Review Article
Interleukin 13 and the evolution of asthma therapy

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Summary: This is a concise review on Interleukin (IL)-13 and the evolution of asthma therapy, from discovery of the molecule, the identification of its pathogenic role in animal models of asthma, to the development of clinically successful neutralizing agents. The translational path from basic research to clinical application was not sequential as expected but random with respect to the tools (molecular & cell biology, animal models, human studies) used and to the application of academic versus industry research. The experiences with the development of neutralizing anti-IL-13 reagents emphasize the need for inclusion of a biomarker assay in the clinical trials that both identifies individuals that actually have aberrant expression of the pathway of interest and allows determining whether the target of interest is neutralized.

Keywords: IL-13, asthma, therapy, biomarkers

Introduction

Asthma is now the most common chronic medical illness of children and one of the most common of adult diseases. Over the past 100 years, the focus of asthma therapy has progressed from an emphasis on direct mechanical relief from bronchoconstriction to suppressing the presumed underlying inflammatory mechanisms that cause obstruction using increasingly specific interventions. To date, a milestone in this process is the development of neutralizing antibodies to interleukin 13 (IL-13), a cytokine secreted by T helper type 2 (Th2) cells that significantly improves but does not normalize airway obstruction in human asthmatic patients [1]. The history of IL-13 in immunity, especially the effort to develop IL-13 antagonists for asthma, is both interesting and instructive for what lies ahead for therapeutic research in allergic disease and in chronic diseases of the lungs. Perhaps most importantly, the crucial aspect for successfully developing IL-13 targeting therapy has been the cross-informative use of molecular biology, cell biology, mouse model studies, and studies in human patients including specific asthma phenotypes applied by scientists working in industry and academia (**Figure 1**). The general paradigm is that these tools are applied sequentially and that basic scientific research in academia is followed by industry sponsored studies. Surprisingly, instead a random-access approach that enabled switching between bench and bedside research as needed (**Figure 1**) guided scientific discovery that led to the cloning of IL-13 [2], the identification of the crucial role of IL-13 for the asthma phenotype [3-5], the production of neutralizing reagents [1, 6-12], the development of biomarkers [13-15] and to the successful clinical trial [1].

IL-13 in asthma – a Cinderella story

The manuscript published by Dr. Corren and colleagues in the New England Journal of Medicine on September 7, 2011 [1] describes the results of a clinical trial of an anti-IL-13 antibody, a study funded by Genentech; ClinicalTrials.gov number, NCT00930163. The study shows a significant improvement, but not a restoration, in airway function measured by FEV1 (forced expiratory volume in 1 second) in pa-
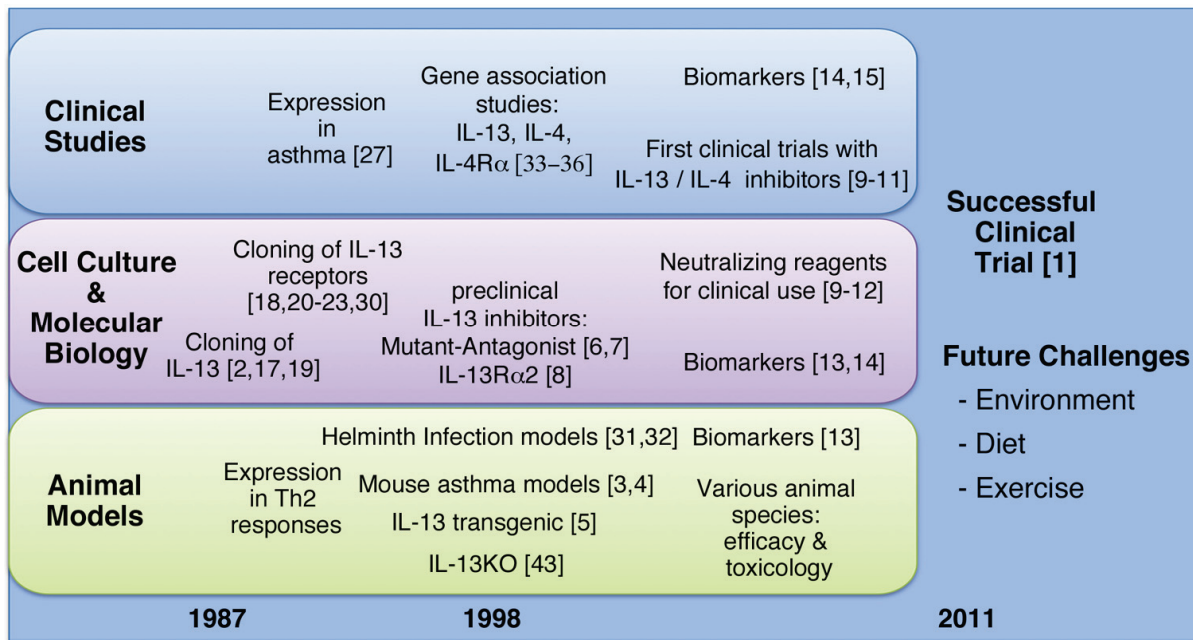
Figure 1. A random-access, cross-disciplinary approach that led to the successful development of an anti-IL-13 inhibitor for asthma. The interlacing utilization of clinical studies in humans, cell culture, molecular biology, and mouse models was essential for IL-13's journey from cloning [2], to the successful clinical trial in asthma [1].

tients who have Th2 dependent asthma as measured by specific biomarkers [1]. This stepping-stone in the successful management of asthma is the culmination of some 25 years of work on IL-13.

Discovery and early characterization

The discovery of IL-13 was one of many seminal observations made during a remarkable period in the history of immunology. Originally designated as p600, IL-13 was discovered in the laboratory of Dr. Mossman [2] who, together with Dr. Coffman, first described Th1 and Th2 cells [16] and thereby established the enduring paradigm that T cells exist in functionally distinct forms characterized by different patters of secreted cytokines. The human IL-13 homologue and its receptors were cloned by groups led by Drs. Minty and Caput from France [17, 18] and Zurawski, McKenzie and de Waal Malefyt in the United States [19, 20], respectively. A surprise from this research was how strongly IL-13 resembled the previously characterized IL-4. Not only is the IL-13 gene located extremely close to the IL-4 locus, it is transcribed together with IL-4 in a direction opposite to all other neighboring genes and otherwise strongly resembles IL-4 at primary, secondary and tertiary

structural levels. Moreover, it quickly became apparent that IL-13 and IL-4 both share receptor components and exert similar effects on immune cells. Based on the differential expression of two such receptor components [18, 20-23], IL-13Rα1 and IL-2Rγ, a model, still in use today, emerged to explain the relatively few differences in the then-known biology of these cytokines. Specifically, IL-4 is more potent in inducing Th2 cell differentiation and IgE secretion from B cells. For all practical purposes, then, IL-13 was virtually an orphan cytokine, strongly resembling, but clearly weaker than, it's more famous cousin IL-4, and having no obvious independent identity.

IL-4 and IL-13 in allergic inflammation

The key to unraveling the importance of IL-13 lay not in comparing its importance to IL-4 in terms of lymphocyte function, where it was clearly of secondary relevance, but in translational studies of cytokine function using more complex *in vivo* disease models. Several years after the discovery of IL-13, independent research groups were closing in on the immunological basis of allergic disease, focusing on two disease models: parasite infestation of the gut and allergic airway disease, a model of

asthma. Despite involving two entirely different organs (gut and lung, respectively), these models are otherwise remarkably similar, involving at a purely immune level substantially similar patterns of inflammation involving Th2 cells, eosinophils and IgE-secreting B cells, and at a physiological level, substantially similar outcomes of this inflammation that include enhanced luminal smooth muscle-based contractility and excess mucus secretion that cause transient obstruction. For the parasitized gut, these changes, which are directly mediated by Th2 cells, were shown to be adaptive as they resulted in the expulsion of the causative organism. In asthma models, these changes lead to airway obstruction and were therefore believed to be maladaptive- precisely mirroring the clinical impression that asthma is a harmful response to otherwise innocuous inhaled substances masquerading as parasites. The question for both models became, what is the essential molecule(s) that mediate the all-important physiological changes?

Given that they had previously been linked to allergic disease for many decades, IgE and eosinophils seemed to be obvious targets, and IL-4 and IL-5 were eventually shown to be the principal cytokines driving these markers of allergic disease, respectively. Although dissenting views are readily found, our studies [24, 25] and those of others [26] indicated that IL-5, IgE, and eosinophils are dispensable for mediation of airway obstruction in the setting of acute allergic inflammation. What is agreed to, however, is the importance of IL-4 for both allergic inflammation and airway obstruction. However, neutralization of IL-4 inhibited Th2 cell priming and airway hyperreactivity only when applied to the entire period of allergen sensitization; anti-IL-4 antibodies were almost entirely ineffective when given to mice after completion of antigen priming [25]. This subtle, but crucial, insight suggested that another immune factor mediated the airway obstruction caused by Th2 cells. Immune-phenotyping studies [27] supported the notion that IL-4 and IL-13 were important players in asthma pathogenesis. But which factor?

Role of IL-13 in experimental asthma

Simultaneous with studies of Th2 cytokines and IgE in experimental asthma, two research groups, ours [24, 25] and that of Drs. Finkelman and Wills-Karp [28], were exploring the importance of the IL-4 signaling pathway in the CD4 T cell dependent [29] mouse models of asthma. Studies of IL-4 receptor signaling deficiency using mice without the IL-4Rα gene revealed a striking phenotype never previously observed: these mice were utterly resistant to developing mucus cell hyperplasia, eosinophilia and airway obstruction in response to allergen challenge, even after receiving Th2 cells from wild type mice, or recombinant IL-13 or recombinant IL-4 intranasally [4]. This resistance to allergic disease was far greater than that seen with IL-4-deficient mice, and because IL-4Rα was also required for IL-13 signaling, this of course provided the first clear indication that IL-13 was in fact an important effector molecule in asthma.

But how to prove this? Dr. Donaldson and her colleagues made the first high affinity, specific IL-13 inhibitor, a recombinant chimeric protein containing the ligand binding region of IL-13Rα2 [8, 30], one of two potential components of the complete IL-13 receptor. Collaborative studies among Drs. Finkelman, Donaldson, Urban and Wynn showed that blockade of IL-13 using recombinant IL-13Rα2 exacerbated helminth-dependent allergic disease of the gut, reduced the efficiency of parasite expulsion and was the cause of liver fibrosis [31, 32].

Alerted to this work, we realized that recombinant IL-13Rα2 was the reagent we had long sought. Dr. Donaldson agreed to provide this important reagent to two groups almost simultaneously, those of Dr. Wills-Karp and ours. Together [3, 4], our studies showed that IL-13 is the major cytokine mediating most aspects of the asthma phenotype (airway hyperreactivity, goblet cell hyperplasia, eosinophilic inflammation) in mice. At the same time, Dr. Elias' group had made transgenic mice that expressed IL-13 in airway epithelial cells and showed that these mice developed the asthma phenotype [5]. Simultaneously, these studies clarified a distinction between IL-4 and IL-13: Whereas IL-4 controls the development of T lymphocytes, especially Th2 cells, IL-13 functions during the effector phase of immunity, mediating the physiological response of the target organ to Th2- induced inflammation.

Translational research

These data rekindled the interest in IL-13 by the

pharmaceutical industry. Many groups made inhibitors, targeting IL-13 or IL-4Rα. A critical task was to determine the importance of IL-13 in human asthma - a process that required 13 additional years and remains incompletely resolved. There were three major road-blocks: (a) production of a high-affinity IL-13 inhibitor, (b) assembly of convincing scientific evidence that IL-13 is critical in human asthma, (c) development of a suitable biomarker tool kit that identifies an appropriate human asthma phenotype to target, in this case, IL-13 dependent asthma and that allows for monitoring of antibody activity (blockade of IL-13) in the patients.

In addition to the inhibitor that showed clinical efficacy in asthma [1], potent neutralizing reagents with specificity for IL-13 and / or IL-4 were made [6, 7] and are currently in the clinical trial phase [9-12]. The future promises that neutralizing IL-13 / IL-4 reagents will be available from a variety of sources with the ability to choose between injection and inhalation routes of administration.

Gene-linkage studies showed associations of polymorphisms in the IL-13 and the IL-4Rα [33-36] genes in allergic asthma, confirming the significance of IL-13 for asthma. However, not all asthma is IL-13 dependent. The most convincing scientific argument for this came from studies in mice showing that IL-13 inhibition is highly effective during Th2-IL-13 driven asthmatic inflammation, but is much less effective in mice that have airway inflammation involving a mixed Th1/Th2 immune responses [37]. Other studies in mice showed that the asthma phenotype, specifically airway hyperreactivity, can be dependent on Th1 or Th17 cytokines, particularly IFN-γ or IL-17A [38, 39].

Gene expression profiling was essential for biomarker discovery. Studies of human airway epithelial cells stimulated with IL-13 and airway epithelial cells or whole lung lysates from mice exposed to IL-13 revealed a strikingly consistent IL-13 gene expression signature [13]. Using this knowledge, studies in human patients and controls demonstrated that approximately one half of the asthmatic individuals have an IL-13 driven gene expression signature, the other half does not [15]. The IL-13-dependent blood biomarker profile turned out to be surprisingly simple [1]: IgE [40] and eosinophils [41], the first identified markers of asthma, the chemokines

CCL13 (MCP-4) and CCL17 (TARC) [42], and the cytokine periostin [14, 15], all of which in part comprise the IL-13 dependent airway gene expression signature of humans and mice.

Marketing challenges had to be met in that a new cytokine inhibitor for asthma needed to be better than or at least equivalent to both older, well established therapies (corticosteroids, bronchodilators), and more recently developed therapies (leukotriene antagonists, omalizumab), and safe. The study design led by Dr. Matthews at Genentech addressed these challenges by enrolling patients whose asthma symptoms were not controlled by the above standard therapy [1]. Surprisingly to many, the clinical trial showed that in patients with uncontrolled asthma who exhibit an IL-13 biomarker blood profile, anti-IL-13 therapy, led to a rapid increase of FEV1, and this persisted for 3 months following the last injection of anti-IL-13. Levels of the biomarkers IgE, CCL13 and CCL17 in the blood fell in response to treatment demonstrating the neutralizing activity of the anti-IL-13 antibody [1]. Thus unlike other interventions, clear improvement in lung function could be obtained. Importantly, while the rise in FEV1 was significant, considerable airway obstruction remained in the patients.

Future challenges

The persistence of physiologic improvements with anti-IL-13 therapy and the decrease of Th2 serum markers opens the possibility that in humans, like in mice [43-45], blockade of IL-13 might normalize the activity of innate immune cells (epithelial cells, dendritic cells) that modify or present allergen to T cells and thereby reduce the ability of dendritic cells to exacerbate and maintain Th2 immune responses. This might be the beginning of the development of more durable asthma therapies with a reduced need for corticosteroid use. The future may also bring the combination of IL-13 neutralizing reagents with mild to moderate physical exercise and a balanced diet program in asthma patients with the goal to further improve airway obstruction. IL-13 neutralizing reagents may also have applications in a subpopulation of patients suffering from other chronic lung diseases, in particular chronic obstructive pulmonary disease and pulmonary arterial hypertension. IL-13 inhibitors might have application for some subtypes of cancer, in specific forms of breast can-

cer and lymphoma. Further research is also needed to understand the mechanism by which exogenous pollutants, which upregulate cytokines such as thymic stromal lymphopoeitin (TSLP) [46] that induce IL-13, and the endogenous (microbiome [47]) environment fosters or protects from IL-13-induced diseases such as asthma. Tests for gene polymorphisms promise to become powerful pharmacogenetic biomarkers [48] and predictors of ethnic variables that contribute to asthma [49, 50]. Polymorphisms in genes such as IL-33 and TSLP that are modified by environmental exposures and induce IL-13 show promise in the latter regard [49, 50].

The cross-disciplinary, random access approach that made the clinical success of IL-13 blockers possible will also be essential to efficiently meet these future challenges. Random access is the ability to access data at an arbitrary position in a sequence in equal time, independent of sequence size, as made possible by arrays for example. In the case of understanding the role of IL-13 in asthma, each scientist working and publishing on pieces of the whole puzzle was part of the random access structure that was the key to success. We emphasize, however, that the unraveling of the importance of IL-13 would not have been possible without the use of animal models of human allergic disease. As, curiously, the debate regarding the utility of especially mouse models of asthma continues [51], such animal models will remain critical tools in defining the future use of anti-IL-13 and further novel therapies for asthma and other allergic diseases. The concerted effort of scientists using clinical studies, cell culture, molecular biology and animal models as necessary is expected to be key to further improving airway obstruction in asthma and in blocking allergic diseases.

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