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Review

Th2 cytokines and asthma: an introduction

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Asthma is a highly complex disease that is still poorly understood and whose cause remains unknown. One of the striking advances in the last decade has been the recognition that cytokines play a critical role in orchestrating, perpetuating and amplifying the inflammatory response in asthma. Indeed the increased and abnormal expression of cytokines in airway cells is one of the major targets of corticosteroid therapy, by far the most effective controller treatment for asthma currently available. Many cytokines and chemokines are involved in the pathophysiology of asthma [1,2]. While some of these cytokines, such as interleukin (IL)-1, tumour necrosis factor-α and IL-6, are involved in many inflammatory diseases, including chronic obstructive pulmonary disease, rheumatoid arthritis and inflammatory bowel disease, others are more specific to allergic inflammation. These cytokines, IL-4, IL-5, IL-9 and IL-13, are derived from T helper type 2 (Th2) cells, although they may also derive from other cell types. Th2 cells are recognised by their secretion of IL-4, IL-5, IL-9 and IL-13, as opposed to Th1 cells, which secrete IL-2 and interferon-γ, although the clear distinction between Th1 and Th2 cells is not as distinct in humans as in mice. Th2 cytokines may play an important role in the pathophysiology of allergic diseases, including asthma. They may be useful therapeutic targets in the future management of allergic diseases, and several approaches to inhibiting these cytokines are now being tested in clinical trials or are in active development [3].

In this issue of *Respiratory Research* we focus on Th2 cytokines and their potential role in allergic diseases, such as asthma. John Steinke and Larry Borish [4] discuss the role of IL-4 in the pathogenesis of asthma and make the point that this is an upstream cytokine that regulates allergic inflammation by promoting Th2 cell differentiation and IgE synthesis. Early studies with an IL-4 antagonist, soluble recombinant IL-4 receptor (altrakincept), show therapeutic benefit as a steroid-replacing agent in moderately severe asthma [5] and longer term clinical trials are now underway. IL-5 is discussed by Scott Greenfeder and colleagues [6]. IL-5 is a cytokine that is highly specific for eosinophilic inflammation and antibodies that block IL-5 actions are effective in reducing eosinophilic inflammation and airway hyperresponsiveness (AHR) in various species. Recently, studies of a humanised anti-IL-5 monoclonal antibody (mepomizulab) in asthmatic patients have confirmed its extraordinary efficacy in reducing eosinophils in the circulation and the airways, but surprisingly no reduction in response to allergen or in AHR [7]. This result has been confirmed in a preliminary clinical trial of asthmatic patients whose symptoms were not controlled with inhaled corticosteroids and who showed no clinical improvement with anti-IL-5 antibody, despite a marked suppression of circulating eosinophils [8]. These studies confirm the importance of IL-5 in eosinophilic inflammation in man, but question the role of eosinophils in asthma. IL-13 has many actions similar to those of IL-4 and also regulates IgE production but, unlike IL-4, it does not regulate T cell differentiation to Th2 cells and T lymphocytes do not respond to IL-13. The role of IL-13 in asthma was recently reviewed in this journal by Marsha Wills-Carp [9]. IL-9 has been less intensively investigated than the other Th2 cytokines, but appears to amplify Th2-cell-mediated responses, as reviewed by Roy Levitt and colleagues in this issue [10]. They make a persuasive case for this cytokine as a target for inhibition in asthma.

The reason why Th2 cells should be more prominent in allergic diseases such as asthma is still unknown but the hygiene hypothesis is a persuasive theory, suggesting that lack of infection and exposure to endotoxins in dirt may alter the balance between Th1 and Th2 cells. This hypothesis now has increasing support from experimental animals and from epidemiological studies, as will be discussed by Fernando Martinez in the next issue of *Respiratory Research*. This has important therapeutic implications and suggests that stimulating Th1 cells might suppress Th2 cells and allergic inflammation. Genetic polymorphisms

may be one of the factors predisposing to the imbalance between Th1 and Th2 cells, including single nucleotide polymorphisms (SNPs) of the endotoxin receptor CD14. SNPs and predisposition to asthma are also discussed in this issue of *Respiratory Research* by Lyle Palmer and Bill Cookson [11], and several SNPs of the genes encoding Th2 cytokines (which are situated together in a cluster on chromosome 5q) and their receptors have now been associated with increased risk of atopy and asthma.

We live in exciting times, when the availability of new molecular and genetic techniques is beginning to elucidate some of the complexities of asthma. It is likely that this will lead to even more effective and specific therapies in the future that may be targeted to individual patients. The prospect of a cure for asthma is coming closer.

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