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Interleukin-13: prospects for new treatments

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Summary

IL-13 is a T-helper type 2 cytokine. Animal models have implicated IL-13 as a critical cytokine in the development of asthma and chronic obstructive pulmonary disease (COPD). *In vitro* IL-13 exerts important effects on both structural and inflammatory cells within the airway and has the capacity to drive the clinical features of airways disease. In asthma, this view is strongly supported by associations with IL-13 genetic polymorphisms and increased mRNA and protein expression in blood, sputum and bronchial submucosa. In particular, IL-13 up-regulation is associated with severe disease. Current evidence in COPD is conflicting, with some reports supporting and others refuting a role for IL-13. Early clinical trials of anti-IL-13 therapies in asthma have shown promise, and the results of further efficacy studies are eagerly awaited.

Introduction

IL-13, a T-helper type 2 (Th2) cytokine, was first described in 1993, identified by molecular cloning in activated human T lymphocytes [1]. In the same year, IL-13 was reported to direct cells towards the Th2 pathway, with induction of B cell production of IgE [2], and its gene position was mapped in close proximity to IL-4 on chromosome 5q 23–31 [1].

Straddling the new millennium, a cluster of reports from murine models of asthma and chronic obstructive pulmonary disease (COPD) positioned IL-13 as critical in the immuonpathogenesis of obstructive airways disease [3-5]. The view that IL-13 is pivotal in asthma was further supported by associations with genetic polymorphisms, increased expression in disease and the biological effects it exerts on airway inflammatory and structural cells. The role of IL-13 in COPD is more contentious, with the initial enthusiasm in animal models dampened by conflicting reports in human disease. The interest in anti-IL-13 strategies in asthma has led to considerable investment in the development of novel biological and small molecule approaches to modulate IL-13. These are beginning to enter early-phase studies. Therefore, we shall shortly have a greater understanding of the role of IL-13 in airways disease. This review will summarize the biology of IL-13, the current evidence positioning its role in asthma and COPD and will explore the potential effects of its inhibition on clinical outcomes in asthma.

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Interleukin-13 signalling

Several cell types have been reported as sources of IL-13. In particular, T cells, mast cells and eosinophils are the predominant source of IL-13 in asthma, with a contribution from the macrophage in COPD [1, 6-8]. Other inflammatory cells and structural cells have the capacity to produce IL-13 in airways disease. The crystal structures of the IL-4/IL-13 receptor system have been described recently [9]. IL-13 exerts its effects predominantly via a dimeric receptor comprising of IL-4Rα and IL-13Rα1 (IL-4RII). IL-13 binds IL-13Rα1 with a low affinity and then IL-4Rα binds to form a high-affinity cytokine-binding heterodimer. IL-13Rα1 is expressed by airway epithelium, fibroblasts, smooth muscle and most leucocytes including mast cells within the airway, except T lymphocytes [10-14]. Binding of IL-13 to this receptor activates the tyrosine kinases Jak 1, Jak 3 and Tyk 2. These kinases phosphorylate tyrosine residues on the IL-4α receptor, which in turn leads to recruitment and subsequent phosphorlyation of signal transducer and activator of transcription 6 (STAT6). STAT6 dimerizes and translocates to the nucleus and modulates gene expression [15]. In addition to IL-13 and its cognate receptor, this signalling pathway presents potential novel targets to modulate the IL-13 axis.

IL-13Rα2 binds IL-13 exclusively and with high affinity. This receptor lacks a signalling motif and exists in soluble and membrane-bound forms. These characteristics led to the view that coupling to this receptor disallows binding of the IL-13 protein with IL-13Rα1, and therefore IL-13Rα2 acts as a ‘decoy’ receptor. Recently, the functional purpose of the IL-13Rα2 subunit has gathered much speculation. *In vitro* studies with human airway fibroblasts suggest that activation of the IL-13Rα2 subunit may attenuate the actions of IL-13 and -4 [16]. In support of this view, comparison of the effects of lung-targeted transgenic IL-13 in mice with wild-type and null Rα2 loci demonstrates that IL-13Rα2 is a selective and powerful inhibitor of IL-13-induced responses [17]. However, in the bleomycin model of lung fibrosis, a controversial role for the IL-13Rα2 subunit was proposed, which suggested that activation of this receptor led to induction of TGF-β and the development of lung fibrosis [18].

Evidence of a critical role for interleukin-13 in the pathogenesis of asthma

Animal models

A considerable weight of evidence supporting a role for IL-13 in airways disease is derived from animal models. In 1998, Grunig and colleagues first reported that in a murine model of allergic asthma, selective neutralization of IL-13 led to reversal of airway hyperresponsiveness (AHR) and inflammation. In addition, they found that administration of IL-13 conferred an asthma-like phenotype to non-immunized T cell-deficient mice by an IL-4Rα-dependent pathway [3]. Similarly, Wills-Karp et al. [4] found that the addition of IL-13 to non-immunized mice was sufficient to induce the pathophysiological features of asthma independent of IgE and eosinophils.

Subsequent murine studies suggested that IL-13 may exacerbate airway responsiveness via direct effects on epithelial cells [19] and airway smooth muscle [20]. Mice lacking STAT6 were protected from all pulmonary effects of IL-13. Reconstitution of STAT6 only in

epithelial cells was sufficient for IL-13-induced AHR and mucus production in the absence of inflammation, fibrosis or other lung pathology, highlighting the importance of the effects of IL-13 on epithelial cells. IL-13 also exerts direct effects on airway smooth muscle, leading to increased force of contraction as a consequence of augmentation of G protein-coupled receptor-associated calcium signalling [20].

Polymorphisms of interleukin-13 and its receptor

A recent report re-examined the published asthma genetic studies [21], including candidate gene studies and positional cloning, up to the end of December 2007. Two of the four genes with the highest number of positive association reports were IL-4R and IL-13. Indeed, polymorphisms within the IL-13 gene have been associated with various aspects of the asthma phenotype. Analysis of an adult Dutch population demonstrated that the −1111 promoter region is strongly associated with asthma disease, AHR and atopy [22]. In addition, polymorphisms within the IL-13 gene have been identified to predict asthma [23] and higher serum IL-13 levels [24]. Recombinant IL-13 protein of one of these variants (glutamine substitution for arginine at position 110 on the mature protein-Arg110Gln) has demonstrated greater biological activity, implying that genetic variations in the IL-13 gene influence the asthma phenotype [23]. The IL-13 gene locus is associated with atopy and allergy in the broader sense, with four single nucleotide polymorphisms (SNPs) associated with a variant in the IL-13 gene (Arg130Gln polymorphism), resulting in elevated IgE in three separate populations of children [25].

Interleukin-13 expression in asthma

Blood

As described above, peripheral blood T cells, eosinophils and basophils, but not neutrophils [26], are important sources of IL-13 [1, 6-8, 27, 28]. The IL-13 concentration in peripheral blood is increased in asthma across disease severity in a stable state [29, 30] and is up-regulated at exacerbations [31]. The potential functional importance of this increased IL-13 expression is underscored by comparisons between asthma and non-asthmatic eosinophilic bronchitis (EB). EB is a common cause of chronic cough [32] and can be distinguished from asthma by the absence of variable airflow obstruction and AHR. Therefore, differences between these conditions may provide important clues as to the pathogenesis of the disordered airway physiology in asthma. Both conditions share many immunopathological features, with the notable exception of increased mast cell infiltration of the airway smooth muscle bundle in asthma [33-36]. Interestingly, following stimulation *ex vivo* T cells from asthmatics demonstrate increased IL-13 expression compared with subjects with EB or controls [37, 38]. This suggests that for the same stimulus, cells derived from asthmatics have a greater capacity to release IL-13. Similarly, T cells from atopic individuals upon stimulation with grass pollen and house dust mite showed elevated IL-5 and -13 production compared with non-atopic controls [39, 40].

Sputum

Induced sputum provides a non-invasive assessment of airway inflammation and allows for the measurement of inflammatory cells and important pro-inflammatory cytokines. The use

of the mucolytic dithiothreitol aids cell dispersion to produce a more reliable sputum cytospin, but can affect the measurement of cytokines. For this reason, the IL-13 measurement in sputum has been dogged by technical problems. This has been overcome using a number of approaches including sputum dialysis [41]. Again, important differences have been observed between asthma and EB, with increased concentrations in asthma [41] and in particular in severe disease [35]. The IL-13 concentration in sputum was related to asthma control [35]. This increased IL-13 expression in asthma is confirmed by examination of sputum cytokine mRNA expression [42] and by *ex vivo* stimulation of sputum T cells [43].

Bronchoalveolar lavage Fluid

Following a segmental allergen challenge, bronchoalveolar lavage (BAL) IL-13 is increased in asthma [44, 45], is associated predominantly with the late asthma phase and is correlated with eosinophil numbers [45]. *Ex vivo* BAL T cells express IL-13 mRNA [46] and its expression in $CD4^+$ and $CD8^+$ cells was inversely related to forced expiratory volume in 1 s % predicted [47]. In addition, BAL-derived macrophages are a potential source of IL-13 with significant amounts of IL-13 mRNA found within BAL enriched for alveolar macrophages, which correlated with BAL eosinophils [48]. Importantly, in severe asthma, the proportion of macrophages staining for IL-13 was increased. In nocturnal asthma, the number of BAL cells expressing IL-13 mRNA was increased [49]. This expression was only in part attenuated by dexamethasone. BAL-derived alveolar macrophages from these subjects demonstrated overexpression of glucocorticoid receptor (GR)-β (a receptor complex that competes with the active GR-α receptor), but reduced expression when treated with IL-13 neutralizing antibodies [49]. This provides a possible explanation for the reduced GR affinity seen when IL-13 is incubated with peripheral blood monocytes [50].

Bronchial mucosa

Several studies have consistently reported up-regulated IL-13 expression in bronchial biopsies [41, 45, 51-55]. Increased IL-13 mRNA expression was first described within the submucosa in bronchial biopsies from a small population ($n = 9$) of stable asthmatics compared with healthy control. IL-4 mRNA expression was also assessed and the number of $IL\text{-}13^+$ mRNA cells was significantly higher compared with $IL\text{-}4^+$ mRNA cells. All cells that expressed $IL\text{-}4^+$ mRNA co-expressed IL-13 mRNA concurrently. In contrast, only 60% of $IL\text{-}13^+$ mRNA cells co-expressed $IL\text{-}4^+$ mRNA. Ninety percent of the cells expressing $IL\text{-}13^+$ mRNA were characterized as CD3 T lymphocytes [51]. IL-13 mRNA [52] and protein [35] were increased in moderate to severe disease. Surprisingly, IL-13 expression within the airway is not closely related to atopy, but there was an association with eosinophilic inflammation [35, 41]. IL-13 protein expression has been quantified using immunohistochemistry in large airway biopsy specimens from subjects with corticosteroid-naïve asthma, EB and healthy controls. Increased inflammatory cells expressing IL-13 were found within the submucosa of the asthma group in comparison with the controls and EB. Although mRNA expression is usually associated with T cells, over 80% of cells expressing IL-13 protein were eosinophils, with 8% of cells being identified as mast cells [41]. This apparent anomaly may be a consequence of T cell secreting its synthesized IL-13 rapidly, whereas IL-13 may be stored by eosinophils and mast cells. Mast cells are an important

source of IL-13 in the lung [6] and in asthma mast cells within the airway smooth muscle bundle, express IL-13 [55].

Evidence of a role for interleukin-13 in the pathogenesis of chronic obstructive pulmonary disease

Animal models

In addition to asthma, murine models have highlighted a role of IL-13 in COPD. Zheng et al. [5] reported that IL-13 overexpression in the adult murine lung induced emphysema, mucus metaplasia, inflammation and fibrosis. These effects were mediated by matrix metalloproteinase (MMP) and cathepsin-based proteolytic pathways and were reversed by the addition of MMP or cysteine proteinase antagonists. Potentially, IL-13 regulation in emphysema may also be related to up-regulation of IL-18. Transgenic IL-18 murine models resulted in increased IL-13 coupled with pulmonary inflammation and structural changes reflective of emphysema [56].

Recently, murine models have been used to extend previous concepts that chronic lung disease is a result of an innate immune response to low-grade infection [7]. Mice infected with Sendai virus demonstrated development of mucus metaplasia and AHR mimicking features of asthma and COPD despite clearance of the virus. In the acute phase, $CD4^+$ T lymphocytes were the predominant source of IL-13 but in the chronic phase, macrophages stimulated by invariant natural killer cells became the most significant source. These findings provide new insights into a novel iNKT-macrophage mediated IL-13 overproduction, leading to chronic lung disease, and expand the possible role of IL-13 in the onset and chronicity of airways disease.

Polymorphisms of interleukin-13 and its receptor

In COPD compared with smokers and never smokers, there was an association with the changes of cytosine to thymine at −1055 within a promoter region associated with IL-13 [57]. Smoking has an influence on specific SNPs, with subjects with extensive smoking exposure possessing the −1112 C/T allele developing worsening airflow obstruction [58]. Importantly, these polymorphisms (−1055 and −1112) are the same and are also known as rs1800925. Therefore, in COPD IL-13 polymorphisms have been associated with disease, although the strength of this association is not as compelling as for asthma.

Interleukin-13 expression in chronic obstructive pulmonary disease

Increased IL-13 expression is a consistent feature of asthma in peripheral blood, sputum, BAL and bronchial biopsies. In contrast, the data for COPD are conflicting. In peripheral blood, IL-13 has been reported to be increased [59], but this finding has not been replicated in another study [60]. In sputum, IL-13 concentration was not increased across severities compared with smoking and non-smoking controls [53]. In *ex vivo* BAL T cells from COPD subjects IL-13 mRNA was expressed [47]. However, IL-13 protein quantification within BAL has not been determined. Intriguingly, BAL IL-13 mRNA expression from asymptomatic smokers was decreased compared with healthy never smokers [61], again questioning the role of IL-13 in smoking-related COPD. In the bronchial submucosa in

smokers with chronic bronchitis, IL-13 expression was increased [62], whereas in another study, the IL-13 expression was not different between subjects with COPD, smoking and non-smoking controls [53]. Contrary to murine models, IL-13 mRNA and protein expression was decreased in severe emphysema [63], but was increased in another group of COPD subjects and related to mucus cell metaplasia [7]. The role of IL-13 in COPD is therefore uncertain. Current evidence perhaps suggests that IL-13 is important in the development of some aspects of the COPD phenotype, but not others.

Effects of interleukin-13 on airway inflammatory and structural cells

IL-13 exerts effects on both inflammatory and structural cells implicated in the pathogenesis of asthma summarized in Fig. 1.

Recent evidence from clinical trials of anti-IL-5 has implicated eosinophils as pivotal in the pathogenesis of severe exacerbations in refractory asthma [64, 65]. IL-13 plays a role in the development and persistence of eosinophilic airway inflammation. Trafficking of eosinophils from the blood compartment to target tissue is mediated in part by IL-13. Adhesion of eosinophils to the endothelium is promoted by IL-13 through the up-regulation of P-selectin, suggesting that IL-13 is implicated in the first stages of transmigration of peripheral blood eosinophils to tissue [66]. IL-13 also augments eosinophil survival and activation [67, 68]. IL-13 is important in allergic inflammation. Together with IL-4, IL-13 drives B cell isotype switching [2] and up-regulation of mast cell FcεR1 expression [14]. IL-13-primed mast cells demonstrate increased proliferation and activation following IgE/anti-IgE activation. These effects were inhibited by a specific IL-13 blocking antibody [14]. In monocytes and macrophages, IL-13 enhances the expression of integrins [69], but inhibits the production of pro-inflammatory mediators including prostaglandins [70] and reactive oxygen species [71]. This inhibition is in contrast to the pro-inflammatory effects exerted on other inflammatory cells and is possibly mediated by suppression of nuclear factor κ B [72].

In addition to inflammatory cells, IL-13 exerts important effects on structural cells. The airway epithelium presents a physical barrier and provides a critical interface between the environment and the underlying structural and inflammatory cells. IL-13 modulates epithelial barrier function, increasing epithelial permeability as measured by mannitol influx and down-regulating proteins associated with maintaining a tight junction within these barriers [73]. In addition, IL-13 drives epithelial cells into a hypersecretory phase, contributing to increased airway inflammation [74]. Indirectly, IL-13 promotes myofibroblast activation via release of TGF-β 2 from epithelial cells, which in turn influences myofibroblasts into releasing cytokines, chemokines and α-actin smooth muscle [75]. Both IL-13 and 4 induce granulocyte macrophage colony stimulating factor and IL-8 release from *ex vivo* epithelial cell lines in the presence or absence of Der p 1 [11]. Mesenchymal cell differentiation and function is modulated by IL-13 with induction of fibroblast to myofibroblast transformation [76], augmented by the synergistic effect of TGF-β [75]. These effects may, in part, contribute to airway remodelling. The release of many important mediators that participate in airway inflammation and inflammatory cell recruitment including β-1 integrin, vascular adhesion molecule 1, monocyte chemoattractant protein 1 and IL-6 is promoted by IL-13 [77]. Perhaps one of the most interesting effects of

IL-13 is its modulation of airway smooth muscle. IL-13 has been implicated in playing a key role in airway smooth muscle contraction and the potential development of AHR. *In vitro* IL-13, but not IL-4, has been shown to attenuate airway smooth muscle relaxation to β-agonists [13] and augment contractility to acetylcholine [78]. Airway smooth muscle is also an important source of mediators. Following stimulation with IL-13, airway smooth muscle releases increased CCL11 and other chemokines. This IL-13-mediated effect is augmented in combination with TNF [79], IL-9 [80] and IL-4 with IL-1β [81]. Importantly, IL-13-induced release of CCL11 from airway smooth muscle is increased with airway smooth muscle derived from subjects with asthma compared with healthy controls [82]. Interestingly, conditioned medium from IL-13-stimulated airway smooth muscle is chemotactic for mast cells [81], suggesting that airway smooth muscle-derived chemokines may be important for the selective recruitment of mast cells to the airway smooth muscle bundle [81, 83].

Therefore, IL-13 has the capacity to influence key aspects of the asthma paradigm including allergic inflammation, persistence of eosinophilic airway inflammation, airway remodelling and the development of AHR. These potentially broad-spectrum effects have made IL-13 an attractive target for drug development.

Clinical studies of treatments targeted towards the interleukin-13 axis in asthma

Early studies with a soluble recombinant human IL-4 receptor [Altrakincept, Immunex (Amgen), Thousand Oaks, CA, USA] in patients with mild-to-moderate asthma showed some efficacy in maintaining asthma control when inhaled corticosteroids were being withdrawn [84], but this effect was not subsequently confirmed and development was stopped. Two recent placebo-controlled allergen challenge studies showed that an IL-4 variant (pitrakinra) administered subcutaneously or nebulized can inhibit the binding of IL-4 and -13 to the IL-4Rα subunit. Pitrakinra reduced the allergen-induced late-phase response and the need for rescue medication in asthmatic patients [85]. Trials are now underway using an inhaled preparation [86]. Similarly, a humanized monoclonal antibody IMA-638 inhibited both the early and the late allergen challenge response, but did not affect allergen-induced hyperresponsiveness to methacholine [87]. Intriguingly, although preclinical data support the view that IL-13 is critical in the development of AHR, to date, studies that have included allergen-induced AHR have failed to show an effect on this outcome. Whether anti-IL-13 strategies have an impact on ‘wild-type’ AHR needs to be addressed. Several other monoclonal antibodies against IL-13 or IL-4Rα have completed early safety trials in humans, including CAT-354 [88] and AMG 317 [89], and are undergoing clinical trials for asthma. To date, there are no studies of anti-IL-13 therapies in COPD.

Future implications

We are now entering a new therapeutic age for airways disease. Over the next 2–3 years, findings from clinical trials will define the role of anti-IL-13 strategies. In parallel, the positioning of other novel therapies including those directed towards other cytokines, chemokine receptors, immunomodulators [90] and thermoplasty [91] will provide us with a

choice, particularly in those with severe asthma. It is unlikely that these treatments will suit all patients, and therefore the recognition of asthma and COPD as heterogeneous conditions will become increasingly important [92]. The application of current and the development of novel outcome measures and biomarkers will be needed to ensure that the most appropriate treatment or combinations of treatments are selected for patients.

The wealth of data implicating IL-13 as a pivotal cytokine in the pathogenesis of asthma presents a compelling case to predict the likely success of anti-IL-13 in the clinic. In the not too distant future, we shall either be able to use a new therapy for our patients with asthma or we will need to revise the asthma paradigm.

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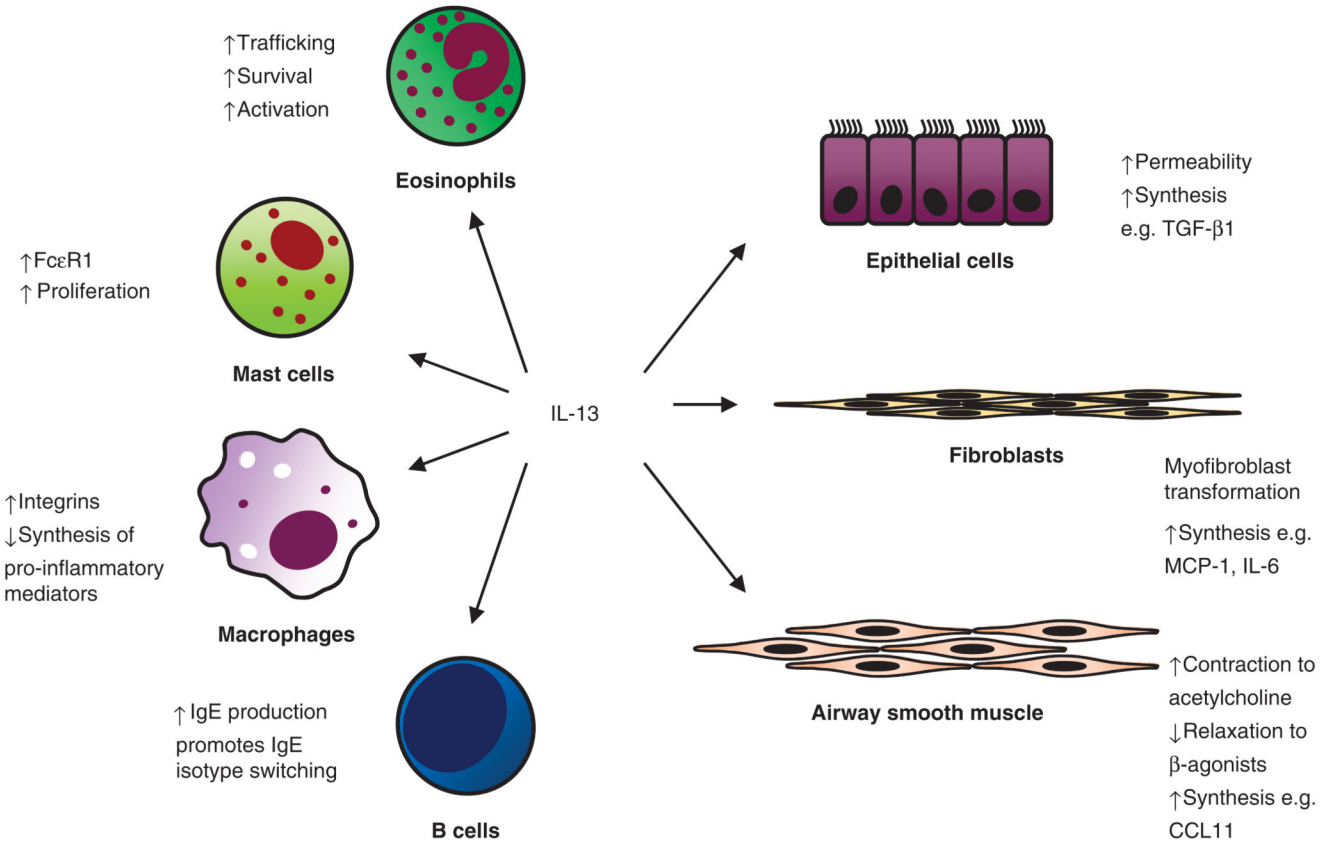

Fig. 1.
Summary of the effects of IL-13 on important structural and inflammatory cells (see text for details).

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