Anti-interleukin 5 strategies as a potential treatment for asthma

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Abstract
A paradigm shift, championed largely by cellular immunologists, has redefined asthma as an immune mediated phenomenon characterised by an interleukin 5 (IL-5) driven eosinophilic bronchitis. This change in emphasis has provoked intense interest in the possibility that inhibitors of IL-5 production, or antagonists of its activity, will provide a new generation of anti-asthma drugs.

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Resistance to helminthic infections has probably provided the selective pressure for the evolution of eosinophils although, paradoxically, perhaps the commonest clinical manifestation of tissue specific eosinophilia in modern western society is allergic disease. Until the last decade asthma was thought of in terms of bronchial hyperreactivity or mast cell instability. Pulmonary eosinophilia was either ignored or interpreted as a mechanism for containing the pro-inflammatory effects of mast cell degranulation. Drug therapy based on these ideas has proved to be either ineffective, as with the so called “mast cell stabilisers”, or has lacked specificity, as with the $\beta_2$ adrenergic agonists and glucocorticosteroids. In fact, the narrow toxic to therapeutic ratio allowed by most of the conventional anti-asthma agents may have contributed in part to the alarming increase in asthma related morbidity and mortality.

Perhaps as a result of dissatisfaction with the conventional wisdom and its therapeutic options, a number of studies undertaken in the last decade have forced a re-evaluation of our approach to the understanding of asthma and its treatment.

Scientific basis
WHY TARGET IL-5 AND EOSINOPHILS?
One possible strategy in the search for less toxic anti-asthma drugs is to identify and target a disease specific process. Pulmonary eosinophilia presents itself as one such target because (1) the isolated eosinophilia seen in parasitic infestation or non-atopic asthma suggests a control mechanism specific for eosinophil proliferation and independent of other haemopoietic cell lineages; (2) eosinophilia is a characteristic feature of the pulmonary late phase reaction and the extent of this reaction correlates strongly with various indices of clinical severity in asthma; and (3) eosinophil derived granule proteins are responsible for the destruction of the respiratory epithelium, mucosal oedema, bronchial hyperreactivity, and air flow limitation that characterise asthma.

While IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF), as well as IL-5, can stimulate eosinophil production in vitro, experiments with IL-5 transgenic and IL-5 deficient mice have shown that the expression of IL-5 by T lymphocytes is both a necessary and sufficient condition for the proliferation of eosinophils. Furthermore, the lungs of allergen sensitised mice deficient in IL-5 do not develop the typical histological and functional changes of asthma (including reactive eosinophilia) when challenged, despite a progressive rise in allergen specific IgE. However, pulmonary eosinophilia, tissue destruction, and air flow limitation follow allergen challenge when IL-5 expression is reconstituted in these IL-5 deficient mice.

THE IL-5 MODEL OF ASTHMA
Given these findings, a simple model of asthma is proposed. Activation of the cellular immune system results in the production of IL-5 which, in turn, locates to the bone marrow via the blood to stimulate the production of eosinophils. These then migrate to the lung to cause an eosinophilic bronchitis which is manifest clinically as asthma (fig 1). This model suggests two strategies for drug development; firstly, inhibitors of IL-5 production and, secondly, antagonists of IL-5 activity.

Therapeutic potential
TRANSCRIPTIONAL REGULATION AS A DRUG TARGET
The expression of most cytokine genes is thought to be primarily regulated at the transcriptional level. Such inhibition is a realistic target for drug development since both corticosteroids, some macrolide antibiotics, and cyclo-
suggested that small molecules may be capable of blocking the interaction. Too little is known of the interaction with the β chain or the signalling mechanisms to predict whether these might also be drug targets.

Despite the lack of small molecules or basic information which might allow the rational design of antagonists, studies with antibodies suggest that antagonists will be clinically efficacious. Competitive blockade of IL-5 with anti-IL-5 antibody has been demonstrated in vivo. In these experiments, parasite or allergen induced eosinophilia was completely abrogated when animals were pretreated or treated after infestation with an anti-IL-5 antibody. This antibody did not block the effect of IL-3 or GM-CSF on other granulocytes. Sch 55700 is a humanised variant of a rat monoclonal antibody against human IL-5. When given one hour before challenge to Ascaris responsive primates at a dose of 0.3 mg/kg intravenously, reactive pulmonary eosinophilia was decreased to 75% that of control primates. Surprisingly, six months after this statum dose, pulmonary eosinophilia in response to Ascaris challenge was still 75% less than that of the control response.

A single injection of anti-IL-5 receptor antibody has been shown to reduce the peripheral blood eosinophil count in IL-5 transgenic mice to control levels for several weeks. Whether the antibody acts by blocking the binding of IL-5 to its receptor or whether cells expressing the receptor are eliminated by an immune mechanism is unknown. Nevertheless, these experiments indicate that the IL-5 receptor is also a potential drug target.

Although anti-IL-5 antibody therapy shows great promise, the fact is that most asthmatic patients are well controlled on low to moderate dosages of inhaled glucocorticosteroid. If clinical trials prove humanised anti-IL-5 antibody to be efficacious, then the problems of cost, availability and administration will probably limit the use of IL-5 to the treatment of chronic severe asthma or asthma that is refractory to conventional therapy. For those patients already well controlled on inhaled glucocorticosteroids, however, the reasons for instituting anti-IL-5 therapy would probably reduce to issues of patient compliance, acceptability and, possibly, cost.

Undoubtedly the effectiveness of an antibody in the clinic will strengthen the argument for investment in the search for small molecule antagonists since modern techniques for producing biologically active antibody fragments make this a distinct possibility.

**Figure 1** The allergic cycle in asthma. The allergic reaction in the lung leads to the production of antibody and cytokines. IL-5 is carried by the blood to the bone marrow, stimulating eosinophil production. The eosinophils migrate to the lung where they cause tissue damage resulting in asthma. This presents two opportunities for intervention: inhibition of IL-5 production and antagonism of the interaction of IL-5 with its receptor on eosinophil precursors.

**ANTAGONISTS**

IL-5 interacts with a receptor heterodimer consisting of a cytokine specific α chain and a signal transducing β chain which is common to the receptors for GM-CSF and IL-3. No small molecule antagonists of any cytokine have yet been described. Pessimists would say that such multipoint interactions will be impossible to block with a small molecule. On the other hand, mutation of a single amino acid in IL-5 can result in a 100 fold decrease in activity, suggesting that small molecules may be capable of blocking the interaction. Too little is known of the interaction with the β chain or the signalling mechanisms to predict whether these might also be drug targets.

**POTENTIAL COMPLICATIONS**

Although anti-IL-5 blockade promises target specificity, it might also compromise immunity to parasites and exacerbate a small proportion of cancers. For example, parasite infestation may define a subgroup of patients in whom anti-IL-5 treatment is a contraindication. So little is known about the role of reactive eosinophilia in mucosal immunity and parasite...
infestation that the degree of risk can only be assessed by clinical trials.

Conclusions
Drugs specifically targeting IL-5 are a realistic possibility for the treatment of asthma and other allergic diseases. Experimental work with anti-IL-5 antibody provides encouragement that antagonists will work in the clinic. Studies on the expression of the IL-5 gene suggest that more specific transcriptional regulators may also offer a new generation of anti-asthma drugs. Realistically, it is only when such agents become available for clinical trials that their usefulness can be determined, particularly in relation to the already well established inhaled corticosteroids.

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