

Future of anti-inflammatory therapy in asthma

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A number of clinical therapeutic trials have demonstrated the effectiveness of anti-inflammatory therapy for asthma. Indeed anti-inflammatory agents such as inhaled steroids have been shown to be more effective in asthma treatment than bronchodilators (1-3). This finding is not surprising in light of the fact that pathology studies have shown the presence of chronic airway inflammation in almost all patients with asthma (4, 5). Thus, anti-inflammatory therapy should be first-line therapy for asthma, except in its mildest form (6-8). Therefore, further therapeutic developments will focus on the search for new anti-inflammatory compounds; this paper discusses some of these current and future therapeutic approaches.

The standard of anti-inflammatory treatment for asthma is the inhaled steroid class of drugs. Several studies have now demonstrated that such treatment modifies various characteristics of the chronic airway inflammation in this disease (9-11). Chronic treatment with inhaled steroids reduces the number of inflammatory cells in the airway mucosa and submucosa, and, more specifically, reduces the number of mast cells, eosinophils and lymphocytes. Steroid treatment is associated with repair of the airway epithelial structure. These treatment-induced morphological changes are associated with clinical efficacy and a decrease of airway hyperresponsiveness. It is not known at the moment which of the morphological changes induced by treatment with inhaled steroids are a necessary requisite for their therapeutic activity. Further therapeutic developments will be necessary to answer this question.

The pathogenesis of the chronic airway inflam-

mation in asthma is best understood for so-called allergic asthma, asthma characterized by the presence of IgE-antibodies to inhalant allergens. Other asthma causes may initiate the airway inflammation response differently, but the pathological end result appears to be very similar for all causes. Once the inflammation becomes established, it seems to be maintained by a tissue-driven response.

Allergic asthmatic airway inflammation is thought to find its origin in the development of a specific immune response to an inhaled allergen in the airways. The allergen is captured and processed by antigen-presenting cells (APC) (12). Dendritic cells are the major APC in airway mucosa. Following the capture of the antigen, these APC move to the regional lymph nodes in the airways, where they present the allergen in association with major histocompatibility antigen class II molecules to lymphocytes.

A characteristic of allergic asthma is the selective development of CD4-positive lymphocytes of the Th2-type (13). The mechanisms governing the selective development of the Th2-like lymphocytes in asthma are incompletely understood to date. Experimental data demonstrate that this selective development of Th2-type lymphocytes is promoted by Interleukin 4 (IL-4) and inhibited by Interferon-gamma (IFN- γ) and Interleukin 12 (IL-12). Genetic and/or environmental factors controlling antigen handling by APC, the interaction between APC and T-lymphocytes, and the pattern of T-lymphocyte activation may be responsible for the preferential switch to Th2-type lymphocytes. Once the allergen-specific lymphocytes are differentiated

and multiplied in the lymphoid structures and regional lymph nodes of the airways, they subsequently enter the circulation and redistribute to various tissues, selectively homing into the submucosa and the mucosa of the airways. Through the production of various cytokines, these lymphocytes expand the inflammatory reaction into the characteristic airway inflammation of asthma. IL-4 seems to be a crucial cytokine in the development of allergic airway inflammation, not only because of its role in triggering the differentiation of T-helper lymphocytes into the Th2-type but also by differentiating B-lymphocytes and thereby stimulating IgE-production. Both activities of IL-4 are antagonized by IFN- γ , a cytokine produced essentially by natural killer cells following stimulation by macrophages and monocytes via the production of IL-12 and IFN- α . IL-12 is an important cytokine for the development of the subtypes of T-helper lymphocytes (14). IL-12 selectively promotes the development of Th1-type lymphocytes. IL-13 is yet another cytokine that, like IL-4, stimulates the role of IgE-production by B-lymphocytes (15).

The production of allergen-specific IgE-antibodies takes place essentially in the lymphoid

structures in the airways and in the regional lymph nodes of the airways. Locally produced or circulating IgE-antibodies bind to high-affinity IgE-receptors on mast cells, basophils, eosinophils and dendritic cells and to low-affinity IgE-receptors on eosinophils, monocytes, macrophages, lymphocytes, dendritic cells and platelets. Cross-linking of the IgE-receptors by allergen on the surface of these cells leads to their activation and the release of various preformed and newly formed mediators in the intercellular spaces of the airways. The further differentiation and development of mast cells is enhanced by lymphocyte-produced IL-6 and by fibroblast-produced stem cell factor (SCF) (16). The attraction, activation and prolonged survival of eosinophils in the airway submucosa and mucosa is caused by the production and secretion of IL-3, GM-CSF, IL-5, RANTES and Tumor Necrosis Factor alpha(TNF- α) (Fig. 1) (17). The movement of circulating eosinophils and other inflammatory cells into the airways is controlled by priming of the cells by cytokines, the local production of chemokinetic and chemotactic factors, and by the expression of adhesion molecules on the inflammatory cells, the endothelium, and the extracellular matrix.

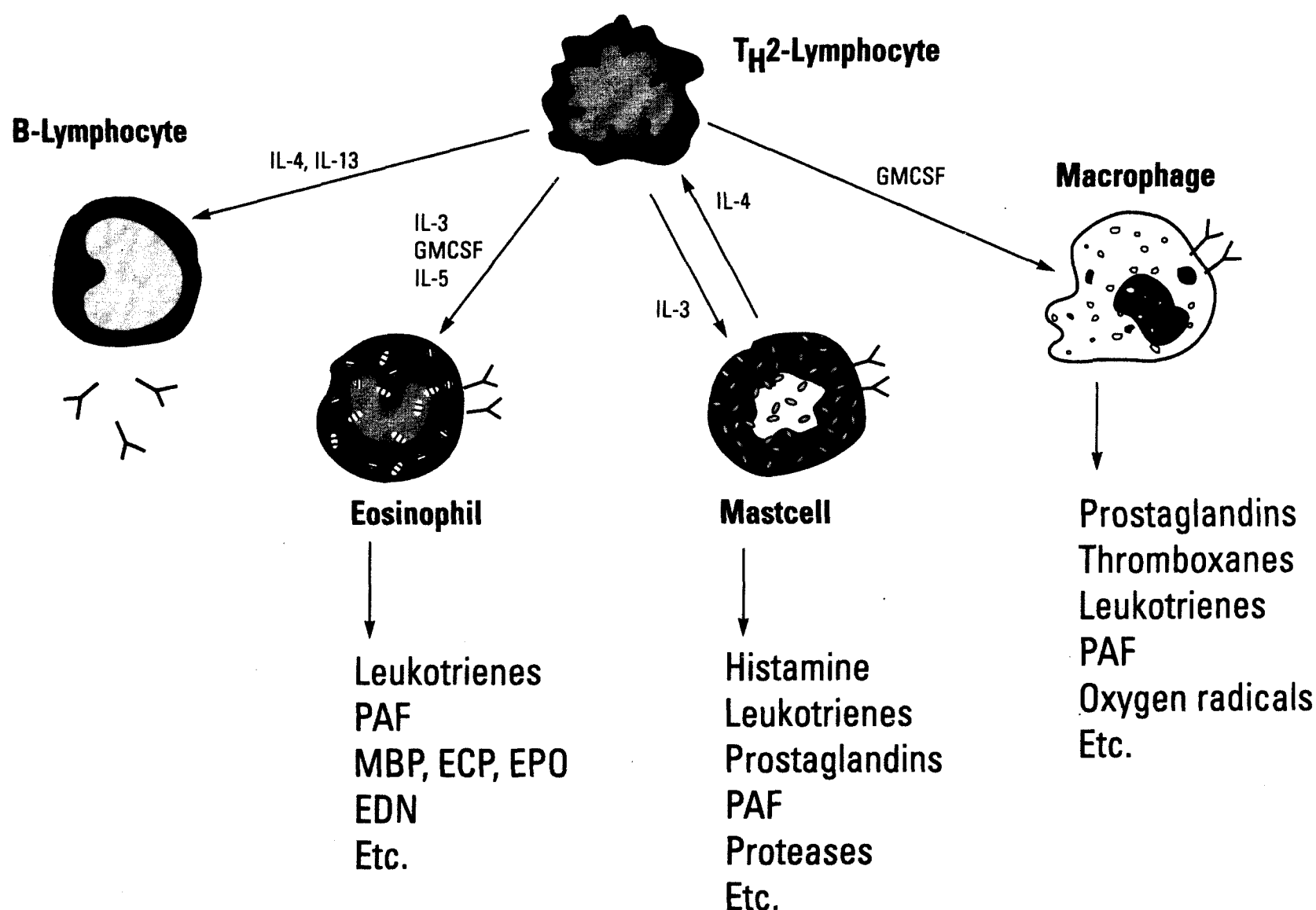


Fig. 1. Factors affecting the production and release of immune cell compounds present in asthma.

Mediators known to be released from activated mast cells and basophils include histamine, prostaglandin D₂, and, to a minor extent, lipid mediators such as leukotrienes and thromboxanes. Mast cells are also known to release various proteases. Eosinophils produce, upon stimulation, relatively large amounts of leukotriene C₄ (LTC₄) and Platelet Activating Factor (PAF). They also release a variety of toxic proteins including Major Basic Protein (MBP), Eosinophil Cationic Protein (ECP), Eosinophil Derived Neurotoxin (EDN) and Eosinophil Peroxidase (EPO) (18). Activated monocytes and macrophages release lipid mediators such as leukotriene B₄ and C₄, thromboxane A₂, prostaglandins, and PAF. They also release a variety of enzymes. It will be clear that the interaction between allergen and IgE-antibodies on the surface of different cell types may lead to the release of a high number of biologically active substances in the airway mucosa and submucosa. Further studies using selective mediator-, cytokine- and adhesion molecule-antagonists will be necessary to identify the specific role of individual molecules. An important characteristic of chronic airway inflammation in asthma is that constitutional and secondary inflammatory cells may play a role in its maintenance. Indeed, epithelial cells and fibroblasts have been shown to produce various pro-inflammatory cytokines such as GM-CSF, TNF α and IL-8 (19-22). Mast cells and eosinophils present in the asthmatic airways have similarly been shown to produce cytokines such as IL-4, IL-5, and TNF α (23-25).

Taken together, the chronic inflammation that characterizes asthma is maintained not only by the production of pro-inflammatory cytokines by sensitized lymphocytes, but also by an expanded role of mast cells, eosinophils, and constitutive cells such as epithelial cells, endothelial cells, and fibroblasts, all of whom seem to play a role in the maintenance of chronic inflammation. The exact role of each cell type and each mediator in generating the characteristic pathological changes in asthma is currently unknown. Finding the answers to these questions will only be possible if specific and potent antagonists or synthesis inhibitors of the different mediators, cytokines, and adhesion molecules, etc., are developed and tested in human asthma. This is, of course, almost impossible, and it will take a lot of imagination, perseverance and serendipity. The bonus side is, of course, that we will end up with a number of effective anti-asthma therapies. Not many people would have predicted, five years ago, that leukotriene D₄-receptor antagonists and 5-lipoxygenase inhibitors would have clinically significant therapeutic activity in asthma, but there is now sufficient evidence to suggest that

the leukotrienes play a role in maintaining the chronic inflammatory response. The effect of the leukotriene-receptor antagonists and synthesis-inhibitors on the chronic airway inflammation of asthma looks promising but requires further study.

Some of the novel approaches to anti-inflammatory therapy in asthma are presented in Table 1. Many of these approaches are still in a very early research state. The most advanced are lipid mediator antagonists and synthesis inhibitors. Clinical therapeutic studies have shown that leukotriene D₄-receptor antagonists and the 5-lipoxygenase inhibitor zileuton have clinically significant therapeutic activity in asthma (see further in this issue). PAF-antagonists (26) and thromboxane-antagonists have, up to now, completely failed in clinical trials in asthma. The role of H₁-antagonists in the treatment of asthma has been investigated in a number of clinical studies and, although some statistically significant improvements in some clinical parameters have been found, it is generally accepted that these drugs have no role in the treatment of asthma because of insufficient clinical therapeutic activity (27).

Table 1. Future asthma treatments' points of action

Broad therapeutic targets	Specific mechanistic approaches
Lipid mediators	Leukotriene D ₄ receptor antagonists 5-lipoxygenase inhibitors Thromboxane antagonists Platelet-activating factor (PAF) antagonists Lipocortin-analogues Phospholipase-inhibitors Bradykinin antagonists Antihistamines
Neurotransmitters	Specific receptor antagonists (NK-1 and/or NK-2)
Contractile mechanisms	VIP analogues Inhibitors of neurotransmitter release
Inflammatory cell activation mechanisms	Arachadonic acid metabolism inhibitors Anti-allergy drugs without antihistamines Phosphodiesterase inhibitors Protein kinase C inhibitors Immunophilin ligand inhibitor
Cytokines	Cytokine-receptor antagonists Cytokine-receptor agonists Cytokine synthesis and secretion inhibitors Cytokine receptor analogues
Adhesion molecules	Monoclonal antibodies to ICAM-1, VLA-4, LFA-1, VCAM, etc. Inhibitors of adhesion molecule expression. Antagonists of cell adhesion
Immune processes	T-cell vaccination Allergen-derived peptides

Selective and potent low molecular weight antagonists of the neurokinin receptors NK1 and NK2 have entered human trials. It is still too early to know if these neuropeptides and neurokinin receptors have a significant role in asthma. Selective NK1-antagonists may have anti-inflammatory activity whilst NK2-antagonists could act as bronchodilators (28). A VIP-analogue has been developed and shown to be a potent bronchodilator on isolated human airways. Further exploration of the anti-inflammatory activity of this and similar compounds appears to be worthwhile (29). Theophylline, a drug used in the treatment of asthma for many decades, has now been shown to have significant anti-inflammatory activity in asthma (30). The notion that this drug was only a bronchodilator and the risk of serious toxicity has resulted in a decreased use of theophylline. Based on the hypothesis that theophylline acts via inhibition of intracellular phosphodiesterase (PDE) and on the detection of iso-enzymes of phosphodiesterase that are selectively expressed in specific cell types, selective PDE-iso-enzyme inhibitors have been developed. PDE III (smooth muscle) and PDE IV (inflammatory cells, smooth muscle cells) inhibitors are currently in development for the treatment of asthma. Especially selective PDE IV and possibly mixed PDE III and IV inhibitors have the potential of anti-inflammatory treatment in asthma, but none of these compounds has yet reached the stage of clinical therapeutic trials.

Even further from the stage of clinical trials are cytokine-antagonists, agonists, etc. Target molecules for inhibition are IL-4 and IL-5. Useful molecules might be IL-10, IL-12 and IFN- γ or analogues. The pharmacological targeting of adhesion molecules is approximately in the same stage as that of the cytokines and suffers from the same problem with redundancy and plethora.

It is obvious that many of these approaches have therapeutic potential, but that only clinical therapeutic trials will bring us the ultimate evidence of the role of one or another mediator, cytokine or molecule. The positive side of these developments is that we will without any doubt learn more about asthma and that we will end up with some new effective therapies. This is especially interesting in view of the increasing prevalence of this disease.

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