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Review

Interferon at the crossroads of allergy and viral infections

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ABSTRACT

IFN-α/β was first described as a potent inhibitor of viral replication, but it is now appreciated that IFN signaling plays a pleiotropic role in regulating peripheral T cell functions. Recently, IFN-α/β was shown to block human Th2 development by suppressing the transcription factor GATA3. This effect is consistent with the role for IFN-α/β in suppressing allergic inflammatory processes by blocking granulocyte activation and IL-4-mediated B cell isotype switching to IgE. With the consideration of recent studies demonstrating a defect in IFN-α/β secretion in DCs and epithelial cells from individuals with severe atopic diseases, there is an apparent reciprocal negative regulatory loop in atopic individuals, whereby the lack of IFN-α/β secretion by innate cells contributes to the development of allergic Th2 cells. Is it possible to overcome these events by treating with IFN-α/β or by inducing its secretion in vivo? In support of this approach, case studies have documented the therapeutic potential of IFN-α/β in treating steroid-resistant allergic asthma and other atopic diseases. Additionally, individuals with asthma who are infected with HCV and respond to IFN therapy showed a reduction in symptoms and severity of asthma attacks. These findings support a model, whereby allergic and antiviral responses are able to cross-regulate each other, as IgER cross-linking of pDCs prevents IFN-α/β production in response to viral infection. The clinical importance of upper-respiratory viruses in the context of allergic asthma supports the need to understand how these pathways intersect and to identify potential therapeutic targets. *J. Leukoc. Biol.* 98: 185–194; 2015.

Introduction

The antiviral cytokine IFN is one of the oldest characterized cytokines to date. The effects of IFN-α/β were described with regard to plant immunology in 1933 [1], and in 1957, Isaacs and Lindenman [2] described the "interference" caused by this cytokine in a viral infection model and coined the name "interferon". Decades later, it is well appreciated that this cytokine regulates hundreds of genes in almost all cells in the body [3–5]. To date, 3 unique families of IFNs have been characterized. IFN-α/β and IFN-λ are critical for the control of viral infections and regulate the expression of hundreds of ISGs in a STAT2-dependent manner (**Fig. 1**). Classic activation of STAT2 leads to the regulation of ISGs by binding to ISREs within the promoters of these genes [6]. In contrast, IFN-γ is important for bacterial and viral infections and acts primarily through STAT1 activation (Fig. 1).

The antiviral cytokines IFN-α/β and IFN-λ bind distinct receptors but induce similar changes to the cellular transcriptome profile, albeit with varied kinetics and intensity [7]. The IFN-α/β receptor is expressed on most nucleated cells, including the cells that play a deleterious role in driving allergic asthma. The IFN-α/β receptor has been shown to be expressed on human granulocytes, B cells, $CD4^+$ and $CD8^+$ T cells, NKT cells, APCs, and epithelial cells, to name a few. Many different immune cells have been reported to produce IFN-α/β, including conventional DCs and pDCs, macrophages and monocytes, and epithelial cells; however, the majority of IFN-α/β is produced by pDCs in response to viral infection [8]. In contrast, IFN-λ is produced primarily by stromal and epithelial cells, and the expression of the IFN-λ receptor on immune cells is controversial. Similar to IFN-α/β, IFN-λ-triggered signaling regulates canonical ISGs [9]. However, unlike IFN-α/β, IFN-λ receptor expression is limited to a select subset of cells [10]. Epithelial cells, DCs, macrophages, and some nonimmune cells, including hepatocytes, are able to respond to IFN-λ. It is unclear whether all subsets of T cells are able to respond to IFN-λ; however, there is evidence that naïve $CD4^+$ T cells can be regulated by this cytokine under specific conditions [10, 11].

In contrast to IFN-α/β and IFN-λ, IFN-γ drives the regulation of genes through GAS elements that are bound by STAT1 homodimers (Fig. 1) [12]. Most immune cells express the IFN-γ receptor, including T cells, B cells, and APCs. Similar to the production of IFN-α/β and IFN-λ, unique subsets of cells produce IFN-γ, including $CD4^+$ and $CD8^+$ T cells, ILC1s, NK and

Abbreviations: CNS-1 = conserved noncoding sequence, DC = conventional dendritic cell, GAS = γ–activated sequence, H3 = histone 3, H3K27me3 = histone 3 lysine 27 trimethylation, HCV = hepatitis C virus, IFN-α/β = type I IFN, IFN-γ = type II IFN, IFN-λ = type III IFN, ILC1/2 = innate lymphoid type 1/2 cell, IRF = IFN regulatory factor, ISG = IFN-sensitive gene, ISRE = IFN-stimulated response element, pDC = plasmacytoid dendritic cell, SOCS1 = suppressor of cytokine signaling 1, TSLP = thymic stromal lymphoprotein

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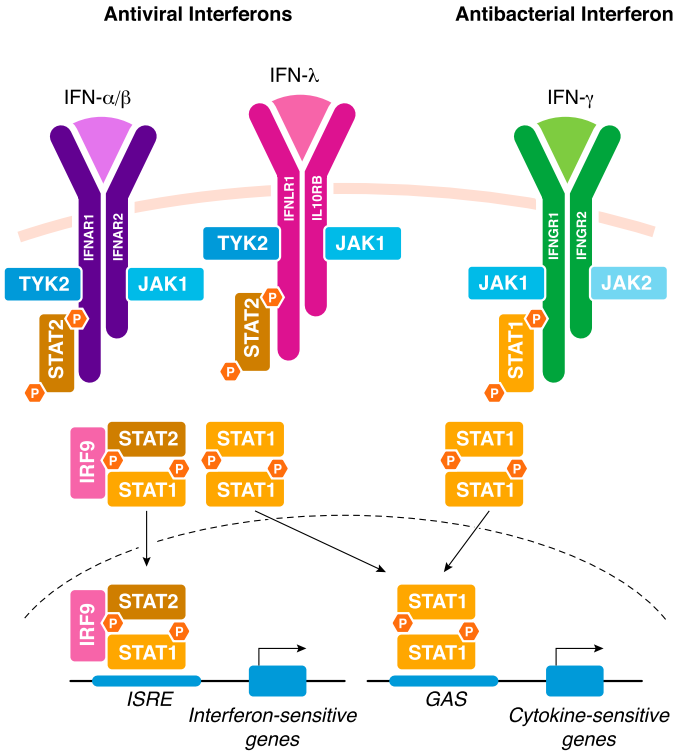

Figure 1. The classic IFN signaling pathways. IFN-α/β and IFN-λ signaling induces the activation of STAT2, leading to the formation of the INF-stimulated gene factor 3, which consists of STAT2, STAT1, and IRF9. This complex binds to the promoters ISGs that contain the ISRE DNA motif. IFN-α/β and IFN-λ signaling can also induce the formation of STAT1 homodimers, binding the canonical GAS elements, which promotes of hundreds of cytokine-sensitive genes. IFN-γ signaling predominantly signals through STAT1 homodimer activation and does not activate STAT2. TYK2, Tyrosine kinase 2; IFNAR, IFN-α/β receptor; IFNLR, IFN-λ receptor; IFNGR, IFN-γ receptor; p, tyrosine phosphorylation.

NKT cells, neutrophils, and most APCs [12]. Although IFN-γ and IL-4 seem to antagonize each other's affects reciprocally, there seems to be no direct role for IFN-γ in negatively regulating the Th2-dominant response in the context of atopic disease in humans or mice [13, 14]. However, there does seem to be a defect of IFN-γ production, similar to the other IFNs, in allergic asthmatics and other atopic diseases in response to viral infection [15, 16].

ALLERGIC SENSITIZATION IN THE LUNG

Atopic diseases are initiated as an antigen-specific response to otherwise innocuous substances, including cat dander, ragweed, and house dust mite. Allergic asthma affects >300 million individuals worldwide, with 250,000 deaths occurring annually. In 2009, an estimated 10% of children and 8% of adults in the United States were diagnosed with asthma [17]. Although asthma is a heterogeneous disease with a variety of clinical presentations, 70% of individuals suffering from asthma have an allergic-mediated disease, in which symptoms are triggered by allergens [18]. The hallmark cellular mechanism that drives allergic diseases is an increase in circulating IgE antibodies and the development of an allergen-specific Th2 response, characterized by IL-4, IL-5, and IL-13 production in response to allergen-mediated T cell activation.

Research over the past 25 years has led to a greater understanding of how the immune system responds to allergen. Epithelial cells lining the upper airways are the first cells to have direct contact with allergen and in response to allergic stimulation, produce TSLP, IL-33, and IL-25. TSLP suppresses IL-12 production by DCs [19], and IL-33 has been shown to be necessary for the secretion of IL-13 from mast cells [20]. IL-25 directly induces the production of collagen from fibroblasts and recruits endothelial progenitor cells to the lung, resulting in airway remodeling [21]. In response to these cytokines, as well as direct uptake of allergen, innate cells further enhance the inflammatory environment. ILC2s become activated in response to IL-25, IL-33, and TSLP, which drive subsequent production of IL-5, IL-9, IL-13, and amphiregulin, a member of the epidermal growth factory family of proteins. IL-5 recruits and activates eosinophils, driving degranulation of preformed proteases, lipid mediators, and further production of cytokines. IL-13 is directly responsible for increased mucus production in response to allergen by driving goblet cell hyperplasia and increased airway hyper-responsiveness [22]. Furthermore, work by Wills-Karp and colleagues [23] demonstrated that IL-13 induces a specific response in the lung that is unique from that of IL-4, despite similar signaling pathways in response to receptor ligation. IL-13 regulates a unique set of genes in epithelial cells that drive allergen-mediated inflammation in the murine system. Several allergen-induced genes were responsive to IL-13, but not IL-4, including eosinophil-specific chemokine Ccl11 and goblet-specific gene resistin-like β, both of which play a role in the Th2-mediated response to allergen and helminth infection [23]. This demonstrates that IL-13 signaling drives a specific gene response that results in enhanced Th2-dominated inflammation and alters the gene expression of epithelial cells, leading to increased mucus production.

Allergen also directly activates cells by binding allergen-specific IgE antibodies bound to the FcεRs expressed on granulocytes, monocytes, macrophages, DCs, platelets, and B cells. The high-affinity FcεR (FcεRI) is expressed as a tetramer (αβγ2) on mast cells, basophils, and DCs or at lower levels as a trimer (αγ2) on other APCs. The low-affinity receptor, FcεRII (CD23), is expressed on B cells, platelets, and APCs [24]. In different cell types, allergen-induced IgεR cross-linking leads to cytokine production, degranulation of preformed molecules, and the production of lipid mediators, including PGs and leukotrienes [25]. Mast cells and basophils contain preformed granules that release histamine, proteases (tryptase, chymase, and heparin), and lipid mediators (PGD2 and leukotriene B4, C4, D4, and E4) [26]. IgεR cross-linking leads to immediate degranulation, releasing the contents into the surrounding area, which increases vascular permeability, enhances mucus secretion, and induces the contraction of smooth muscle in the airways [27]. This pathway is the cause of the immediate symptoms seen in response to allergen; however, the activation of the adaptive immune response is what leads to permanent dysregulation and chronic Th2 bias. APCs, including conventional DCs and pDCs, present processed allergen in the context of MHC class II to naïve T cells in the lymph nodes and spleen. This T cell

activation, in the presence of IL-4, leads to Th2 commitment, which is driven by the master transcription factor, GATA3 [28, 29]. Once activated, Th2 cells will migrate to the site of allergen challenge and secrete IL-4, IL-5, and IL-13, reinforcing the Th2 phenotype and enhance inflammation. $CD4^+$ T cells also mediate IgE class-switching and B cell survival. In response to allergen and IL-4, B cells produce IgE antibodies specific to the insulting allergen. The activation of B cells is a critical juncture in developing chronic atopic disease. In addition to allergen-specific, IgE-sensitizing granulocytes and APCs to allergen, circulating IgE is correlated directly with the expression of high-affinity FcεR present on mast cells, basophils, and DCs [30]. Thus, the more IgE present, the more FcεRI is expressed, and the further the allergic phenotype is reinforced. In addition to the Th2 response, Th9 cells have been shown to play a critical role in driving allergic asthma and other atopic diseases. Kaplan and colleagues demonstrated that mice deficient in PU.1, the transcription factor critical in driving Th9 commitment, had attenuated allergic inflammation in the lungs in response to allergic challenge, despite having intact Th2 development and function [31]. IL-9 activates mast cells and induces mucus production by epithelial cells in an IL-13-dependent manner, further reinforcing the allergic environment [32, 33]. Together, these different cell types reinforce the atopic environment and promote a dysregulated immune response.

The development of atopic diseases is a relatively new phenomenon that is correlated with industrialization and enhanced sanitary conditions. Th2- and Th9-mediated inflammation is important for the immune response against extracellular parasites, such as helminth infections, and individuals in developing countries that are exposed to extracellular parasites seem to be less likely to develop atopic disease [34]. The hygiene hypothesis suggests that the lack of exposure to infection contributes to the development of atopic disease [35]. A recent study provided compelling evidence to support the hygiene hypothesis. In 560 children from different inner-city environments, those exposed to cockroach, mouse, and cat allergens and specific bacteria of the *Firmicutes* and *Bacteroidetes* taxa within the first year of life were less likely to develop wheezing and asthma compared with children who were sensitized to these allergens over the first 3 yr of life and lacked exposure to these bacterial taxa [36]. This study suggests that the first months of life are critical in tolerizing the immune system to allergens. How this mechanism occurs and what other factors (intrinsic or environmental) contribute remain to be determined. However, the question remains: how do we induce permanent tolerance in those that are genetically predisposed to develop atopy and in those that struggle to control chronic Th2-mediated inflammation in the lung?

RECIPROCAL ANTAGONISM BETWEEN THE ALLERGIC AND ANTIVIRAL RESPONSES

The lungs are one of several mucosal barriers that are in constant interaction with the environment and the microorganisms contained within it. Viral pathogens, such as rhinovirus, have evolved to bind epithelial cell-surface markers to infect these cells directly. Pathogen invasion drives the activation of innate-immune pathways, leading to the secretion of cytokines that mobilize the immune response. Epithelial cells respond to pathogens by producing many antimicrobial peptides, including defensins, reactive oxygen species, and cytokines, such as TSLP, all of which directly impact clearance of the pathogen [37]. Asthmatic individuals seem to have a dysfunctional response to viral infections, including rhinoviruses [38–40]. For example, bronchial epithelial cells isolated from asthmatics stimulated with dsRNA produced more TSLP and less IFN-β compared with bronchial epithelial cells from healthy controls [41]. This suggests that epithelial cells from asthmatic individuals are predisposed to the allergic response, and this pathway appears to over-ride the antiviral response. Furthermore, rhinovirus enhances TSLP production in nonallergic cells as well, and cotreatment with IL-4 or IL-13 enhances TSLP gene expression [42]. Thus, the Th2-dominant environment that exists when an asthmatic individual becomes infected with a respiratory viral infection appears to alter the nature of the epithelial cell response to infection. It is important to note that asthmatic individuals clear respiratory viral infections at a rate similar to nonasthmatic controls, but these respiratory infections are the leading cause of asthma exacerbations in children and adults [43]. Eighty percent of asthma exacerbations are associated with viral respiratory infection, and human rhinovirus and respiratory syncytial virus are the most commonly associated viral infections found to induce asthma exacerbations [43]. Interestingly, human rhinovirus isolates are more commonly found in asthmatic individuals than healthy individuals, suggesting that allergic asthma may be linked to a possible defect in the ability to clear rhinovirus infection completely, or atopic individuals are more susceptible to respiratory viral infections [44, 45].

Rhinovirus infection seems to correlate with enhanced viral- and allergic-mediated disease in asthmatics, but how this primary viral infection modifies the immune response to a concurrent bacterial infection requires further analysis. It is well documented that influenza infection leads to a greater susceptibility to respiratory Pneumococcus infection [46, 47]. Furthermore, a positive correlation exists between rhinovirus infection and concurrent bacterial infections in healthy individuals, including *Haemophilus influenzae* and *Staphylococcus aureus* [48]. A recent study from Gern and colleagues [49] observed that children with rhinovirus infection were more often infected with concurrent respiratory bacterial infection compared with rhinovirus-negative children. However, allergic asthma had no effect on the risk of becoming infected with a secondary bacterial infection, suggesting that primary rhinovirus infection, but not atopic disease, plays a role in concurrent pulmonary infections [49]. Despite no apparent link between allergic asthma and susceptibility to secondary bacterial infection, *Streptococcus pneumoniae* and *Moraxella catarrhalis* infection seemed to contribute to the severity of respiratory illness and asthma exacerbations [49]. It is hypothesized that rhinovirus-induced epithelial damage could play a role in concurrent bacterial infection, and some pathogenic bacteria have been shown to bind to extracellular matrix proteins that are only available when the basement membrane has become compromised [48, 50]. Furthermore, different

respiratory viral infections have altered the immune response to bacterial infections. For example, mice infected with influenza infection produced less pulmonary IFN-γ in response to secondary pneumococcal infection [51]. Furthermore, influenza-mediated IFN-α/β production also suppress neutrophil recruitment during subsequent bacterial infection [52]. These observations correlate with a study in which individuals with rhinovirus infection, who were treated with intranasal rIFN-α(2b), required antibiotic treatment more often for "presumed secondary infections" than individuals that received a placebo treatment; however, the identification of these secondary infections was not determined [53]. Based on these studies, it seems that primary respiratory viral infection predisposes individuals to develop concurrent bacterial infections as a result of dampened antibacterial responses in the lung. Furthermore, the available data show no positive correlation between allergic asthma and the development of secondary bacterial infections.

It is well documented that TLR signaling in pDCs and certain conventional DCs induces the expression of IFN-α/β and IFN-λ [54], and this mechanism also occurs in epithelial cells, which have been shown to produce IFN-λ [55]. How allergic diseases alter the antiviral response is not well defined. However, reports have revealed a role for IgE cross-linking in dampening the antiviral response (Fig. 1). Gill et al. [56] demonstrated that there are intrinsic differences between pDCs isolated from healthy versus atopic individuals in response to viral infection. When pDCs from nonatopic adults were cultured in vitro with an anti-IgER-cross-linking antibody, the cells produced less IFN-α in response to human influenza infection compared with isotype-treated cells. Furthermore, pDCs from asthmatic adults produced less IFN-α in response to in vitro human influenza infection compared with pDCs isolated from nonatopic adults. Finally, there is a negative correlation between serum IgE levels and the amount of IFN-α that can be produced in response to human influenza infection in vitro [56]. This observation is present in pediatric cases of allergic asthma as well. Not only did pDCs from asthmatic children have higher expression of the IgER than healthy controls, but also, IgER cross-linking resulted in a substantial reduction in IFN-α and IFN-λ in response to in vitro rhinovirus infection [57]. These reports demonstrate that IgER activation on pDCs is dominant over the production of IFN-α/β and IFN-λ in response to viral challenge. In addition to pDCs, epithelial cells from asthmatics are impaired in their ability to produce IFNs. Studies have demonstrated that bronchial lavage cells from asthmatic children and adults produce less IFN-λ and IFN-β compared with nonasthmatic cells when infected with rhinovirus in vitro [58, 59]. This phenomenon has been validated by use of in vivo models of human rhinovirus infection as well. Contoli et al. [60] have shown that remarkably, primary human bronchial epithelial cells from asthmatics produced less IFN-λ compared with healthy controls in response to an experimental rhinovirus challenge, which correlated with an increase in virus-induced asthma exacerbations. However, there are other studies that demonstrate that bronchial epithelial cells from asthmatics with well-controlled disease produce equivalent amounts of IFNL2 and IFNB1 gene expression compared with cells isolated from healthy controls [61]. Lopez-Souza et al. [62] have reported this observation in nasal and bronchial epithelial cells; asthmatic and healthy cell samples produced similar IFN-β1 in response to rhinovirus infection. Furthermore, Sykes et al. [58] observed that although differences in IFN-β, IFN-α, and IFN-α2 production could be detected in bronchial lavage cells infected with rhinovirus, there was no difference in the production of these cytokines by PBMCs from asthmatic individuals versus healthy controls. Based on the donor information provided by these studies, it seems that there is similar expression of IFN when the atopic disease is mild and easily controlled. Taken together, these studies demonstrate that the allergic and antiviral pathways are engaged in reciprocal antagonism, especially in difficult-to-treat atopic asthma.

Exactly how engagement of the IgER and other exogenous cues on pDCs suppresses IFN-α production remains unclear. One report demonstrated that although antiviral signaling proteins, such as TLR3, were expressed by bronchial epithelial cells isolated from asthmatic patients, there was a defect in signaling when cells were challenged with rhinovirus in vitro [63]. Sykes et al. [58] reported no difference in IRF7 expression by bronchoalveolar lavage cells from asthmatic and healthy individuals in response to rhinovirus infection, and Roponen et al. [64] observed that TLR7 signaling in PBMCs was impaired from asthmatic adolescents compared with healthy controls, although the overall expression of TLR7 was comparable in both populations. However, other studies demonstrated reduced expression of TLR7, IRF7, and STAT1 in rhinovirus-mediated activation of pDCs. Furthermore, the blocking of IFN-α/β signaling in healthy cells reduced the expression of these genes in PBMCs from healthy individuals [65]. These conflicting reports could correlate with the observation that individuals with well-controlled asthma do not have a defect in the production of IFN-α/β or IFN-λ, whereas more severe cases do. Recently, the SOCS1 protein was shown to play a role in mediating reduced production of IFN in severe asthmatics' response to rhinovirus infection [66]. Enhanced SOCS1 protein expression was present in bronchial epithelial specimens from mild-to-moderate asthmatic individuals compared with that of healthy controls. Furthermore, bronchial epithelial cells from severe asthma children expressed more SOCS1 at baseline, and the expression of SOCS1 was inversely correlated with the expression of IFN-λ from these cells [66]. Together, these studies suggest that allergen-mediated signaling antagonizes IFN production through multiple mechanisms in individuals with difficult-to-treat atopic disease.

In addition to IgER cross-linking, other cues are likely enhancing this negative regulatory pathway. For example, pDCs are sensitive to histamine, which has also been shown to suppress CpG-mediated IFN-α production [67]. Furthermore, several studies have demonstrated a role for C-type lectin receptors in mediating the DC response to allergens [68]. The C-type lectin receptor, Dectin-2, was shown to bind glycan from house dust mite and *Aspergillus fumigatus*, inducing the expression of cysteinyl leukotrienes from murine DCs [69], which induce bronchial smooth-muscle constriction and vascular permeability [70]. Furthermore, the C-type lectin receptor blood DC antigen 2 has been shown to antagonize the production of IFN-α/β by pDCs in response to receptor ligation [71]. The downstream effects of C-type lectin receptors have also been demonstrated,

and peanut allergen, but not deglycosylated peanut allergen, was shown to enhance DC expression of MHC and costimulatory molecules and enhanced the ability to drive Th2 development [72]. It is likely that multiple signals, including cytokines, such as IL-33 and TSLP, as well as IgE- and C-type lectin-receptor activation, contribute to the defect in IFN-α/β and IFN-λ production and induce an environment more amenable to Th2 cell development. Further studies are needed to understand how this cross-talk occurs and whether the addition of endogenous IFN-α/β or IFN-λ can over-ride the allergic response. If IFN-α/β treatment can restore the defect in antiviral IFN production in severe atopic individuals, and then perhaps the Th2-dominant environment can be overcome in a manner that induces long-term tolerance.

INTERFERONS AND THE REGULATION OF TH2-MEDIATED DISEASE

IFN-α/β has been demonstrated to regulate negatively several aspects of the allergic response in humans (**Fig. 2**). Recent studies have demonstrated that IFN-α/β negatively regulates Th2 function. Pritchard et al. [73] determined that depletion of pDCs from nonatopic human PBMC cultures enhanced Th2 cytokine production in response to in vitro human rhinovirus challenge. Schandené et al. [74] showed that IFN-α treatment suppresses IL-5 and enhances IL-10 production from human bulk $CD4^+$ T cells. Furthermore, Shibuya and Hirohata [75] observed that IFN-α treatment suppressed IL-5 and IL-13 production and enhanced IL-4 production in bulk $CD4^+$ T cells. Interestingly,

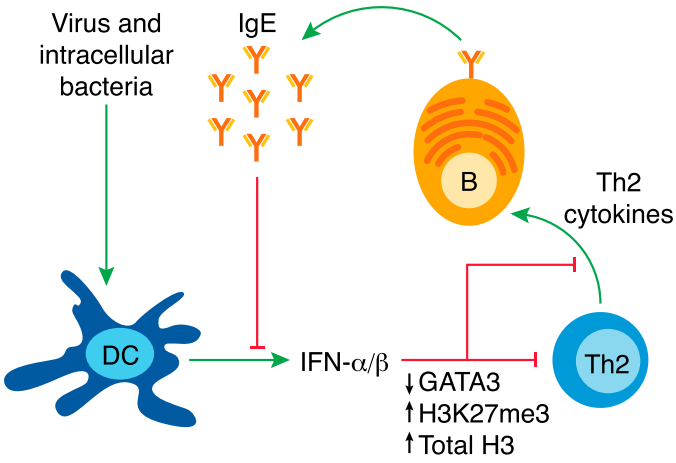

Figure 2. Reciprocal regulation of allergic stimulation and IFN-α/β-mediated Th2 suppression. IFN-α/β produced by activated pDCs potently suppresses Th2 development and function. IgER cross-linking potently suppresses IFN-α/β production, thereby preventing downstream regulation of Th2 development and B cell (B) class-switching. IFN-α/β signaling destabilizes Th2 development through the suppression of GATA3 expression and over-rides IL-4-mediated epigenetic modifications of the GATA3 gene locus, making it inaccessible to transcription factor-mediated expression. IFN-α/β therapy would reduce the Th2 bias and IgE expression by suppressing these specific cell types, and the pairing of IFN-α/β therapy with Omalizumab could be sufficient to induce a more permanent tolerance in severe allergic asthma patients.

murine Th2 cells do not respond to IFN-α/β in the same manner, and early studies by Murphy and colleagues [76] demonstrated that IFN-α treatment alone had no effect on IL-4 production by murine $CD4^+$ T cells. Our recent study [77] demonstrated that IFN-α/β failed to block IL-4-mediated Th2 development in murine $CD4^+$ T cells. Furthermore, there are 2 reports demonstrating that IFN-λ may also play a role in negatively regulating the Th2 phenotype. IFN-λ treatment of human $CD4^+$ T cells markedly suppressed IL-13 expression in the presence of mitogen or DC-induced stimulation, and a follow-up study from the same group demonstrated that IFN-λ treatment can suppress naïve $CD4^+$ T cell production of IL-13 and GATA3 [11, 78]. Finally, studies from our group demonstrated that human Th2 development is disrupted by IFN-α treatment, even when IL-4 is present. IFN-α, but not IFN-γ, suppressed GATA3 mRNA and protein expression, demonstrating that IFN-α signaling disrupts the feed-forward, autoregulatory loop induced by GATA3 that stabilizes Th2 development (Fig. 2) [77]. In a follow-up study, we uncovered the molecular mechanism for destabilizing the Th2 phenotype in primary human $CD4^+$ T cells. IFN-α suppressed IL-4-mediated GATA3 expression as a function of cell division, suggesting that this cytokine is able to over-ride the epigenetic modifications induced by IL-4 signaling. Furthermore, IFN-α enhanced the content of the nucleosomal modification, H3K27me3, and enhanced overall nucleosome content at an upstream CNS-1 within the GATA3 promoter (Fig. 2). As a result, IFN-α reduced DNase hypersensitivity at the CNS-1 site, as well as GATA3 binding to this region, even in the presence of additional IL-4 [79]. These studies demonstrate that IFN-α signaling prevents GATA3 from enhancing its own expression, thus destabilizing Th2 lineage commitment. Other groups have demonstrated that IFN-α/β negatively regulates other cell types involved in the allergic response as well, which suggests that the use of this cytokine as a therapeutic tool to treat steroid-resistant atopic diseases has implications for mediating the dysregulated response as a whole. Capron and colleagues [80] demonstrated that human eosinophils express the IFN-α/β receptor, and in vitro treatment of these cells with IFN-α inhibited the release of granule proteins, including neurotoxin and eosinophil cationic protein. Furthermore, IFN-α signaling reduced the overall production of IL-5, a cytokine critical for the inflammatory effects induced by granulocytes. Chen et al. [81] showed that IFN-α treatment of human basophils prevents IL-3-mediated priming, resulting in reduced IL-4 and IL-13 production. The study also showed that IFN-γ had no effect on negatively regulating these cells, demonstrating that this pathway is induced specifically by IFN-α/β [81]. In addition to regulating Th2 cells and granulocytes, IFN-α has been shown to regulate IL-4-mediated B cell isotype switching to IgE in mouse and human (Fig. 2) [82, 83]. Finally, the development and activation of human and murine Th17 cells are also negatively regulated by IFN-α/β [84, 85]. Taken together, these studies demonstrate that IFN-α/β is able to regulate different cell fates within the adaptive immune response, including Th2 and Th17 cells, as well as many innate-immune cells that have critical roles in driving the immediate inflammatory response to allergen.

The data described above have many implications for the use of IFN-α/β to treat severe atopic disease. Allergic diseases are

predominantly caused by a Th2 bias and enhanced IgE expression; however, there is also a subset of allergic diseases that is mediated by the Th17 response and neutrophil activation. It is intriguing that the antiviral cytokine IFN-α/β is a potent inhibitor of the Th2 and Th17 pathways. How this regulatory mechanism evolved in humans is unclear, but perhaps viral infections represent a more serious threat than helminth infections in some circumstances, and the suppression of the Th2 or Th17 responses to combat viral infection favors survival. Regardless of the evolutionary advantage to this pathway, the use of IFN-α/β as a therapeutic target could benefit many individuals suffering from atopic diseases whose symptoms are not controlled by conventional therapies.

IFN-α/β AS A THERAPEUTIC TOOL TO TREAT ATOPIC DISEASES

IFN-α/β is widely used to treat a variety of severe chronic diseases, including multiple sclerosis, HCV infection, and certain cancers. In cases of HCV and multiple sclerosis, some subjects respond favorably to IFN therapy, whereas others do not, and the exact mechanism for this variability is not well understood. Regardless, the impact of these diseases has been reduced greatly by IFN-α/β therapy, which remains a viable treatment regardless of the well-characterized side-effects.

The use of IFN-α/β therapy to treat atopic diseases has only been explored recently through clinical case studies or by retrospective analyses of prior clinical trials, and representative examples can be found (see Table 1). Schmitz and colleagues [86] documented that the use of low-dose IFN-α rapidly improved lung function and cellular responses, including an increased Th1 cell population and enhanced expression of IL-10 by PBMCs. In the same study, the use of prednisone to control disease symptoms in all participants was reduced significantly, 5–10 mo after IFN-α therapy began. Within weeks of receiving therapy, all patients showed an increase in lung function and reported greater physical activity [86]. Another case study demonstrated that the use of IFN-α injections almost abolished daily asthma attacks in a small group of severe glucocorticoid-dependent asthmatics [87]. This observational case study also reported a ≥60% reduction in the daily use of short-acting β2 agonists and reduced emergency room visits/yr by at least 70% in all participants [87]. Other case studies have reported similar results, and all have commented on the side-effects that exist [88]. However, in the majority of patients in all of the documented case studies, most of the side-effects were transient and only occurred at the onset of therapy. However, very few studies have reported on patients receiving IFN-α/β therapy after 2 yr of therapy, and long-term follow-up will be critical to determine whether the benefits of IFN-α/β therapy outweigh the side-effects of this cytokine therapy (**Table 1**). The severity of atopic symptoms should determine whether IFN-α/β therapy is an option; if conventional therapies fail to relieve symptoms, and hospitalization is common, then the use of IFN-α/β may be the best option.

There are a handful of reports in HCV patients, demonstrating that IFN-α/β can mitigate allergic symptoms in a subset of asthma patients during treatment for the chronic viral infection. One case study showed that a patient's adult-onset asthma was cured, even after cessation of IFN-α/β therapy [98]. Another study demonstrated that individuals with HCV infection that responded to IFN-α/β therapy had reduced levels of IL-33 in their serum [99]. Other reports are not as clear; a preliminary study in 2003 demonstrated that IFN-α responders, treated for HCV infection, showed control of asthmatic symptoms when their conventional asthma therapies failed at the onset of IFN-α/β therapy [92]. How a persistent viral infection alters the immune response in an atopic individual remains unclear; however, there does seem to be a correlation between IFN-α responders and the suppression of asthmatic symptoms. Controlled clinical trials are needed to determine the efficacy of IFN-α/β as a treatment for severe allergic asthma and other chronic atopic diseases. To date, the only published randomized trial with IFN-β in allergic asthma patients showed promising results [97]. The study enrolled 147 asthmatics who use inhaled corticosteroids to control their symptoms and who had a history of virus-induced exacerbations. The participants were given inhaled IFN-β (n = 72) or placebo (n = 75) within 24 h of developing symptoms from influenza or rhinovirus infection. IFN-β did not significantly reduce the endpoint of viral infection; however, individuals with severe asthma receiving IFN-β treatment had enhanced morning peak-expiratory flow recovery and a reduced need for additional therapy to control symptoms during the viral infection [97]. Additionally, in smaller studies within the clinical trial, IFN-β treatment led to a reduction in virally induced moderate asthma exacerbations, and patients used their rescue inhalers less on days 5 and 6 of the infection compared with placebo controls [97]. The use of IFN-β in this clinical trial to control virus-induced exacerbations provides evidence that this cytokine could be useful in specific atopic individuals, and further studies regarding the efficacy of this treatment are urgently needed. Furthermore, how this treatment could be paired with other biologics, such as Omalizumab, should be defined in allergic asthma. Omalizumab binds serum IgE, leading to a substantial reduction in eosinophils and Th2 cells, and reduces the number of exacerbations and hospitalizations in adults and children with allergic asthma [100]. As IgER cross-linking on pDCs reduces the amount of IFN-α made in response to viral infection, it is plausible that Omalizumab therapy would enhance virus-induced IFN-α production by pDCs from asthmatic patients (Fig. 2). It is possible that pairing Omalizumab with IFN-α/β therapy could regulate the immune response to the insulting allergen, shifting the balance away from the Th2-dominant response.

CONCLUDING REMARKS

The existence of a cross-regulatory mechanism between the antiviral and allergic arms of the immune system is evident based on the in vitro and in vivo human studies described in this review. Atopic diseases are an important health concern, and many of the current therapies only relieve the disease symptoms but do not target the underlying molecular dysfunction. Furthermore, a handful of studies demonstrates that steroid-based therapies may actually contribute to a Th2-dominant phenotype [101—103]. The use of steroid-based therapies during

TABLE 1. Reported use of IFN-α/β therapy to treat atopic diseases

No. Study participants, disease notes	Disease details, study type	IFN type/dose	Outcome	Side-effects	Ref.
1, Refractory to conventional therapy	Hypereosinophilic syndrome, case study	IFN-α(2b) 4e6 IU/d; reduced to 2e6 IU/mo after ~6 mo	Discontinued prednisone use, reduced eosinophil counts	Malaise and fever controlled with acetaminophen	[89]
6, 5/6 Refractory to conventional therapy	Idiopathic hypereosinophilic syndrome, phase I study	IFN-α(2b), daily s.c. injection; 1-8e6 IU/d at least 9 mo; dose was unique to each individual	100% Patients tapered/discontinued prednisone; reduced blood eosinophil counts and mean serum level of eosinophil MBP	Thrombocytopenia at higher doses, nausea, constitutional problems	[90]
4, Refractory to conventional therapy	Churg-Strauss syndrome with cardiac involvement, case study	IFN-α(2b) and IFN-α(2a), s.c. injection 3-63e6 IU/wk, varied doses depending on patient	Reduced eosinophil counts in a dose-dependent manner in 3/4 patients; 1/4 patients well-controlled disease not necessarily a result of IFN therapy	None provided, poor tolerance of IFN-α(2b) in 50% patients, switched to IFN-α(2a)	[91]
1, Uncontrolled symptoms	Corticosteroid-resistant asthma, case study	7.5e6 IU/d for 2 wk, reduced to 6e6 IU/d for 6 mo, then 3e6 IU until study ended 9 mo later	Enhanced FEV1 at onset of IFN therapy; reduced prednisone use, eosinophil counts, and IL-5 production from PBMCs stimulated in vitro	Headache and vomiting; resolved at lowest dose	[88]
40, HCV infection	HCV infection with asthma, prospective observational study	75% HCV+ patients received 6e6 IU 3×/wk IFN-α by i.m. injection for 6 mo	11/30 patients were IFN responders; of these, FEV1 enhanced and HCV RNA absent 1 yr post-therapy	None reported	[92]
16, Uncontrolled symptoms	Persistent asthma, case study	9 mg IFN-α-con s.c. 3×/wk for 1 yr	50% Dropout rate as a result of side-effects/cost/noncompliance; 50% of individuals had improved lung function and FEV1 scores, reduced use of rescue medication, corticosteroid use, and ER visits	Most side-effects transient; decreased within 3-4 wk, 2 individuals developed autoimmune thyroiditis	[87]
10	Corticosteroid-resistant asthma; 43% with Churg-Strauss syndrome, case study	3e6 IU/d IFN-α(2a) for at least 5 mo	Enhanced FEV1 and reduced need for corticosteroid therapy; no change in IL-5 or IL-13 production in vitro; enhanced IFN-γ and IL-10 production 2-4 wk post-IFN therapy onset	100% Reported flu-like symptoms; 50% had headache 2-4 wk after start of therapy; 33% reported flu-like symptoms, and headaches persisted 5-10 mo after start of therapy; 20% showed liver toxicity	[86]
3, Glucocorticoid-dependent asthma	Severe glucocorticoid-dependent asthma, case study	IFN-α-con up to 36 mo, each dose patient dependent; 9 μg s.c. 3×/wk	Reduced blood eosinophil counts, ER visits/mo, daily exacerbations; tapered/discontinued corticosteroid use	Headaches, dizziness, fever, lethargy; subsided 2-4 wk after start of therapy	[93]

(*continued on next page*)

TABLE 1. (*continued*)

No. Study participants, disease notes	Disease details, study type	IFN type/dose	Outcome	Side-effects	Ref.
7, Refractory to conventional therapy	Churg-Strauss syndrome, phase II study	IFN-α(2b) 3e6 IU/3×/wk s.c. injection; reduced to 1e6 IU/injection when side-effects occurred	100% Patients entered remission after 3 mo of treatment with tapered steroid use; 2/7 patients still reported asthmatic exacerbations post-therapy	Transient leukopenia and constitutional problems during treatment; leukoencephalopathy in 1/7 patients at long-term follow-up	[94]
6	Idiopathic hypereosinophilic syndrome, case study	IFN-α-con, tapered doses over time; varied doses, most reduced to reduce side-effects	Reduced blood eosinophil counts in 100% patients	Grave's disease, neutropenia, hair loss, lymphocytopenia, and an increase in liver function enzymes	[95]
3	Churg-Strauss syndrome, case study	IFN-α(2b) 9e6 IU/wk up to 131 mo; 2/3 patients relapsed, yet therapy worked postrelapse	Disease remission in 100% cases, even in individuals in which therapy was discontinued; tapered/discontinued prednisone	IFN-induced neuropathy, autoimmune hepatitis, progressive myelosuppression in different patients after at least 4 yr of therapy	[96]
147, With use of inhaled corticosteroids; ClinicalTrials.gov: NCT01126177	History of infection-induced exacerbations, randomized, double-blind, placebo-controlled study	Nebulized IFN-β (6e6 IU) given 1×/d for 14 d, initiated within 24 h of cold/influenza symptoms onset	No significant effect on the endpoint of viral infection between therapy and placebo; enhanced morning FEV1 and reduced need for additional treatment in severe asthmatics	Cardiac disorders reported for 16.5% in the therapy group (but not in placebo); transient that lasted <2 d	[97]

ER, emergency room; FEV1, forced expiratory volume in 1 s; MBP, major basic protein.

virus-induced asthma exacerbations also seems counterintuitive because of the broad-spectrum, anti-inflammatory effects of these therapies, which might contribute to an altered immune response to viral infections in asthmatics. The use of IFN-α/β to treat chronic allergic diseases may be a viable way to induce permanent tolerance and reduce the overall response to allergic stimulation. Future studies will need to demonstrate how permanent the effects of IFN-α/β are and whether continuous therapy is necessary to maintain allergic tolerance. IFN-α/β treatment to compensate for the lack of production from pDCs as a result of IgER cross-linking could have significant effects on the feed-forward loop of the Th2 phenotype (Fig. 2). Furthermore, the pairing of IFN-α/β treatment with allergen-specific immunotherapy might also be a viable option to induce permanent tolerance in an allergen-specific manner.

AUTHORSHIP

Both authors wrote and edited the manuscript.

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DISCLOSURES

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