Interferon-lambda as a new approach for treatment of allergic asthma?

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Asthma is a heterogeneous inflammatory disorder of the lung caused principally by sensitization and exposure to an allergen, but also influenced by environmental factors such as cigarette smoking, stress, exercise, pollution, respiratory virus infection and certain respiratory bacteria. The cardinal features of asthma include wheeze, shortness of breath, variable and reversible airway obstruction, airway hyperresponsiveness, mucus production and airway inflammation. Allergic asthma is the most common form of asthma, caused by sensitization and exposure via the airways to a number of innocuous allergens including proteins from house dust mites, animals, moulds and tree and grass pollens. Sensitization and challenge elicits a response from Th2 helper T cells and, through the actions of interleukin (IL)-4, IL-5 and IL-13, IgE production, airway eosinophilia, mast cell activation, mucus production and airway hyperreactivity ensues. Mild asthma can be well controlled by inhaled steroid therapies or inhaled steroid-β_2 agonist combinations. However, in moderate to severe asthma, adequate control frequently cannot be achieved with these therapies, and new and better treatments are therefore required.

Asthma exacerbations are acute attacks of asthma when an otherwise 'stable' asthmatic experiences a rapid increase in symptoms accompanied by decreased lung function, most often precipitated by a respiratory virus infection. Asthma exacerbations are responsible for the vast majority of the morbidity and mortality associated with asthma; and represent an area not well controlled by current therapy regimes. The search for new asthma therapies remains an intensive area of interest, and the last 10 years have seen a number of novel therapeutic strategies applied to both stable asthma and asthma exacerbations, including new formulations of steroids and β_2 agonists, anti-Th2 cytokine therapies, anti-TNF-α therapies, etc.

The work by Koltsida et al (Koltsida et al, 2011) in this issue of EMBO Molecular Medicine is of outstanding importance in this regard for two reasons. The current study clearly shows that IL-28A, a newly designated type III interferon (IFN)-λ, an anti-viral cytokine, can ameliorate the allergic and Th17-induced inflammation that occurs after sensitization and challenge with aerosolized allergen in mice, which closely resembles that seen in allergic asthma in humans. This data shows that IFN-λs may have additional properties in addition to their anti-viral capacity, such that they may be antagonists of Th2 and Th17 responses and function by inducing the Th1 polarizing cytokines type II IFN-γ and IL-12. The second noteworthy point is that asthmatics have recently been observed to be deficient in type I IFN-β and type III IFN-λs (Contoli et al, 2006; Wark et al, 2005), and a deficiency in IFN-λs may increase the severity of virus-induced asthma exacerbations (Contoli et al, 2006). Together, these studies propose a dual importance of IFN-λ that had previously not been demonstrated.

The IFN system is composed of three types of IFN: the anti-viral type I IFNs (the single IFN-β and the multiple IFN-αs), the type II IFNs and the type III IFN-λs. Type II IFN-γ is fundamentally different, has different cell type-specific expression patterns, is produced by leukocytes upon a number of stimuli, is not strictly limited to virus infection, and has numerous modes of action. Importantly, type I IFNs are only induced after virus infection of a cell or stimulation of certain cell types with type I IFNs and specific Toll-like receptor (TLR) agonists. The type I IFNs signal through the IFN-α receptor complex (IFNAR), composed of the IFNAR1 and IFNAR2 chains. Type I IFN signalling results in the transcription of a broad range of anti-viral genes (ISGs) aiming to eliminate or prevent virus replication. IFN-αs are produced more readily by leukocytes, with dendritic cells (DCs) being powerful inducers of IFN-αs upon viral provocation. IFN-β can be produced by both structural cells and leukocytes and is often first produced at the site of infection by cells directly infected by viruses, where it then signals through IFNAR to induce more of itself

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and the IFN-αs. The IFN-λs, including IL-29 (IFN-λ1), IL-28A (IFN-λ2) and IL-28B (IFN-λ3) in humans (IL-28A and IL-28B in mice) have similar anti-viral properties to the type I IFNs (Meager et al, 2005) as they induce a similar set of ISGs, but are thought to be expressed preferentially at mucosal surfaces and act on epithelial cells. They use a unique receptor complex composed of IFN-λR1α chain (CRF2-12 or IL-28Rα in mice) and IL-10Rβ chain (CRF2-4). Previously, the IFN-λs were thought to be strictly regulated by infection, although some data support a role in anti-cancer defense through their anti-proliferative effects. However, whether IFN-λ are induced directly in cancer in the absence of infection, or by infection and cancer together, such as in Hepatitis B infection and heptocellular carcinoma, is unclear.

Koltsida and colleagues utilized mice deficient in the IL-28Rα chain, administration of exogenous IL-28A and infection with adenovirus encoding IL-28A in a mouse model of sensitization and challenge to the egg allergen ovalbumin (OVA) to investigate the role of IFN-λs in allergic airway inflammation. Over-expression of IL-28A by adenovirus or administration of recombinant IL-28A to the airways resulted in reduced Th2 signature cytokines (IL-5 and IL-13), reduced IL-17, but increased IFN-γ production from mesenteric lymph node-derived T cell cultures and reduced eosinophil and neutrophil recruitment to the airways. Mucous staining was also reduced and lung function was significantly improved compared to OVA sensitized and challenged control mice. Interestingly, OVA challenged and sensitized mice also revealed low levels of IL-28A protein in concentrated BAL fluid, suggesting IL-28A may be induced as part of the allergic cascade. The IL-28Rα$^{-/-}$ mice developed strong mediastinal lymph node-derived Th2 cytokine and IL-17 responses after OVA challenge, increased BAL eosinophils and neutrophils and decreased lung function. Furthermore, experiments with DCs showed that the effect of IL-28 is exerted on CD11c^{+} DC effector function, and DCs cultured with IL-28A *in vitro* expressed high levels of the pro-Th1 transcription factor T-bet, whereas, DCs from IL-28A adenovirus-treated mice polarized T cells to the Th1 rather than Th2 phenotype. CD11c^{+} DCs expressed high levels of IL-28Rα mRNA, while RT-PCR analysis and immunohistochemistry showed that T cells and other infiltrating leukocytes within the airways did not express IL-28Rα, clearly suggesting that DCs rather than T cells respond to IL-28 *in vivo.* Finally, the novel effects of IL-28A on T cell differentiation were not observed in IFN-γdeficient or mice depleted of IL-12 p40, showing that IL-28A induces Th1 effector function via IL-12 and IFN-γ. These findings are of particular importance as IL-28 was previously believed to be an anti-viral or anti-cancer cytokine and its powerful immunomodulatory effects on DCs indicate a wider role for IL-28 in T cell immunoregulation.

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The proto-typical Th1 cytokine is IFN-γ, produced by and responsible for polarizing Th1 cells and working in an antagonistic manner to IL-4 and IL-13, the signature cytokines and inducers of Th2 cells and their responses. The fact that IL-28 induces IFN-γ and IL-12 and, therefore, functions in a Th1 polarizing manner may cause a re-think in the hierarchal order of T cell polarizing cytokines. While how IL-28 fits into the natural order of Th1, Th2 and Th17 cell development is yet to be thought out in detail; its role in T cell development in allergic asthma (in the absence of infection) is a novel finding. Of particular interest is how is IL-28 induced in this model, by what cell type and in which anatomical location is the DC receiving IL-28? While the present study shows that IL-28 is induced by OVA challenge, and clearly shows the effects of IL-28 administration on DC function, the exact mechanism responsible for IL-28 induction in this context remains to be investigated. Further, these studies raise the question whether this ability of IL-28 is shared by the type I IFN-β or IFN-α. Early work by Romagnani and colleagues suggests a similar Th1 skewing potential of IFN-γ and IFN-α (Parronchi et al, 1992), but these studies have not been followed through to impact on therapy. While these issues were beyond the scope of the article by Koltsida et al, the discovery of IL-28 as an immunoregulatory cytokine affecting T cell differentiation is important and could potentially impact on asthma and allergy treatment.

The finding that asthmatics are deficient in type I and type III IFNs, with IFN-λs being important in the pathogenesis of asthma exacerbations has led to the proposal that anti-viral IFNs may be attractive therapies for virus-induced asthma exacerbations. Indeed, inhaled type I IFN-β is currently being developed as a novel therapy for asthma exacerbations, and has recently entered a phase II clinical trial. The work of Koltsida et al extends this knowledge and suggests that such therapeutic approaches may not be limited to asthma exacerbations, but could also be efficacious in non-exacerbating, stable allergic asthma. The Th2 suppressing and Th1 augmenting ability of IL-28 in mice has implications for human asthma and other allergic diseases such as rhinitis, as it could be used to dampen down or ameliorate Th2 responses to specific allergens. As previously noted, anti-Th2 cytokine therapy is not a new approach to allergic asthma; however, in the past only individual cytokines have been targeted through, for example, anti-IL-5 antibodies or IL-4R antagonism that targets two cytokines IL-4 and IL-13, which both signal through the IL-4Rα chain (O'Byrne et al, 2004). While these therapies yielded mixed results in clinical trials, IL-28 may offer a subtlety different approach in that a Th1 inducing cytokine may effectively combat the effects of all Th2 cytokines and, thereby, be sufficient to tip the balance of Th1 over Th2 by directly modulating DCs that polarize T cells in the presence of antigen.

In summary, Koltsida et al have identified IL-28 as a T cell polarizing cytokine in models of allergic asthma. IL-28 acts via CD11c^{+} DCs, effectively promoting Th1 and suppressing Th2

responses. The work is novel and important, and highlights a previously unknown role for IL-28, a cytokine normally associated with the anti-viral response. The work supports the idea that IL-28 may be a future therapy for both stable allergic asthma and for asthma exacerbations, by its dual function: controlling allergic asthma through its Th1 modulating ability and virus-induced asthma exacerbations through its anti-viral activity.

The authors declare that they have no conflict of interest.

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