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Virus/Allergen Interactions in Asthma

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Abstract

Understanding the underlying mechanisms that cause and exacerbate allergic asthmatic disease is of great clinical interest. Clinical studies have revealed that allergies and viral respiratory illnesses are strongly linked to the inception and exacerbation of asthma, and suggest the possibility that there are interactive inflammatory mechanisms. Recent work has revealed a number of mechanisms of virus and allergen cross-talk that may play a role in the pathophysiology of allergic asthma, including (1) deficiency in virus-induced interferon responses, (2) defective epithelial barrier function, (3) increased release of epithelium-derived cytokines (*e.g.*, thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, IL-33), (4) dysregulation of lymphocytes (*e.g.*, innate lymphoid cells (ILCs), regulatory T cells (Tregs)) and (5) altered activation of purinergic receptors. One or more of these processes may provide targets for new therapeutics to treat allergic asthma and prevent disease exacerbation.

Keywords

Asthma; Virus; Allergen; Atopy; Interactions; Rhinovirus; Exacerbations; eATP; TSLP; IL-33; IL-25; Treg; ILC; P2X7; FcεR1; Dendritic cells

Introduction

Viruses, allergens, and interactions between the two have been linked to the inception of asthma as well as exacerbations of established asthma. Asthma exacerbations and their associated costs have a significant clinical and societal impact including school/work absenteeism, interference with parental schedules, costs of medications, emergency department visits, and hospitalizations [1]. Given the increasing prevalence, cost and utilization of healthcare resources, and effect on long-term lung function, it is important to gain new insights into causes of asthma inception and exacerbation.

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Viruses and Allergens in Disease Inception

Wheezing illnesses due to viral respiratory infections are frequent in childhood and are a common cause of morbidity, hospitalization, and utilization of healthcare resources. [2]. Up to 50% of children have had a wheezing illness by the age of six [3]. Since the first wheezing illnesses for most children with asthma are viral in origin, and the clinical features of viral wheeze and asthma are quite similar, this led to speculation that some viral respiratory infections could cause asthma. In fact, wheezing illnesses due to respiratory syncytial virus (RSV) infections were found to increase the risk of asthma in school aged children [4-6]. Whether severe RSV illnesses cause asthma is an area of significant controversy, with evidence supporting [6] and opposing [7] this theory. In an interventional study, treatment of mildly premature infants with palivizumab prevented recurrent wheeze, but only in non-atopic infants [8].

Further studies undertaken with improved molecular diagnostics suggest that the etiology of viral wheezing affects the risk of subsequent asthma. Infants who were hospitalized for human rhinovirus (HRV) wheezing illnesses in infancy were more likely (OR 4.14) to develop asthma compared to those infants hospitalized with wheezing illnesses due to other viruses [9]. A prospective birth cohort study found that among viral wheezing illnesses in infancy, human rhinovirus (HRV) infections were the most significant predictors of the subsequent development of asthma at age six [10]. While wheezing illnesses due to human rhinovirus (HRV) were associated with nearly a 10-fold increase in asthma at age six, the risk was noted to be even greater when infections occurred in the third year of life. Similarly, human rhinovirus (HRV) wheezing was a risk factor for subsequent asthma in a birth cohort based in Perth, Australia, especially if there were signs of atopy [11].

Atopy is a well-recognized risk factor for childhood asthma, and this is particularly true for children who are sensitized to allergens in the first two years [12]. While allergen sensitization has long been a recognized contributor to asthma inception, it was previously unclear whether allergen sensitization or early viral infections with wheezing occurred first. Recent studies have suggested that sensitization precedes viral wheezing. When examining allergic sensitization and viral wheezing in high-risk children enrolled in a prospective birth cohort, it was demonstrated that sensitization to aeroallergens in the first year of life predisposes children to HRV-induced wheezing illnesses [13]••.

Viruses and Allergens in Disease Exacerbation

Viral respiratory infections are important causes of exacerbations in both children and adults with asthma [14-16]. Heymann and colleagues evaluated viral infections in relation to age, atopic status, and season in which children had been admitted for wheezing [17]. In children younger than three years of age, RSV was the predominant virus isolated in winter admissions, but between the months of April and November, HRV was the most common virus isolated. Similarly, in patients older than three years of age, HRV was the most commonly identified virus and the only virus associated with wheezing [17, 18]•. In the outpatient setting, 80-85% of asthma exacerbations in children are also due to viral illnesses and up to two-thirds of these have been attributed to HRV infection [15, 19]. Interestingly, HRV burden in the lower airway was similar between asthmatics and nonatopic healthy adults, suggesting that mechanisms other than viral load account for the enhanced cold symptoms seen in asthmatics [19].

When examining the interplay between atopy and viral-induced wheeze, higher levels of immunoglobulin (Ig)E and more evidence of wheezing were found in children older than three years of age with wheezing [17]. Subsequent studies have demonstrated that concurrent viral illness and allergic sensitization increases the likelihood of asthma

exacerbations and hospitalizations due to severe symptoms [20, 21]. Analysis of weekly samples of nasal secretions from asthmatic children during peak HRV seasons revealed that both virus-positive weeks and allergic sensitization were associated with greater cold and asthma symptom severity [21]. Although rates of infection were similar between sensitized and non-sensitized children, those sensitized to aeroallergens had 47% more virus-associated illnesses per season. In adults, a similar synergism between viruses and allergies was seen in asthmatics admitted to hospitals for exacerbations [20]. Interestingly, a recent study examining the serum of 287 school-age asthmatic children demonstrated that increasing serum titers of allergen-specific IgE antibody substantially increased the probability of HRV-induced wheeze, supporting a role for atopy in modulating host anti-viral responses [22]•. Finally, seasonal peaks for asthma exacerbations correlate with seasonal increases in viral illnesses, and significant peaks in wheezing illnesses and asthma have been noted in the fall [23, 24], with a smaller peak in the spring months. These peaks may be in part due to viral infections but may also correlate with fall and spring allergy seasons, which may be contributing to illness severity.

Human rhinoviruses are classified into three species (A, B and C), and there is evidence that some HRVs may be more virulent with respect to respiratory illnesses and asthma symptoms. In children aged 2-16 years evaluated for acute asthma exacerbations, HRV C viral infections were associated with greater symptoms than the HRV A or B infections [25]. Other studies investigating relationships between HRV infections and illness have noted increased pathogenicity from both A and C strains [26-29]. A recent study described a correlation between winter seasonality and increased severity of HRV illnesses [29]•. In concordance with previous studies, HRV A and C strains were found to be more virulent than B strains in infants with risk for developing asthma and allergies, and HRV A and C strains were more associated with wheezing illnesses.

In experimental HRV inoculation studies of adult volunteers with vs. without asthma, cold symptoms severity is generally similar, while lower airway symptoms are increased with asthma [30, 31]. Notably, HRV infection enhanced eosinophilic responses to inhaled allergen in allergic individuals [32], but administration of inhaled allergen before HRV inoculation had little or no effect in the severity and duration of cold symptoms in adult rhinitis and asthmatic subjects [33, 34]. Thus, virus/allergen interactions that are observed in clinical studies have been difficult to reproduce in experimental infection models.

Mechanisms of virus-allergen interactions

It is widely accepted that allergic diseases are the result of an exaggerated immune response, leading to sensitivity to otherwise innocuous substances (*i.e.*, allergens). Most allergic responses ultimately revolve around the activation of Th2-skewed CD4+ T cells, and recent work has revealed new insights into the mediators and immune cells that modulate the differentiation and activation of Th2 cells. There have been many proposed mechanisms to explain how allergy and viral infections interact, and some of the more recent hypotheses in the context of allergic asthma inception and exacerbation are discussed below, and summarized in Figure 1.

Relationship of FcεR1^{+} Dendritic Cells to Release of Antivirals

The hallmark of atopy is the production of allergen-induced IgE, and elevated serum IgE levels are associated with increased asthma severity [35]. FcεRI is the high affinity surface receptor for IgE, and is expressed on dendritic cells as well as mast cells, basophils, and others [36]. Expression levels of FcεRI on peripheral blood cells correlate with serum IgE levels [36, 37]. Gill and colleagues found that there is a significant inverse correlation between FcεR1 on plasmacytoid dendritic cells (pDCs) and influenza-induced IFN-α

responses [38]. Furthermore, influenza-induced IFN-α secretion was inversely correlated with serum IgE levels, and crosslinking IgE prior to influenza infection further attenuated IFN-α secretion from pDCs [38].

A similar relationship was seen after HRV infection of peripheral blood mononuclear cells (PBMCs). Durrani and colleagues [39]• reported that allergic asthma was associated with significant reductions in HRV-induced IFN-α and IFN-λ1 secretion. Further, the percentages of FcεR1+ pDCs inversely correlated with HRV-induced IFN-α and IFN-λ1 responses. Interestingly, serum total IgE was positively correlated with the percentages of FcεR1+ pDCs, and inversely correlated with HRV-induced IFN-α production.

The mechanism by which FcεR1 expression on pDCs leads to decreased IFN production has yet to be determined, but may be through activation of intracellular signaling by the FcεR1γ subunit, which contains immune receptor tyrosine-based activation motifs (ITAMs) that can activate various kinases such as Src and Syc [40, 41]. These studies support a role for pDCs in predisposing atopic asthmatics to an impaired anti-viral response.

IFN Deficiency in Viral-Infected Atopics

Clearance of viral pathogens begins with interferon secretion, and the underproduction of these factors has been postulated to lead to viral-induced exacerbations [42-44]. There are three types of interferons (based on the receptors they bind): Type I (IFN-α/β), Type II (IFN-γ) and Type III (IFN-λ). Numerous *in vivo* and *ex vivo* experiments have monitored the virus-induced release of these IFNs from epithelial and mononuclear cells from atopic asthmatics (Table 1).

Results of a number of studies suggest that virus-induced IFN responses may be impaired in asthma [38, 39, 42-47], however, others have found no difference, or even enhanced IFN responses, in atopic asthmatics [18, 30, 48-51]. Of note, a recent prospective study of respiratory secretions in 409 asthmatic children found that *in vivo* IFN-λ1 levels during HRV infections were higher in wheezing versus non-wheezing children and IFN-λ1 levels were positively related to symptom severity [18]. In the absence of infection, adults with allergic asthma were found to have increased IFN-λ levels in allergic airway mucosa during peak allergy season, and allergen stimulation of PBMCs led to increased expression of IFN-λ1 by CD14+ cells [51]. These contradictory findings in different studies may be due to a number of factors, including timing, magnitude and location of the IFN response. These differences also suggest that exuberant IFN responses could lead to more severe clinical symptoms by enhancing airway inflammation,

Epithelial Cell Barrier Abnormalities

The airway epithelium provides the first line of defense against inhaled pathogens, but can lose barrier function after mechanical damage or exposure to numerous agents, including viruses [52-54]. Moreover, there is evidence that both atopy and asthma in children are associated with damaged airway epithelium [52]•. The apical layer of epithelium is more resistant to viral infection than the basal layer [55, 56], therefore agents that decrease the integrity of the epithelium could increase the susceptibility of the host to pathogen-induced damage. Furthermore, compromise of the epithelial barrier in asthma is associated with disrupted tight junctions, impaired innate immunity and attenuated antioxidant properties [57], which may contribute to increased sensitivity to infections and allergens.

Common Epithelial-derived Mediators in Allergy and Viral Illnesses

There is emerging evidence that viruses and allergens can act on the epithelium to initiate innate immune responses in the respiratory microenvironment that promote Th2 inflammation. In particular, both viruses and allergens induce epithelial cell-derived "alarmins", TSLP, IL-33 and IL-25, which promote the differentiation and activation of innate lymphoid cells (ILCs) and suppress the activation of regulatory T (Treg) cells. Furthermore, there is increasing support for a role for extracellular nucleotides and the activation of nucleotide receptors in potentiating allergen- and viral-effects in human cells.

TSLP

TSLP (an IL-7-like cytokine) is primarily released from epithelial cells and keratinocytes at barrier surfaces, but is also expressed in lung fibroblasts, airway smooth muscles, and various immune cells including mast cells, macrophages and dendritic cells [58]. For instance, mast cells release TSLP following FcεR1 aggregation [59]. TSLP expression is induced by both allergens and viruses. [58, 59]. Of note, HRV infection of bronchial epithelial cells can induce TSLP expression and release [60]. In addition to numerous murine allergic inflammation models supporting a role for TSLP in driving Th2 inflammation [61], elevated levels of TSLP in the epithelium of atopic asthmatics and allergic rhinitis patients positively correlate with airway obstruction (FEV_1) [62-64].

Human TSLP potently upregulates antigen presenting receptors on myeloid dendritic cells (mDCs) and subsequently prime mDCs to release Th2-attracting chemokines and induce the differentiation of naïve Th0 cells to Th2 cells [65, 66]. Interestingly, TSLP-activated thymus-derived human mDCs and pDCs in young children (0–2 years old) have been linked to the generation of Fox3P+ Tregs, which are general suppressors of inflammation [67]. The link between TSLP and the development of immunologic tolerance during infancy suggests that TSLP induces age-dependent differential effects on T cell maturation/activation.

IL-33

IL-33 expression in humans appears to be primarily confined to epithelial cells, endothelial cells, fibroblasts and smooth muscle cells [68, 69]. IL-33 is released from necrotic cells in response to inflammation/infection, and has been recently proposed to be a potential asthma therapeutic target [70], given that asthmatic lung epithelia basally express more IL-33 than healthy controls [71], and IL-33 levels correlate with increased asthma severity [71]. Exposure of primary human epithelial cells to airborne allergens also leads to IL-33 release, possibly be releasing ATP which stimulates purinergic receptors (P2X7 or P2Y2) [72]. Infection of human epithelial cells with influenza also increases IL-33 mRNA expression [73].

IL-33 can activate numerous immune cells (*e.g.*, mast cells, DCs, Th2 cells, eosinophils) to amplify Th2-type responses [69, 70, 74]. Current work exploring the therapeutic use of anti-IL-33 for allergic rhinitis is promising; treatment of OVA-sensitized mice with anti-IL-33 decreases both IgE levels and eosinophil infiltration to the nasal cavity [75].

IL-25

IL-25, unlike other IL-17 family members that promote neutrophilic inflammation, induces Th2 cytokines from memory Th2 cells, basophils, and other immune cells [61, 76]. IL-25 is primarily made by epithelial cells, but eosinophils and basophils may also contribute [76]. Elevated expression of IL-25 and IL-25 receptor transcripts has been detected in asthmatic lung tissues, and the presence of eosinophil-derived IL-25 promotes IL-5 and IL-13

synthesis and Th2 cell expansion [76]. Interestingly, when dsRNA-treated nasal epithelium is cotreated with IL-25, TSLP release from nasal epithelium is significantly elevated, suggesting a positive feedback loop for Th2-mediated inflammation [63].

ILCs

Many of the Th2-promoting events induced by IL-33 and IL-25 are attributed to the activation of ILCs, which produce IL-13 and IL-5 after stimulation with these alarmins. ILCs are lineage-negative cells that are potent sources of cytokines at epithelial surfaces, including the lung. Of the four types described to date, CRTH2+ type 2 ILCs (found in the gut, lung and peripheral blood) [77, 78] are of particular interest. Stimulation of human type 2 ILCs with IL-25 or IL-33 leads to the secretion of IL-5 and IL-13, further promoting a Th2 microenvironment [77, 78]. Considering both allergens and viruses are able to induce the release of IL-25 and IL-33, ILCs may provide an important aspect of virus/allergen interactions in asthma.

Role of Tregs in Allergen/Viral Immunity

Tregs play in important role in fine-tuning the balance between effector and tolerogenic immune responses. There are two major Treg types: natural Tregs (nTregs), and induced/adaptive Tregs (iTregs) [79]. nTregs are a subset of CD4+ T cells that differentiate in the thymus express constitutively high amounts of the IL-2 receptor α-chain (CD25) and the transcription factor forkhead box P3 (Foxp3), and play a pivotal role in maintaining peripheral tolerance and limiting chronic inflammation [80]. In addition to nTregs, iTreg cells can also be generated in the presence of TGF-β, IL-10 and IL-35, and these cytokines are subsequently produced by iTregs to limit inflammation [80].

There is evidence that Treg cells might be functionally deficient in atopy and asthma. TSLP levels in bronchial alveolar lavage fluid (BALF) of allergic asthmatics have been correlated with impaired Treg suppressive function [79, 81, 82]. Moreover, $CD4^{+}CD25^{hi}$ Treg cells expressed in atopic subjects were significantly less effective at suppressing proliferation and IL-5 release from $CD4^{+}CD25^{-}$ T cells, as compared to non-atopic subjects [83]. Furthermore, BALF isolated from non-ICS treated asthmatic children had fewer $CD4^{+}CD25^{hi}$ Treg cells than non-asthmatic controls [84]. Interestingly, asthmatic children who were on ICS treatment had similar $CD4^{+}CD25^{hi}$ Treg levels as non-asthmatic controls [84], supporting a role for corticosteroids in activating Treg differentiation and subsequent IL-10 release [79].

During viral infection, Tregs may protect against viral-induced inflammation by suppressing the proliferation, cytokine production and cytotoxicity of effector $CD8^{+}$ T cells, as well as suppressing $CD4^{+}$ T cell function [85]. Accordingly, during HRV infections, Tregs suppress DC activation of T cells [86].

Although Tregs have been studied extensively in the context of allergies and viral infections, very little work has examined the effect of both allergens and virus together on Treg function. Recently a study in mice has implicated a potential role for early RSV exposure in suppressing Treg development and increasing subsequent susceptibility to allergic disease [87]. More work in human *in vivo* models need to be performed to determine whether Tregs are key players in allergen/virus signaling crosstalk.

Extracellular ATP and Purinergic Receptors

Viral infection and allergen exposure can both cause cells to release nucleotides into the extracellular space [88, 89], leading to millimolar concentrations of extracellular ATP

(eATP) in an inflammatory microenvironment [90]. Of note, allergen activation of mast cells leads to the release high concentrations of eATP stored in their granules [90]. One mechanism by which Tregs are believed to suppress inflammation is through expression of ectoATPases (*e.g.*, CD39, CD73) that metabolize eATP into adenosine, leading to attenuation of effector T cell proliferation and decreased DC function [80].

Cellular nucleotide receptors have been linked to inflammatory responses and asthma. Approximately 35% of asthmatics have attenuated P2X7 function [91], and recent clinical studies also support a potential role for the P2X7 in allergen sensitization and viral-induced asthma exacerbations. P2X7 is expressed on the surface of epithelial cells and numerous innate immune cells, including macrophages, DCs, eosinophils and mast cells [89, 90, 92]. Interestingly, there appears to be a difference between P2X7 function on the cells of children versus adults. In children, attenuated P2X7 function was associated with lower rate of asthma and less sensitization to aeroallergens [93]. Conversely, adults with attenuated P2X7 function present with decreased viral-induced nasal inflammation and are at a higher risk for viral-induced loss of asthma control despite maintenance therapy [91, 94].

Recent Treatments to Control Asthma Exacerbations

Current therapeutic research is primarily focused on preventing exacerbations of asthma and maintaining symptom control. Eosinophilic inflammation is a risk factor for more severe viral illnesses and asthma exacerbations [17, 30], suggesting that treatments that inhibit eosinophilic airway inflammation might be beneficial. In that respect, mepolizumab, a humanized monoclonal antibody against IL-5, significantly reduces eosinophil levels in the lungs and circulation [95], and reduces asthma exacerbations [96]. However, it must be noted that mepoluzimab treatment did not significantly improve persistent asthma symptoms for most individuals [95]. Another medication known to reduce eosinophilic inflammation and asthma exacerbations is montelukast (a leukotriene receptor antagonist). Addition of montelukast to asthma maintenance therapy has been shown to reduce September exacerbations and recurrent wheeze post-RSV bronchiolitis in some, but not all, studies [97, 98].

Another promising drug in preventing exacerbations and maintaining symptom control is omalizumab, a humanized monoclonal anti-IgE antibody. Omalizumab lowers the frequency of exacerbations and reduces asthma symptoms and requirements for other controller medications [99, 100]. Interestingly, omalizumab therapy substantially inhibited seasonal peaks in asthma exacerbation in children with moderate to severe asthma, supporting its potential efficacy in preventing viral-induced exacerbations [99]••.

Conclusions

Both allergens and viruses are important risk factors for the inception and exacerbation of asthma. Improving our understanding of the mechanisms for these effects is important to identify opportunities for treatment and to identify strategies for primary prevention of childhood asthma.

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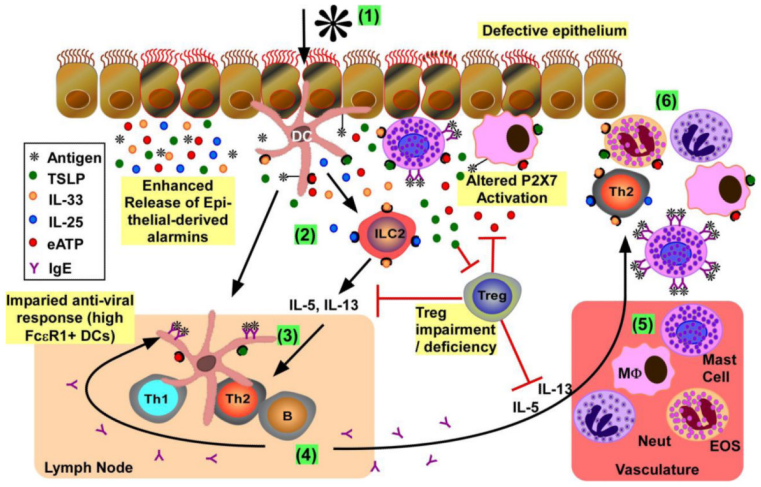

Figure 1. Overview of mucosal immune response to allergens and viruses in atopic asthma

(1) Initial activation of epithelium and resident innate immune cells: Allergens and/or viruses activate epithelium to induce release of mediators, including alarmins (e.g., TSLP, IL-25, IL-33 and ATP). When epithelia are damaged, there is increased epithelial-mediated alarmin release together with exposure of resident immune cells (*e.g.*, DCs, macrophages, mast cells) to pathogens to further promote pro-inflammatory mediator release. Resident antigen presenting cells (*i.e.*, DCs, macrophages) process and present antigens to activate the adaptive immune response. Mast cells with bound IgE to FcεR1 can bind allergens, inducing FceR1 crosslinking and mediator release (*e.g.*, histamine, TSLP, ATP). Released ATP from mast cells and/or damaged cells activates purinergic receptors on the surface of multiple immune cells (*e.g.*, DCs, macrophages, mast cells) to further promote pro-inflammatory mediator release; the availability of active ATP for purinergic receptor binding is regulated by Tregs. ***(2) DC skewing and type 2 ILC (ILC2) expansion:*** Exposure of DCs to IL-33 and TSLP skews the DCs to support differentiation of naive T cells to Th2 in draining lymph nodes. IL-25 and IL-33 induce the maturation and activation of type 2 ILCs, which subsequently release IL-5 and IL-13. Tregs can inhibit the release of Th2 cytokines, but are suppressed by TSLP. ***(3) Th2 differentiation:*** The combination of primed DCs and released Th2-promoting cytokines (*i.e.,* IL-4, IL-5, IL-13) lead to the maturation/activation of Th2 lymphocytes in the draining lymph nodes. ***(4) IgE production:*** Th2 cells induce B cell immunoglobulin isotype switching, leading to the release of antigen-specific IgE. Increased expression of FceR1 on DCs is inversely related to antiviral (*i.e.*, IFN release) responses. (5) Recruitment of pro-inflammatory leukocytes from vasculature: Release of aforementioned mediators potentiates the release of chemokines from activated innate immune cells/ epithelium to promote immune cell recruitment from the vasculature. ***(6) Chronic Inflammation:*** Recruited immune cells release more proinflammatory mediators, leading to exaggerated and chronic cellular inflammation.

Table 1

Summary of studies comparing IFN levels between atopic asthmatics and healthy controls.

IFN	Virus	mRNA / Gene	Protein Release	Decrease in asthmatics?	Reference
Epithelial Cells					
IFN-β	HRV-1 b, 16	X		yes	[46] *[*]*
IFN-β	HRV-1 b, 16		X	ND	[46] *[*]*
IFN-β	HRV-1a	X		no	[48]
IFN-β	HRV-16	X		no	[49]
IFN-β	HRV-16	X	X	yes	[44]
IFN-β	HRV-16		X	yes	[52] *[*]*
IFN-λ	HRV-1b, 16		X	ND	[46] *[*]*
IFN-λ	HRV-16		X	yes	[42]
IFN-λ IFN-λ IFN-λ1	HRV-1b		X	yes	[45]
	HRV-16		X	yes	[52] *[*]*
	HRV-1b, 16	X		yes	[46] *[*]*
IFN-λ1	HRV-16	X		yes	[42]
IFN-λ2	HRV-1a	X		no	[48]
IFN-λ2/3	HRV-1b, 16	X		yes	[46] *[*]*
IFN-λ2/3	HRV-16	X		yes	[42]
Blood Cells / Serum					
IFN-α	HRV-16		X	yes *[**]*	[39] *[*]*
IFN-α	influenza A		X	yes	[38]
IFN-α (+α2)	HRV-16		X	no	[47]
IFN-β	HRV-16		X	no	[47]
IFN-γ	HRV-16		X	yes	[43]
IFN-λ1	HRV-16		X	yes *[**]*	[39] *[*]*
IFN-λ1	uninfected		X	no	[51]
IFN-λ2/3	uninfected		X	no	[51]
Nasal and Bronchial Lavage / Sputum					
IFN-α2 IFN-α (+α2)	HRV-16		X	no	[30]
	HRV-16		X	yes	[47]
IFN-β	HRV-16		X	yes	[47]
IFN-γ	HRV-16		X	no	[30]
IFN-λ IFN-λ1 IFN-λ2/3	HRV-16		X	yes	[42]
	uninfected	X		no	[50]
	uninfected	X		no	[50]

ND= not detected,

[*] Pediatric Study;

[**] need FcepsilonR1 cross-link to see differences