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Molecular mechanisms of atopy

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Introduction

There have been important recent advances in understanding the molecular mechanisms of atopy in terms of identification of key cells, the role of cytokines and other mediators, and the cell signalling pathways involved. This has given new insights into the epidemiological trends in atopic diseases and has provided novel molecular targets for the development of new therapies.[1,2]

Immunoglobulin E

Production of specific immunoglobulin (Ig)E is the characteristic abnormality of atopy. IgE is produced by B lymphocytes under the influence of interleukin (IL)-4 and IL-13. IgE binds to high-affinity IgE receptors (FcεRI) on mast cells to induce degranulation and mediator synthesis. IL-4 enhances the activation of FcεRI to augment the production of cytokines and lipid mediators.[3] These receptors may also be expressed on other cells such as basophils, monocytes and eosinophils. IgE may also activate low-affinity IgE receptors (FcεRII or CD23) that are expressed on B lymphocytes, T lymphocytes, macrophages and airway smooth muscle cells.[4] CD23 expression is enhanced by IL-4. Recently, a humanised murine monoclonal antibody (E25) directed against IgE has demonstrated a reduction in early and late responses to inhaled allergen and eosinophil counts in induced sputum, and reduced airway hyperresponsiveness.[5,6] There is a profound reduction in circulating IgE, which may be due to switching-off IgE production from B cells. In patients with severe asthma who require oral steroids there is a significant reduction in oral steroid requirements, and several patients are able to completely withdraw oral steroids in comparison with a placebo.[7] E25 may also reduce signalling through CD23 as IgE levels are lowered and this might explain its efficacy in chronic asthma, through an inhibitory effect on T lymphocytes, macrophages, eosinophils and airway smooth muscle.[8]

T lymphocytes

T lymphocytes play a pivotal role in orchestrating the inflammatory response in atopic diseases, through the release of specific cytokines, resulting in the recruitment and survival of eosinophils and in the maintenance of mast cells in the airways. T lymphocytes are coded to express a distinctive pattern of cytokines, which may be similar to that described in the murine T helper cell (Th)2 type of T lymphocytes, which characteristically express IL-4, IL-5 and IL-9 and IL-13.[9,10] This programming of T lymphocytes is presumably due to antigen-presenting cells, particularly dendritic cells. There appears to be an imbalance of Th cells in atopic diseases, such as asthma, with the balance tipped away from the normally predominant Th1 cells in favour of Th2 cells. The balance between Th1 cells and Th2 cells may be determined by locally released cytokines, such as IL-12 and IL-4.

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There is some evidence that early infections might promote Th1-mediated responses to predominate and that a lack of infection and exposure to endotoxins in childhood may favour Th2 cell expression, and thus atopic diseases.[11] Th2 cells predominate in the foetus but, during neonatal life, there is an increase in Th1 cells that may be driven by exposure to bacterial and viral infections and endotoxins. Reduced exposure to these environmental factors may thus lead to perpetuation of Th2 cells and the development of atopy; the so-called 'hygiene hypothesis' of atopy.[12]

Antigen-presenting cells

Dendritic cells

Dendritic cells are specialised macrophage-like cells in the airway epithelium that are very effective antigen-presenting cells,[13] and therefore play a very important role in the initiation of allergen-induced responses in asthma and other atopic diseases. Dendritic cells take up allergens, process then to peptides and migrate to local lymph nodes where they present the allergenic peptides to uncommitted T lymphocytes, to programme the production of allergen-specific T cells. Immature dendritic cells in the respiratory tract promote Th2 cell differentiation and require cytokines such as IL-12 and tumour necrosis factor-α (TNF-α) to promote the normally preponderant Th1 response.[14]

Macrophages

Airway macrophages may also act as antigen-presenting cells that process allergen for presentation to T lymphocytes, although alveolar macrophages are far less effective in this respect than macrophages from other sites, such as the peritoneum. Macrophages normally have a 'suppressive' effect on lymphocyte function, but this may be impaired in asthma after allergen exposure.[15] Macrophages may therefore play an important anti-inflammatory role, preventing the development of allergic inflammation.

Antigen presentation

The molecular mechanisms involved in antigen presentation are now well described. Antigenic peptides processed by the antigen-presenting cell are presented on class II major histocompatibility complex molecules to receptors on helper ($CD4^+$) T lymphocytes. Co-stimulatory molecules play a critical role in augmenting the interaction between antigen presenting cells and $CD4^+$ T lymphocytes. The interaction between B7 and CD28 may determine whether a Th2-type cell response develops, and there is some evidence that B7-2 (CD86) skews towards a Th2 response. Blocking antibodies to B7-2 inhibit the development of specific IgE, pulmonary eosinophilia and AHR in mice, whereas antibodies to B7-1 (CD80) are ineffective.[16] A molecule on activated T-cell CTL4 appears to act as an endogenous inhibitor of T-cell activation, and a soluble fusion protein construct CTLA4-Ig is also effective in blocking airway hyperresponsiveness (AHR) in a murine model of asthma.[17] Anti-CD28, anti-B7-2 and CTLA4-Ig all block the proliferative response of T cells to allergen,[18] indicating that these are potential targets for novel therapies that might be effective in atopic diseases.

Structural cells

Structural cells of the airways, including epithelial cells, fibroblasts and even airway smooth muscle cells, may also be an important source of inflammatory mediators, such as cytokines and lipid mediators in asthma.[19,20] Indeed, because structural cells far outnumber inflammatory cells, they may become the major source of mediators driving chronic inflammation in asthmatic airways. In addition, epithelial cells may play a key role in translating inhaled environmental signals into an airway inflammatory response and are probably a major target cell for inhaled corticosteroids.

Role of cytokines

Cytokines are important in the chronic inflammation of asthma and play a critical role in orchestrating the allergic inflammatory response.[21,22] The cytokines that appear to be of particular importance in asthma include the lymphokines secreted by Th2 cells.

Interleukin-4

IL-4 is critical in switching B lymphocytes to produce IgE, for expression of VCAM-1 on endothelial cells, and for inducing the differentiation of Th2 cells and IL-5, which is essential for the differentiation of eosinophils. IL-4 is of critical importance in the differentiation of Th2 cells and is therefore an 'upstream' cytokine that is an attractive therapeutic target in the treatment of atopic diseases. This is reinforced by the demonstration that a soluble receptor for IL-4 (altrakincept), given by inhalation, has a steroid-sparing effect in patients with moderately severe asthma.[23] IL-4 also enhances IgE-mediated activation of mast cells.[3]

Interleukin-13

There is increasing evidence that IL-13 in mice mimics many of the features of asthma, including AHR, increased IgE, mucus hypersecretion,[24] and induces the secretion of eotaxin form airway epithelial cells.[25] IL-13 signals through the IL-4 receptor α-chain, but

may also activate different intracellular pathways,[26] so it may be an important target for the development of new therapies. A soluble IL-13Rα2-Fc fusion protein, which blocks the effects of IL-13 but not IL-4, has been used successfully to neutralise IL-13 in mice *in vivo*.[24]

The IL-13Rα2-Fc fusion protein markedly inhibits the eosinophilic inflammation, AHR and mucus secretion induced by allergen exposure. IL-13 is expressed in asthma to a much greater extent than IL-4, indicating that it may be a more important target.[27] This suggests that development of IL-13 blockers, such as a humanised IL-13 antibody or the IL-13Rα2, may be a useful approach to the treatment of established allergic diseases.[28]

Interleukin-5

The critical role of IL-5 in eosinophilia has been confirmed by the use of an anti-IL-5 antibody in asthmatic patients, which almost depletes circulating eosinophils and prevents eosinophil recruitment into the airway after allergen.[29]

Interleukin-9

Another Th2 cytokine, IL-9 may play a critical role is sensitising responses the cytokines IL-4 and IL-5.[30]

Interleukin-12

IL-12 is the endogenous regulator of Th1 cell development and determines the balance between Th1 and Th2 cells.[31] IL-12 administration to rats inhibits allergen-induced inflammation[32] and inhibits sensitisation to allergens. IL-12 releases interferon-γ (IFN-γ), but has additional effects on T-cell differentiation. In mice, administration of an IL-12-allergen fusion protein results in the development of a specific Th1 response to allergens rather than the normal Th2 response with IgE formation.[33] This indicates the possibility of using IL-12 to provide a more specific immunotherapy, which might even be curative if applied early in the course of the atopic disease. We have demonstrated that IL-12 therapy in asthmatic patients reduces circulating eosinophils and eosinophils in induced sputum, but does not affect underlying AHR or response to allergen, and is associated with significant toxicity.[34]

Interleukin-18

IL-18, also known as IFN-γ-inducing factor, is an IL-1-like molecule that acts like IL-12 to induce the release of IFN-γ from Th1 cells, and thereby suppress Th2 cells.[35] Unlike IL-12m however, it does not promote the differentiation of Th1 cells.

Interferon-γ

IFN-γ inhibits Th2 cells and mediates many of the inhibitory effects of IL-12. In sensitised animals, nebulised IFN-γ inhibits eosinophilic inflammation induced by allergen exposure.[36] Administration of IFN-γ by nebulisation to asthmatic patients did not significantly reduce eosinophilic inflammation, however (possibly due to the difficulty in obtaining a high enough concentration locally in the airways).[37] Allergen immunotherapy increases IFN-γ production by circulating T cells in patients with clinical benefit[38] and increases numbers of IFN-γ-expressing cells in nasal biopsies of patients with allergic rhinitis.[39]

Interleukin-10

IL-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of many inflammatory proteins, including cytokines (TNF-α, granulocyte macrophage-colony stimulating factor, IL-5, chemokines) and inflammatory enzymes (inducible nitric oxide synthase) that are over-expressed in asthma.[40] In addition, IL-10 inhibits antigen presentation and sensitisation. Indeed, there may be a defect in IL-10 transcription and secretion from macrophages in asthma.[41,42]. In sensitised animals, IL-10 is effective in suppressing the inflammatory response to allergen,[43] suggesting that IL-10 might be defective in atopic diseases. IL-10 may play a key role in the mechanism of allergen immunotherapy.[44] Polymorphisms of the IL-10 promoter may be a determinant of severity in allergic disease such as asthma.[45]

Therapeutic implications

There is persuasive evidence that lack of early infections and a clean environment may increase the risk of atopy in a genetically predisposed individual. This has suggested novel therapeutic strategies to prevent atopic diseases, including exposure to bacterial product to stimulate a Th1-type immunity and to increase IL-12 secretion.[1,11]

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Decreased prevalence of asthma among children with high exposure to cat allergen: relevance of the modified Th2 response

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Introduction

Although there are many possible explanations for the increase in asthma, they can be simplified to three. The first was proposed as early as 1980 and was based on epidemiology from a small group of countries in each of which the increase was related to dust mite sensitivity.[1–3] This hypothesis focused on the increase in exposure that had occurred secondary to changes in housing and lifestyle. Over the next 10 years, it became obvious that increases had occurred in many countries and regions where dust mites were not the dominant indoor allergen. In Sweden and Finland, the increase was clearly