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IFN- λ and IgE-mediated allergic disease: a potential future role?



Reduced early microbial exposure has become a leading candidate to explain the rise in allergic disease, and research has focused on studying the interaction between the developing immune system and the microbial environment. However, despite intense interest, the pathways that lead to dysregulation of the immune system in allergic disease are still poorly understood. The newly described type III IFN- λ molecules were initially shown to exhibit antiviral activity, but these molecules are also likely to have an important role to play in the immune–epithelial interface, given their immunomodulatory functions and restricted receptor expression to immune and epithelial cells. Previous studies on the role of IFN- λ in allergic disease have been limited to allergic asthma. More recently, a genetic variation flanking *IL28B* encoding IFN- λ 3 has been associated with allergic disease. Here, we examine this family and suggest how IFN- λ may be an important player in allergic disease.

KEYWORDS: allergy ■ dendritic cell ■ IFN- λ ■ innate immunity ■ Toll-like receptor

Background

IgE-mediated allergic diseases, including the clinical manifestations of rhinoconjunctivitis, asthma and atopic dermatitis, are the result of a dysregulated reaction triggered by immune responses against usually ‘innocuous’ antigens (allergens), which are ubiquitous in our environment. The steep increase in these diseases over recent decades highlights the vulnerability of the immune system to modern environmental changes [1]. In Australia, allergic diseases are now the most common disorders of childhood with significant personal and economic costs to society [2].

The rising rates of allergic disease in early infancy suggest that genetic predisposition and environmental interactions, even before birth, may play an important role in determining susceptibility to immune-mediated disease [3]. In particular, reduced microbial exposure in early life has become a leading candidate to explain the escalating rise in allergic disease (reviewed in [4]), and research in the last 15 years has heavily focused on studying the interaction between the developing immune system and the microbial environment. Not surprisingly, many aspects of our immune function are immature at birth [5] when there is also a relative dominance of Th2 cytokine production [6]. This Th2 bias is evident even in the neonatal thymus [7]. Furthermore, early microbial exposure is critical for normally occurring suppression of Th2 responses as our immune system matures after birth, as well as

for the activation and maturation of central and peripheral regulatory T cells. However, despite intense interest, the detailed mechanisms that regulate the switch from Th2 to Th1 responses are still poorly understood. There remains an urgent need to identify pathways that lead to dysregulation of the immune system, which forms the basis for subsequent development of allergic disease [8]. Such findings would provide the initial step towards improved and novel treatment options and the implementation of strategies to minimize the incidence of allergic disease.

Ultimately, better understanding of allergic disease development can lead to the development of clinically relevant biomarkers. Biomarkers are clinically useful tools to predict disease susceptibility and severity of the disease or its likely progression and resistance/response to treatment. Particularly, there remains a need for biomarkers that can reliably indicate which infants will go on to acquire allergic disease (risk of atopic phenotype) to direct therapy and clinical management towards infants at high risk. However, despite our knowledge that Th2 signature cytokines, their receptors and transcription factors are unequivocally involved in the development of allergic disease, this work has not been easily translated into novel diagnostics in allergy. Furthermore, research in the area of predicting allergic disease susceptibility has identified promising soluble immune markers such as the measurement of cord blood IgE [9–11] or cytokine profiling [12–14] in early serum samples or EPX in

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urine [15], as well as the measurement of cellular cord blood components such as FOXP3⁺ Tregs [16]; however, none of these have currently been validated enough to be used in routine clinical practice. As for all immune biomarkers relating to the innate and adaptive immune system, global measurement of soluble molecules in serum, such as cytokines, often lacks diagnostic specificity. Overall, it is unlikely that a single biomarker can be reliably used in the clinical assessment of allergy. In this context, the recent identification of the possible involvement of IFN- λ in allergic disease may ultimately contribute to a combination of markers that can identify those subjects that are at increased risk of developing atopic disease.

Recent studies examining the role of dendritic cells & Toll-like receptors in allergic disease

Studies involving prospective longitudinal case-control comparisons of immune development in well-characterized children have revealed striking differences in the biological responses (to microbial products) of children who develop allergic disease [17,18]. These studies have shown that allergic children exhibit increased inflammatory cytokine production at birth and during their neonatal period, compared with children that remain nonallergic, and this is associated with subsequent propensity for allergic Th2 adaptive responses in the allergic children [18]. These results suggest a misguided alteration of the innate and the adaptive compartments of the immune response in children with allergic disease and highlight the dominant influence of inflammatory cytokines during the perinatal period. Likely candidates with high proinflammatory potency include cytokines such as TNF- α , IL-6, IL-1 β , IL-12, IL-18, IL-23 and type I IFNs. In addition, regulatory cytokines involved in microbial responses, such as IL-10 and the newly discovered IFN- λ family, are thought to be important.

Toll-like receptors (TLRs) are crucial activators of the innate immune system, which is the first line of defense against microbial pathogens. They recognize distinct motifs of bacterial, viral and parasitic components at first encounter and are able to establish a first-line immune response as opposed to the expansion of an established immunological 'memory' response. TLR ligand-activated dendritic cells (DCs) are an important source of proinflammatory cytokines that can alter the balance between tolerance and inflammation [19,20]. Recent murine data suggest that

TLR signals modulate peanut-induced DC maturation, leading to profound *in vitro* changes in recall response to the antigen by suppressing T-cell proliferation and Th2 cytokine production [21]. These results suggest that allergen-induced DC signals can be altered by the presence of TLR ligands; however, these results remain to be confirmed in humans.

Allergic children produce more inflammatory cytokines (IL-6, TNF and IL-1 β) following TLR ligation compared with their nonallergic counterparts [18]; a feature that is also observed in children with food allergy [22]. The latter study on food allergy also shows the increased proinflammatory cytokines produced by plasmacytoid DCs (pDCs) is associated with activation of CD4⁺ T cells to produce Th2 cytokines. These studies highlight the differences in developmental trajectory between allergic and nonallergic children and suggest a functional dissociation between the innate (DC) and the adaptive (T-cell) compartments of the immune response in allergic subjects.

pDCs in general are a crucial component of the antibacterial and antiviral immune defense. Targeted ablation of pDCs in mice has shown that pDCs are likely to mediate strong responses to bacteria and as such, mice become resistant to toxic shock following bacterial challenge but become susceptible to viral challenges [23]. Furthermore, they have been associated with the direct activation of Th2 memory cells, including allergen-specific Th2 cells [24]. We know that in humans, pDCs express both innate TLRs and high-affinity IgE/Fc ϵ R and these have been shown to counter-regulate each other by down-regulating receptor expression [20]. Whether a similar paradigm exists *in vivo* and how this is regulated during early life is unknown.

Type III IFN- λ as a mediator of the innate immune response

Type III IFN- λ can be produced by a wide range of hemopoietic and nonhemopoietic cells [25]. IFN- λ levels may differ depending on the nature of the innate stimulus, the rapidity of the cell type response and the level of protein secreted. Similar to the level of response of the type I IFNs, pDCs are considered the major producers of type III IFN following viral stimulation. Indeed, for some viral ligands, pDCs may be the only cell type that will effectively respond with both type I and III IFN production [26,27]. This new IFN family is composed of three closely related molecules in humans: IFN- λ 1 (*IL29*), IFN- λ 2 (*IL28A*) and IFN- λ 3 (*IL28B*) that are

induced by viral infection and exhibit antiviral activity [28,29]. Furthermore, agonists of TLR3, 4, 7, 8 and 9 have been shown to induce IFN- λ production ([26], and reviewed in [30]).

At the genetic level, the IFN- λ genes are clustered on chromosome 19q13.13 and are distantly related to the IFN type I and IL-10-related family (15–19% amino acid identity to IFN- α and IL-22 and 11–13% identity to IL-10) [28]. *IL28A* and *IL28B* are closely related sharing approximately 96% identity at the protein level, with each sharing approximately 75–80% identity with *IL29*. There is evidence to suggest that, in humans, IFN- λ 1 is glycosylated while IFN- λ 2 and λ 3 are not [29]. In mice, *IL29* is a pseudogene, but *IL28A* and *IL28B* are functional with approximately 60% identity at the amino acid level with their respective human orthologs. Unlike humans, murine IFN- λ 2 and - λ 3 appear to be glycosylated (reviewed in [30]).

The IFN- λ family is likely to act via a similar but independent mechanism to type I IFNs as they share the same JAK/STAT pathway and can signal via IFN stimulatory response element sites potentially inducing IFN-stimulated genes. However, unlike type I IFNs, the IFN- λ members interact with IFN- λ R1 and IL-10R2 [28,31]. IFN- λ R1 appears specific to IFN- λ , but IL-10R2 is shared with IL-10 and related cytokines. Interestingly, IFN- λ R1 appears to have splice variants resulting in a likely receptor devoid of signaling capacity and another likely to be a secreted soluble form [28]. The ratio of the different receptor variants may determine the responsiveness of the cell to IFN- λ . Loss or reduced IFN- λ function may be due to the presence of the soluble form of the receptor (sIFN- λ R1), which is highly expressed in immune cells and directly inhibits IFN- λ effects [32].

Although IL-10R2 is ubiquitously expressed, IFN- λ R1 appears to have a more restricted expression pattern (mainly immune and cells of epithelial origin [28]; reviewed in [30]) and constitutes one of the major differences between the type III and I IFN systems in which the type I receptor complex IFNAR1/2 is ubiquitously expressed. This also supports the higher therapeutic potential for IFN- λ versus IFN- α due to the restricted receptor expression minimizing the diverse range of side effects (inhibition of hematopoiesis, neuropsychiatric effects and influenza-like symptoms) observed with IFN- α treatment (in viral infections and cancers). Recent trials using IFN- λ for hepatitis C infection suggest that IFN- λ therapy is likely to be associated with fewer side effects than IFN- α [33].

Aside from antiviral activity, the IFN- λ molecules are likely to have an immunomodulatory function in both the innate and adaptive immune response as studies have shown that IFN- λ 1-treated human DCs can induce proliferation of CD4⁺CD25⁺FOXP3⁺ innate regulatory T cells [34], inhibit *in vitro* naive and memory IL-13 responses in human T cells [35,36], augment antigen-specific IFN- γ release [37] and upregulate expression of TLRs and their response to ligands [32]. Others have suggested a role for IFN- λ in the expression of the Th1-promoting cytokine IL-12 by monocyte-derived DCs [38] and in inducing the expression of the chemokine IL-8, an important component of the innate inflammatory response [39].

IFN- λ in allergic disease

Support for the role of IFN- λ in allergic disease can be extrapolated from relatively few studies that have examined their role in allergic asthma. Contoli and colleagues have shown that deficient IFN- λ induction (IFN- λ 1 and IFN- λ 2/3) by viral (rhinovirus) and bacterial (lipopolysaccharide) stimuli was associated with severity of asthma exacerbations in allergic asthmatics [40]. A recent study clearly demonstrated that IFN- λ 2 can effectively induce Th1 immunity and suppress Th2 immunity, and consequently allergic airway disease in a mouse model of allergic asthma via its action on DCs [41], initiating suggestions that IFN- λ could be used as a new treatment approach for allergic asthma [42]. **FIGURE 1** shows a model of how IFN- λ could influence the Th1/Th2 balance.

It is also worthwhile to note that, although IFN- λ is more similar to type I IFN in relation to sequence identity and reported biological functions, it does share some features with the IL-10 family, including the usage of the IL-10R2 receptor and the exon–intron structure of the genes. Furthermore, the recently solved crystal structure of IFN- λ 3 shows a close relationship to the structure of IL-19 [43]. IL-19, an IL-10 family member, can promote Th2 immune deviation through a positive feedback system. Serum levels of IL-19 in asthmatic patients are approximately twofold greater than in nonasthmatic controls and were strongly correlated with elevated serum IL-4 and IL-13 (reviewed in [44]).

IFN- λ & asthma exacerbations

Costs associated with asthma due to acute exacerbations are significant [45] and are compounded by the often ineffective nature of the typical steroid therapy administered to patients in reducing the

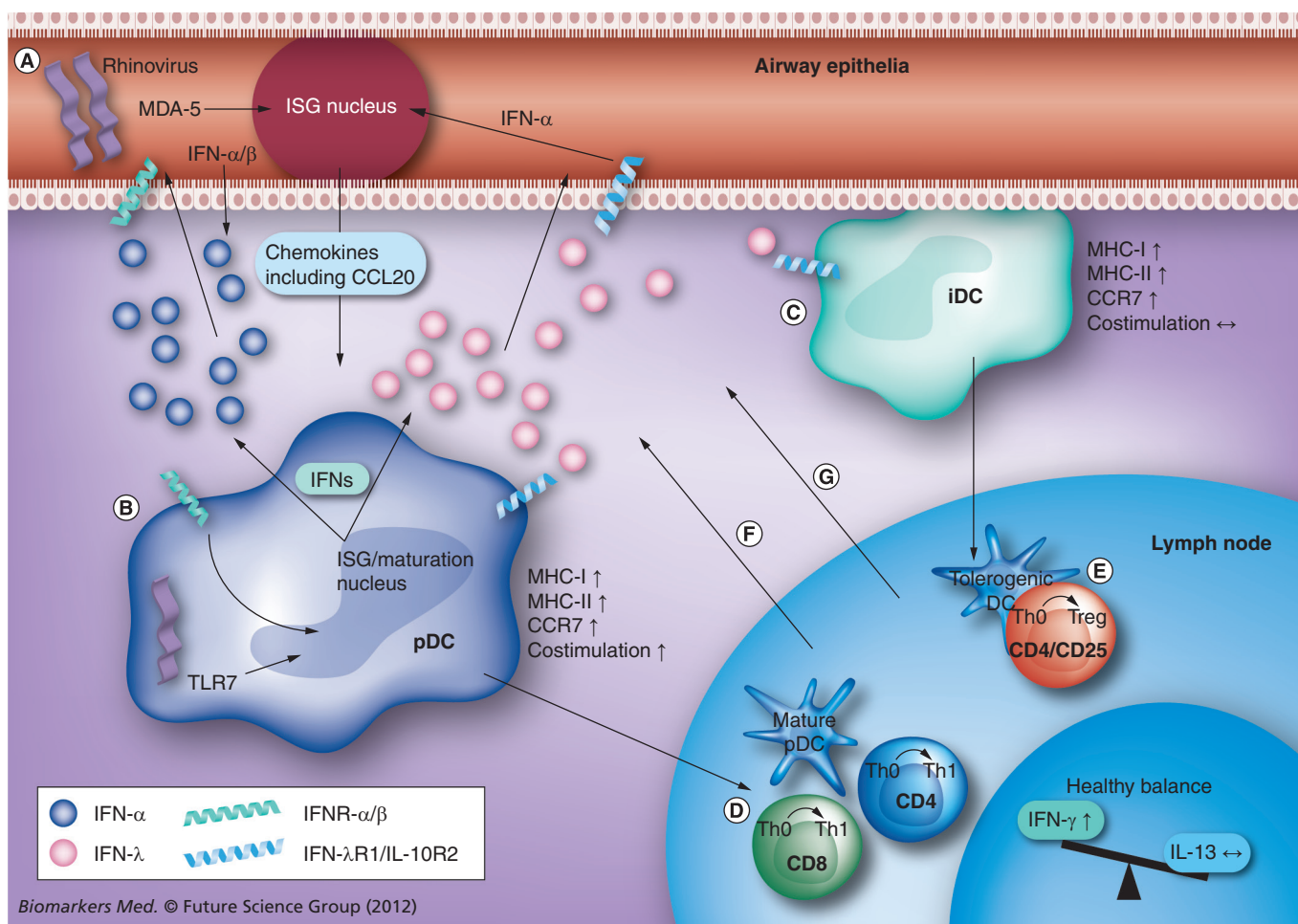


Figure 1. Model to describe the proposed effects of IFN-λ immunomodulation on T-cell responses. Rhinovirus infections are well known to exacerbate asthma and directly infect airway epithelia. (A) Recently, the intracellular dsRNA-sensing molecule MDA-5 has been described [64] to detect replicating rhinovirus and initiate the production of type I IFNs. In addition, virally infected epithelial cells produce a range of chemokines, including CCL20 [65], which act to recruit pDCs (B), which now become exposed to virus and secrete large amounts of both type I and type III IFNs, and (C) recruit inflammatory monocytes that differentiate into iDCs and begin expression of IFN-λR1 [34]. (D) pDCs that express IFN-λR1 become activated by autocrine exposure to type III IFN and become mature [66], migrating to local lymph nodes where they stimulate T cells, leading to (F) a Th1 polarized effector response [68]. (E) Similarly, iDCs respond to type III IFN but only become partially activated and stimulate T cells in local lymph nodes in the absence of costimulation inducing tolerogenic DCs [34], (G) which is predicted to induce a Treg response [69]. This is thought to help resolve the acute inflammation present in the tissue. Variations flanking or within IFN-λ genes (e.g., rs12979860 flanking *IL28B/IFN-λ3*) could influence ISG expression and/or IFN-λ production.

DC: Dendritic cell; iDC: Immature dendritic cell; IFN: Interferon; ISG: Interferon-stimulated gene; pDC: Plasmacytoid dendritic cell; TLR: Toll-like receptor.

frequency and severity of these events [46]. In most cases, asthma exacerbations are due to respiratory viral infections, predominantly with rhinoviruses (reviewed in [47]). The following is a summary of the few studies to date that indicate a functional role for IFN-λ in asthma exacerbations.

Studies have shown that defective *in vitro* innate immune responses to rhinoviruses in asthmatics are closely related to *in vivo* asthma exacerbation markers (several clinical markers/symptoms including airway inflammation [40,48]). Contoli and colleagues went on to show that rhinovirus infection could induce IFN-λ production in bronchial epithelial cells and bronchoalveolar

lavage cells (comprising mainly macrophages) [40]. Similar outcomes had been previously shown for type I IFN (reviewed in [47]). This same group then went on to show deficient rhinovirus induction of IFN-λ in atopic asthmatic primary bronchial epithelial cells *in vitro*. Interestingly, a study by Bartlett and colleagues showed that IFN-λ2 did not directly affect the replication of vaccinia virus *in vitro* but displayed antiviral properties *in vivo* [49]. The antiviral activity exhibited several days following infection was associated with elevated leukocyte and CD4⁺ T cells in murine bronchial alveolar lavage fluid [49], supporting an immunomodulatory role for IFN-λ. Furthermore, IFN-λ

protected mice that did not have functional IFN type I receptors from influenza infection, suggesting IFN- λ can act autonomously in the respiratory tract independent of type I IFN [50].

IFN- λ genetic studies, IgE-mediated allergic diseases & other diseases associated with dysregulation of the immune response

Recent genetic studies have been suggestive of a link between IFN- λ and allergic disease. For example, Chae and colleagues performed an extensive search for single nucleotide polymorphisms (SNPs) within the coding and regulatory regions of the IFN- λ receptor, *IL28RA*, to examine the association between SNPs in *IL28RA* (encoding IFN- λ R1) and allergic rhinitis [51]. They found an association between a SNP in the 3' untranslated region of the *IL28RA* gene and susceptibility to allergic rhinitis in the Korean population, but this SNP did not correlate with total IgE serum levels [51]. A closely linked SNP in the 5' untranslated region of *IL28RA* was associated with peripheral blood eosinophil counts in allergic rhinitis patients [51]. Furthermore, studies on subjects with inborn errors of genes likely to be involved in the IFN- λ -responsive pathway have shown that mutations giving rise to autosomal dominant STAT3 deficiency (hyper-IgE syndrome) [52] and autosomal recessive TYK-2 deficiency (reviewed in [53]), present with atopic dermatitis and high levels of IgE in serum.

Interestingly, genetic variations flanking *IL28B* (IFN- λ 3) have been shown to be associated with herpes simplex virus (HCV) infection outcome (both treatment and natural) [54–57]. HCV infection often leads to a chronic infection associated with dysregulation of the immune response and the *IL28B* variants have been linked with differential expression of IFN-stimulated genes in patients with chronic hepatitis C [58,59]. However, it currently remains speculative if the protective *IL28B* genotype leads to higher or lower levels of IFN- λ secretion (and specifically IFN- λ 3). Recently, a study on a longitudinal cohort of allergic and nonallergic children showed an association between carriage of the T allele ('risk' allele for HCV infection outcome as well) of the tagging SNP rs12979860 3 kb upstream of *IL28B* and allergy in children. This effect was more pronounced in girls [60]. Furthermore, carriage of the 'risk' allele at rs12979860 correlates with differences in the proinflammatory profile during the first 5 years of life suggesting this may contribute to the key differences in subsequent innate immune

development in children and may determine the trajectory of an individual's immune pathway.

Future perspective

Despite a proposed linkage between the level of environmental pathogenic exposure and allergy (hygiene hypothesis), no clear mechanistic linkage has been proposed that might explain the apparent enhanced susceptibility. With allergic diseases reaching epidemic proportions, it is essential that we have a better understanding of the early life influences that lead to disease. Proinflammatory cytokines and the newly discovered IFN- λ family may not only provide valuable, novel insights into early origins of the disease, but are also likely to inform novel diagnostic and future therapeutic strategies.

Given the mounting evidence to suggest a role for IFN- λ in allergic disease, this new type III IFN family may be an important avenue to identify new biomarkers in allergic disease. Levels of IFN- λ at relevant sites for atopic disease have not been established and, specifically, the role of IFN- λ in IgE-mediated diseases and in the Th1/Th2 balance remains of great interest as current management of HCV treatment is partly dependent on the *IL28B* (IFN- λ 3) genotype. However, although assays to assess human IFN- λ protein levels have been available only recently, newly developed assays can differentiate between the closely related IFN- λ 2 and IFN- λ 3 proteins. This is likely to become more relevant as the ability to distinguish between the IFN- λ members will allow the identification of overlapping and specific biological roles of each member, especially as recent data suggest that IFN- λ 3 has more potent activity than IFN- λ 1 and both are more potent than IFN- λ 2 [61]. Finally, if IFN- λ is to be considered in the clinical setting for allergic disease then future studies should examine IFN- λ and allergic disease, in the context of gender, age and ethnicity, as these factors have been shown to be associated with HCV outcome [54,63,63], and our own preliminary data indicate the 'risk' allele of *IL28B* is more strongly associated with sensitization in girls than boys [60].

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Executive summary

- Exaggerated proinflammatory cytokine responses to Toll-like receptor stimulation with microbial products at birth and altered plasmacytoid dendritic cell function predicts subsequent allergic disease.
- The newly described type III IFN- λ family is likely to have an important role to play in the immune–epithelial interface given their immunomodulatory functions and restricted receptor expression to immune and epithelial cells, including plasmacytoid dendritic cells.
- The potential functional role of IFN- λ in allergic disease has, to date, been restricted to a few studies examining its role in allergic asthma. However, recent genetic data suggest a role for IFN- λ 3 in allergic disease.
- The evaluation of an IFN- λ 3 single nucleotide polymorphism as a biomarker to guide clinical decision-making for IFN- α treatment has already commenced for another disease associated with known dysregulation of the immune response (hepatitis C infection).

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