replication, can be restored with exogenous type I IFN treatment [72, 73]. Although mixed, results of these studies suggest that specific targeting of deficient antiviral responses may provide therapeutic benefit in atopic diseases.

Innate Immune Cells—the Key Mediators in the Allergen-Virus Paradigm

Dendritic cells and monocytes, the key innate immune cells, are uniquely positioned in the host tissues where allergens and microbes are first encountered. Several studies report mechanisms impacting functions of these cells in the setting of concomitant atopy and viral infection, and how these may contribute to disease pathogenesis. IgE-mediated disruption of pDC virus-induced IFN α secretion represents one recently recognized mechanism. Purified pDCs [74] and PBMCs [75] from allergic asthmatics exhibit impaired IFN α secretion following *ex vivo* exposure to influenza or RV, respectively. Viral-induced pDC IFN α secretion inversely correlates with pDC Fc ϵ RI α surface expression and serum IgE levels, providing evidence that IgE- and viral-mediated responses are linked [74]. Furthermore, virus-induced IFN α secretion is

significantly inhibited by activation of Fc ϵ RI, the high affinity IgE receptor, via *ex vivo* exposure to an IgE cross-linking antibody [74, 75]. The clinical relevance of this IgE-mediated pathway is highlighted by results of the recent PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study conducted in children with allergic asthma; treatment with anti-IgE therapy (omalizumab) resulted in significant increases in *ex vivo* RV-induced PBMC IFN α responses [76••]. Interestingly, the group with greater increases in *ex vivo* IFN α responses after omalizumab had a significantly lower rate of asthma exacerbations during the outcome period, providing evidence that this mechanism may indeed contribute to disease pathogenesis *in vivo*. In another study conducted in asthmatics with acute exacerbations, PBMCs obtained during viral exacerbations displayed significant up regulation of genes related to both atopy (Fc ϵ RI receptor) and dendritic cell/monocyte activation (TLR7, CD14, and CCR2); increased expression of DC and monocyte Fc ϵ RI protein was also observed during these viral-associated exacerbations. Exposure of monocytes and dendritic cells to Th2 cytokines *ex vivo* recapitulated these transcriptional profiles, and these were inhibited by IFN α treatment [77], underscoring the contributions of both IgE and IFN-mediated pathways in atopic disease.

The effects of allergic stimulation on pDCs extend beyond IFN α secretion, as allergic stimulation with either allergen or IgE cross-linking also down regulates TLRs 7 [74] and 9 [78], both critical in the recognition of viruses. The importance of TLR7 and pDCs was recently demonstrated in a murine model of house dust mite (HDM)-induced allergic airway disease with superimposed RV infection. HDM-sensitized TLR7 deficient mice exhibited impaired RV-induced IFN responses and increased eosinophilic inflammation, which were reversed by adoptive transfer of TLR7-competent pDCs. In addition, lung TLR7 expression was suppressed by eosinophilic inflammation. A similar relationship between TLR7 and eosinophilic airway inflammation was demonstrated in samples from humans; reduced TLR7 was observed in endobronchial biopsies obtained from asthmatics with an inverse correlation between TLR7 expression and airway eosinophil percentages [79••]. These results uncover another potential mechanism by which innate immune cells—in this case eosinophils—may interrupt antiviral responses and contribute to the pathogenesis of viral-associated exacerbations of atopic disease.

Macrophages and monocytes are also affected by allergic sensitization and play important roles in antiviral responses. Reduced TLR7 expression in airway alveolar macrophages has recently been associated with deficient RV-induced IFN responses in severe asthmatics and mechanistically linked to expression of specific microRNAs [80••]. Studies from our laboratory demonstrate that allergic stimulation via IgE cross-linking of primary human monocytes promotes pro-inflammatory cytokine release and inhibition of phagocytic

functions [81]. In the setting of influenza infection, allergic stimulation inhibits monocyte-driven CD4 Th1 cell differentiation via down regulation of the key antigen presenting molecules, MHC I and II, and T cell costimulatory molecules, CD80 and CD86 [82•]. Monocytes and dendritic cells also regulate responses to viruses and allergens in murine models of allergic sensitization. Deletion of the FcεRI receptor on murine conventional DCs resulted in decreased virus-induced airway hyper-reactivity and involved type I interferon and neutrophil-mediated recruitment of these cells to the airway [83, 84].

Other murine studies also demonstrate links between allergen sensitization and virus-induced airway hyper-reactivity similar to that observed in humans. For example, synergistic effects of allergen (ovalbumin or HDM antigen) and RV exposure lead to Th2-predominant cytokine responses, a phenotype specifically linked to the CD11b+ IL-13 secreting monocyte/macrophage population recruited to the airways and lung [85•]. However, other murine studies point to more complex pathogenesis mechanisms. For example, cockroach extract exposure combined with pneumovirus infection induced allergen-specific IL-33-dependent airway hyper-reactivity. Additional mechanistic studies implicated the pDC population, which displayed deficits in types I and III interferon secretion and diminished TLR7 pathway signaling, similar to observations in human pDCs [86•]. TLR7 knockout mice also have enhanced lung pathology in the pneumovirus-cockroach allergen model [87], further supporting a critical role for innate virus-recognition and IFN-inducing pathways in atopic diseases.

This complex environment also results in the recruitment and activation of additional innate cells not previously discussed. A recently recognized cell type, innate lymphoid cells (ILC2), or nuocytes are specifically involved in allergic inflammation and recruited in high numbers by virus infection following allergen sensitization via IL-33 and TSLP-1 release by epithelial and other innate cells [25•, 28•, 86•, 88]. Data from murine models also support an important role for ILC2 cells in the development of allergen-dependent airway pathology in the setting of RSV [29•] and RV [28•] infections. Th2 cytokines and chemokines secreted by multiple innate and adaptive cell types, including IL-13, IL-5, and eotaxin recruit other innate effector cells such as eosinophils, mast cells, and basophils [88], and further propagate Th2-mediated inflammation. The precise roles of these cells in allergen-virus interactions, while largely unexplored, are likely critical in allergen-viral interactions relevant to atopic disease.

Adaptive Immune Responses—the Final Link

Allergic diseases are traditionally characterized by the prominence of Th2 responses [1, 23]. Antiviral responses, however, depend heavily on Th1 effector functions [89] for adequate

cytotoxic CD8-mediated virus clearance and B cell antibody production. Thus, another effect of allergic sensitization could involve an imbalance in appropriate T cell adaptive responses following virus infection. For example, in blood PBMCs from asthmatic donors, responses to ex vivo RV exposure were altered, with decreased Th1 cytokines IFNγ and IL-12, increased Th2 effectors IL-13 and IL-4, and differential expression of T cell costimulatory molecules on APCs [90]. In allergic asthmatics, decreasing serum IgE levels with omalizumab, a treatment known to decrease virus-induced asthma exacerbations [76•], also decreases IL-4 and IL-5 positive cells and T cell infiltrates in the airway [91]. While this study did not take into account coinciding virus infection, one could hypothesize that a Th2-dominant immune response could result in altered virus-induced T cell responses following infection. This is supported by other clinical observations. As previously mentioned, AD patients have impaired virus-specific T cell responses following subcutaneous yellow fever virus vaccination [56•]. Similarly, after experimental RV infection of allergic asthmatics, decreased IFNγ was detected in bronchoalveolar lavage fluid, and this correlated with increased disease severity, viral replication, and Th2 responses including CD4 T cells expressing IL-4, IL-5, and IL-13 [92]. Similar effects were noted in the blood indicating the effect of allergic sensitization is systemic and not isolated to cells recruited to the airways [92, 93]. In contrast, respiratory virus infection in a mouse model of allergic asthma actually increased Th1 cell production, but when combined with allergen sensitization enhanced recruitment of allergen-specific Th2 cells to the airway [94]. Effects on adaptive immune responses are likely also heavily influenced by direct allergen-mediated action on innate immune cells via modulation of antigen presentation, T cell stimulation [95, 96], and the cytokine and chemokine milieu [84].

Genetics Underlying the Impact of Allergic Sensitization on Antiviral Responses

There is a clear genetic influence on the interplay between allergic sensitization and virus-mediated effects on atopic disease. Many genetic loci identified are involved in immune regulation; single nucleotide polymorphisms (SNPs) in interleukin (IL)-33, suppressor of cytokine signaling (SOCS) 1 and 3, IL-10, IFNγ receptor 1 (IFNGRI), and many others [26, 27, 30, 34–37, 39•, 40, 42, 46, 47•] have been linked to the development of allergic diseases. Specific SNPs may enhance or inhibit protein function and potentially impact antiviral responses (Fig. 1 and Table 1). For example, functional SOCS-1 mutations in asthmatics are implicated in the negative regulation of type I IFN production in airway epithelial cells after virus exposure [33•, 34]. SNPs in the gene encoding interleukin-1 receptor 2, an inhibitory IL-1 decoy receptor

[41], correlate with picornavirus (which includes RV), and RSV-induced airway hyper-reactivity [40]. Similarly, the IL-4 receptor alpha subunit [42] and IL-10 [35] genes have been associated with asthma development and RV-induced wheezing and bronchiolitis. Polymorphisms in other genes critical in antigen presentation and T cell stimulation, including CTLA-4, CD86, and CD40 [43–45] have also been linked with atopic disease; these could potentially influence T cell responses following virus infection by either increasing Th2 or reducing Th1 differentiation. Functional studies defining how these respective polymorphisms affect protein functions and immune responses have yet to be performed.

Pathogen recognition by the innate immune system, as previously described, is also affected by allergic sensitization. Polymorphisms in toll-like receptors (TLRs), including TLRs 1, 2, 3, and 4, are implicated in antiviral responses as they relate to atopic disease [40, 42, 97]. Toll-like receptor 4, a protein involved in host cell recognition of bacterial polysaccharides, has been associated with both atopy and severe viral bronchiolitis [46, 98]. In vitro studies of airway epithelial cells and human PBMCs reveal an altered cytokine response to RSV in the presence of certain TLR4 polymorphisms [46], indicating a broader role for this receptor beyond antibacterial responses. Interestingly, not all polymorphisms are associated with worsening atopic disease. For example, certain genotypes of TLR1, which heterodimerizes with TLR2 to recognize both bacterial lipopolysaccharides and allergens [99], protect against development of virus-induced asthma [40]. Thus, evidence is mounting that allergen exposure in individuals with certain genotypes may significantly impact immune responses to concomitant viral infections.

Potential effects of other gene products on antiviral responses are less defined. The 17q21 chromosomal locus has been repeatedly identified in genetic linkage studies [47•, 48•, 49, 100•, 101] and is specifically linked to RV-related wheezing and asthma development [47•]. Two genes, ORMDL3 and GSDMB, were significantly up regulated in PBMCs after in vitro RV exposure, suggesting involvement in RV-induced asthma exacerbations [47•]. ORMDL3 encodes the orosomucoid-like 3 protein involved in sphingolipid biosynthesis. In a mouse model of asthma, overexpression led to increased airway hyper-reactivity, elevated IgE levels, and up regulation of airway remodeling genes [102•]. Although the product of GSDMB, gasdermin B, is associated with development of breast and gastric cancers [103, 104], the exact function of this protein in atopic diseases and viral infections is unexplored. Clinically, individuals homozygous for a specific GSDMB polymorphism had a 26-fold increased risk of developing asthma when combined with a history of prior RV infection [47•].

While most genetic linkage studies have focused on viral-induced wheezing and allergic asthma, many loci identified overlap with either allergic rhinitis or atopic dermatitis. The

17q21 locus is associated with allergic rhinitis in some cohorts [48•, 49]. Similarly filaggrin mutations involved in eczema herpeticum susceptibility are also linked to asthma development [32•]. Deep sequencing analysis of patients with eczema herpeticum also identified mutations in the interferon gamma receptor (IFNGRI) [38, 39•], which could have significant implications for adaptive responses to respiratory viruses in the setting of allergic asthma or rhinitis. Further investigation defining cellular pathways and mechanisms affected by these genetic polymorphisms could greatly expand our knowledge of allergen-mediated modulation of antiviral immunity and provide potential genetic biomarkers to predict which individuals are at greatest risk for viral-induced atopic exacerbations.

Therapeutic Strategies

The mainstays of allergic disease therapy include immunosuppression with corticosteroids, atopic control with antihistamines and leukotriene inhibitors, and in allergic asthma specifically smooth muscle relaxation with beta-adrenergic agonists [105]. Even in well-controlled disease, it remains difficult to prevent viral-induced exacerbations, potentially due to underlying deficiencies in antiviral immune responses not restored by standard therapies [106]. Thus, targeting these pathways specifically is critical for better treatment, and perhaps prevention, of allergic diseases. Both clinical and mechanistic studies link IgE and its cognate receptor, FcεRI, to inhibition of antiviral pathways. Omalizumab, a therapeutic anti-IgE antibody, is used to treat asthma and atopic dermatitis in patients refractory to maximal standard therapy [107–109] and is also effective in seasonal allergic rhinitis [110]. As previously mentioned, lowering IgE with omalizumab reduces seasonal virus-induced asthma exacerbations in children [111]. Results of the PROSE trial demonstrate that this therapy also results in increased type I IFN production by pDCs and directly correlates with improved clinical outcomes [76•]. Additional studies with other humanized monoclonal antibodies targeting Th2 cytokines, such as IL-5, IL-13, and IL-4, are underway in patients with various atopic diseases [112, 113]. However, in contrast to omalizumab, these treatments are unlikely to restore antiviral responses. A recent study directly evaluated the effects of inhaled IFNβ on virus-induced asthma exacerbations in adults. Although there was no significant effect on virus-induced asthma symptoms assessed by the Asthma Control Questionnaire (the primary outcome), sub-analyses revealed that IFNβ treatment promoted faster recovery of morning peak expiratory flow and decreased exacerbations in those with severe steroid-resistant asthma [114•], suggesting a potential future role for type I IFN therapy in atopic asthma. Targeting intracellular viral response pathways may also prove beneficial. For example, the anthraquinone class of antimalarial drugs targets host cell AKT signaling pathways

and treatment in a mouse model decreased allergen-mediated RV-induced inflammation [115]. Theoretically, activation of antiviral signaling pathways, such as TLRs 3, 7, or 9, with small molecule agonists could also restore antiviral signaling deficits. For example, complementation of TLR7 knockout mice with either IFNs or wild-type pDCs ameliorated RV-induced excess inflammation [79•]. One could hypothesize that a small molecule stimulating the TLR7 pathway could overcome any allergen-induced inhibition of antiviral responses. This has, in fact, been tested for TLR9 mediated pathways; intranasal administration of the TLR9 ligand, CpG, decreased airway pathology in a mouse model of allergic rhinitis and asthma [116•], in the absence of virus infection. While animal and in vitro studies are critical to elaborate specific cellular pathways and mechanisms for future drug discovery, high quality human studies are vital to develop safer, more effective therapies.

Conclusions

The effect of allergic sensitization on antiviral responses is multifaceted, likely affecting all branches of the immune system—from barrier function to innate and adaptive responses. Genetic factors also influence an individual's susceptibility to allergic sensitization and impact antiviral responses. This can increase the risk of atopic exacerbation due to a “double hit”—i.e., allergen exposure in a sensitized individual combined with severe viral infection. Many questions regarding the mechanisms linking allergic sensitization and antiviral responses remain. What specific cellular factors are involved in IgE receptor signaling and downstream inhibition of antiviral responses? How do the deficiencies in epidermal/epithelial and innate cell responses directly impact T cell responses on a cell-cell and molecular level? Can cellular functions such as signaling or secretion of soluble effectors in the setting atopy be manipulated to restore antiviral mechanisms for clinical benefit? Answers to these and other unanswered questions may uncover the key pharmacological targets to potentially enhance antiviral responses and ameliorate virus-induced exacerbations of atopic diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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