Viral infections in allergy and immunology: How allergic inflammation influences viral infections and illness

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Viral respiratory tract infections are associated with asthma inception in early life and asthma exacerbations in older children and adults. Although how viruses influence asthma inception is poorly understood, much research has focused on the host response to respiratory viruses and how viruses can promote; or how the host response is affected by subsequent allergen sensitization and exposure. This review focuses on the innate interferon-mediated host response to respiratory viruses and discusses and summarizes the available evidence that this response is impaired or suboptimal. In addition, the ability of respiratory viruses to act in a synergistic or additive manner with T_H2 pathways will be discussed. In this review we argue that these 2 outcomes are likely linked and discuss the available evidence that shows reciprocal negative regulation between innate interferons and T_H2 mediators. With the renewed interest in anti-T_H2 biologics, we propose a rationale for why they are particularly successful in controlling asthma exacerbations and suggest ways in which future clinical studies could be used to find direct evidence for this hypothesis. (J Allergy Clin Immunol 2017;140:909-20.)

Key words: *Virus, allergic inflammation, interferon, asthma, T_H2*

Abbreviations used

ACQ:	Asthma Control Questionnaire
AE:	Asthma exacerbation
AM:	Alveolar macrophage
DC:	Dendritic cell
GWAS:	Genome-wide association study
HBEC:	Primary bronchial epithelial cells
IFNAR:	IFN-α receptor
ILC2:	Type 2 innate lymphoid cell
IRF:	Interferon regulatory factor
ISG:	Interferon-stimulated gene
poly I:C:	Polyinosinic:polycytidylic acid
PRR:	Pattern recognition receptor
RSV:	Respiratory syncytial virus
SOCS:	Suppressor of cytokine signaling
TLR:	Toll-like receptor

Viral infections are associated with asthma exacerbations (AEs) in adults and children.[1] Although the mechanisms behind this association are incompletely understood, recent evidence has shown that viral infection of epithelial cells can produce cytokines, such as ***IL-25*** and ***IL-33***, that interact with allergic inflammation, inducing T_H2 pathways (including both innate and antigen-specific T_H2 cell–related pathways) and resulting in increased T_H2-related inflammation, eosinophilia, and enhanced

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Terms in boldface and italics are defined in the glossary on page 910.

IL-4, ***IL-5***, ***IL-13***, and mucin production.[2,3] Furthermore, cells or tissues from asthmatic patients can respond to infection with a delayed and suboptimal antiviral response exemplified by delayed and deficient production of the innate interferons.[4-6] Although both processes are undoubtedly important in determining disease outcomes, one idea is that these 2 outcomes are linked and that current anti-T_H2 biologics can function not only by reducing harmful T_H2-related inflammation but also by restoring an impaired antiviral response.

This review will examine this hypothesis and discuss the evidence that supports not only impaired interferon production in asthmatic patients but also that impaired interferon production could be caused at least in part by increased T_H2 pathways and allergic inflammation. For simplicity, we will group allergic inflammation and T_H2 pathways together, although we accept that T_H2 cytokines might be made or might function independently of allergen exposure. This review will be limited to the discussion of impaired innate type I (***IFN-α/IFN-β***) and type III (***IFN-λ***s) interferons in asthmatic patients. Some studies have shown a defective or impaired type II ***IFN-γ*** response in cells of asthmatic patients or lower T_H1/T_H2 ratios in atopic asthmatic patients versus control subjects[7]; however, these studies will not be discussed further. Additionally, this review will focus on discussing the role of innate interferons in patients with established

GLOSSARY

CCL5: A chemokine also known as RANTES, it has been shown to be chemotactic for T cells, eosinophils, and basophils and plays an active role in recruiting leukocytes into inflammatory sites. With the help of particular cytokines that are released by T cells, CCL5 also induces the proliferation and activation of certain natural killer cells to form CC chemokine–activated killer (CHAK) cells. It has also been shown to be an HIV-suppressive factor released from $CD8^+$ T cells.

IFN-α: A type of human type I interferon protein that helps regulate the activity of the immune system. IFN-α is produced by leukocytes and has been shown to be mainly involved in the innate immune response against viral infection.

IFN-β: A type of human type I interferon protein produced in large quantities by fibroblasts. IFN-β displays antiviral activity in the innate immune response.

IFN-γ: A type II interferon, IFN-γ is a cytokine required for innate and adaptive immunity against viral, bacterial, and protozoal infections. IFN-γ has been shown to be an important activator of macrophages and inducer of class II major histocompatibility complex molecule expression. IFN-γ is produced predominantly by natural killer (NK) and NK T cells as part of the innate immune response and by CD4 T_H1 and CD8 cytotoxic T-lymphocyte effector T cells once antigen-specific immunity develops.

IFN-λ: This recently classified type III interferon group consists of 3 molecules called IFN-λ1, IFN-λ2, and IFN-λ3 (also called IL-29, IL-28A and IL-28B, respectively). IL-28 (IFN-λ2/3) is a cytokine that comes in 2 isoforms, IL-28A and IL-28B, which play a role in innate immune defense against viruses. IL-28A and IL-28B are highly similar (in amino acid sequence) to IL-29. Both IL-28A and IL-28B have been shown to exhibit antiviral qualities and inhibit tumor cell proliferation while promoting antitumor immune responses. IL-29 is a potent antiviral cytokine through upregulation of MHC class I expression on the cell surface.

IL-4: A cytokine that induces differentiation of naive helper T cells (T_H0) to T_H2 cells. IL-4 subsequently produces additional IL-4 in a positive feedback loop. IL-4 is a ligand for the IL-4 receptor that also binds to IL-13, which contributes to many overlapping functions of IL-4 and IL-13.

IL-5: A major maturation and differentiation cytokine expressed by T_H2 cells and eosinophils in mice and human subjects. IL-5 has been shown to play an instrumental role in eosinophilic inflammation in patients with allergic diseases.

IL-6: A cytokine also known as IFN-β2 is implicated in a wide variety of inflammation-associated disease states. IL-6 has been associated with maturation of B cells and has been shown to act as an endogenous pyrogen capable of inducing fever in patients with autoimmune diseases or infections.

IL-13: A cytokine produced primarily by T_H2 cells that is involved in several stages of B-cell maturation and differentiation and is critical to the pathogenesis of allergen-induced asthma but operates through mechanisms independent of IgE and eosinophils.

IL-25: A proinflammatory cytokine that shares sequence similarity with IL-17 and has been shown to favor the T_H2-type immune response IL-25 activates dendritic cells and innate lymphoid cells (ILC2s).

IL-33: A member of the IL-1 family of cytokines that potently drives production of T_H2-associated cytokines. IL-33 is produced from epithelial cells and activates T_H2 cells and ILC2s.

INTERFERON REGULATORY FACTOR (IRF) 3: A member of the IRF factor family, which plays an important role in the innate immune system's response to viral infection through induction of type I interferons.

MELANOMA DIFFERENTIATION FACTOR 5: A RIG-I–like receptor double-stranded RNA (dsRNA) helicase enzyme that functions as a pattern recognition receptor (recognizing long dsRNA) that is a sensor for viruses.

MYELOID DIFFERENTIATION PRIMARY RESPONSE 88 (MyD88): A universal adapter protein that functions as an essential signal transducer in the IL-1 and Toll-like receptor (TLR) signaling pathways (except TLR3). These pathways regulate activation of numerous proinflammatory genes, including the transcription factor nuclear factor κB.

RETINOIC ACID–INDUCIBLE GENE (RIG) I: A RIG-I–like receptor double-stranded RNA (dsRNA) helicase enzyme that functions as a pattern recognition receptor for short dsRNA and 5′ phosphorylated single-stranded RNA. RIG-I is a sensor for viruses, specifically influenza A, Sendai virus, and flavivirus, resulting in induction of members of the type I interferon family.

SUPPRESSOR OF CYTOKINE SIGNALING 1 (SOCS1): Negative regulators of cytokine signaling that are members of the STAT-induced STAT inhibitor (SSI) family. Expression of this gene has been shown to be induced by a subset of cytokines, including IL-2, IL-3, erythropoietin, CSF2/GM-CSF, type I interferon, and IFN-γ.

SUPPRESSOR OF CYTOKINE SIGNALING 3 (SOCS3): Negative regulator of cytokines that signal through the Janus kinase/signal transducer and activator of transcription pathway. Expression of the *SOCS3* gene is induced by various cytokines, including IL-6, IL-10, and IFN-γ.

TOLL-LIKE RECEPTOR (TLR) 3: A member of the TLR family that plays a fundamental role in pathogen recognition and activation of innate immunity. TLR3 recognizes dsRNA associated with viral infection and induces the activation of interferon regulatory factor 3 and nuclear factor κB.

TOLL-LIKE RECEPTOR (TLR) 7: A TLR that recognizes single-stranded RNA (ssRNA) in endosomes, which is a common feature of viral genomes. TLR7 recognizes ssRNA of viruses, such as HIV and hepatitis C virus, and GU-rich ssRNA.

TOLL-LIKE RECEPTOR (TLR) 8: Similar to TLR7, TLR8 endosomal receptor that recognizes single-stranded RNA (ssRNA) and can recognize ssRNA viruses, such as influenza, Sendai, and Coxsackie B viruses. TLR8 binding to the viral RNA signals MyD88 and leads to activation of the transcription factor nuclear factor κB and an antiviral response. TLR8 also recognizes ssRNA of viruses, such as HIV and HCV.

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