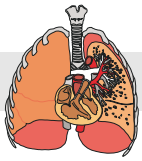

Update on Asthma

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Asthma has now become the commonest chronic disease in industrialized countries and is increasing throughout the world. There have been striking improvements in the management of asthma due to more effective therapy, which has led to an improvement in the quality of life of patients and a reduction in hospital admissions and death from asthma attacks. We now have a much better understanding of the underlying pathophysiology of asthma as a result of applying modern molecular and cellular investigational techniques. However, despite these advances in knowledge, asthma remains widely undertreated [1], the prevalence of the disease is increasing, and none of the currently available treatments are curative. There are many key issues in asthma that have yet to be resolved.

The increasing prevalence of asthma

The global increase in asthma appears to be part of an increase in all atopic diseases, including allergic rhinitis and atopic dermatitis. In some countries the prevalence of atopic diseases approximately doubles every 10 years. The reason for this dramatic increase is still uncertain, but the time scale of the change suggests that it must be due to some environmental factor(s) occurring throughout the world, particularly with westernization of society. Several possible environmental causes have been proposed. Although it is widely believed that air pollution due to road traffic might be responsible, this does not fit well with the epidemiologic evidence. There is no evidence that allergic diseases are more common in areas that are more polluted by traffic or industrial pollutants; in fact, asthma is very prevalent in New Zealand, a country with low air pollution [2].

Another possibility is that people are now exposed to more allergens such as house dust mite or domestic pets. However, there is no good evidence that allergen exposure has significantly increased throughout he world, and the increase in atopy is not specific for any particular allergen. A more likely possibility is that the increase in asthma is related to a reduction in exposure to infections and endotoxins in early life – the so called "hygiene hypothesis" [3]. At birth the immune system is characterized by a preponderance of T helper 2 lymphocytes, typified by secretion of interleukins 4 and 5, which are predominant in fetal life. However, exposure to bacterial and viral infections and to endotoxins in dirt during early childhood converts the immune system to one dominated by Th1 cells [4]. Th1 cells protect against the expression of Th2 lymphocytes through the secretion of interferon-gamma [4]. A cleaner environment and more widespread use of antibiotics may favor the persistence of Th2 immunity and thus an increased risk of developing allergic diseases. This theory remains to be proved, but it obviously has important implications for prevention and even cure of asthma. Another possibility is that changes in diet may predispose to the increased prevalence of atopy. There is epidemiologic evidence that eating oily fish and fresh fruit and vegetables protects against the development of asthma, so a change towards consuming more convenience foods may be another factor predisposing towards the development of atopy [5]. It is likely that an interaction of several environmental factors associated with westernization and affluence lead to the increases in atopic diseases. There is some evidence that the increase in asthma is somewhat greater than the increase in rhinitis, atopic dermatitis and atopy, suggesting that additional, perhaps inhaled, environmental factors are involved.

The role of genetic factors in asthma

There has been an explosion of research into the genetics of asthma. Asthma clearly runs in families and recent studies have shown a high degree of concordance in identical twins [6]. The heritability of asthma is largely due to a strong genetic influence on atopy. Several genes have been implicated in the inheritance of atopy, but there is still poor agreement between studies in different populations [7]. However, the genes that determine atopy cannot explain which atopic people will go on to develop asthma. Indeed, it seems that environmental factors, such as infections and early exposure to inhaled allergens, may be more important. There is now increasing interest in the possibility that genes may determine the pattern of asthma and, in particular, the severity of asthma in individual patients. Some patients have very mild disease with only occasional wheezing, whereas others have very severe airway narrowing and require large doses of medication. The pattern of asthma tends to remain constant with no progression from mild to

Th = T helper

severe disease, and patients with severe asthma having severe disease from the onset. These differences cannot easily be explained by environmental factors and are more likely attributable to multiple genetic polymorphisms. Some of the genetic polymorphisms in the genes that determine inflammation in asthma are now beginning to be elucidated. For example, patients with severe asthma are more likely to have polymorphisms of the anti-inflammatory IL-10 gene that are associated with decreased secretion [8] and with polymorphisms of the gene for transforming growth factor-beta, which is associated with fibrosis [9]. Genetic differences between mild and severe asthma may reveal new targets for treatments and may also predict which patients are at risk of developing severe disease. Genetic factors may also determine differences in response to asthma treatments [10]. This may become increasingly important as more specific therapies, such as anti-leukotrienes, are introduced into asthma treatment.

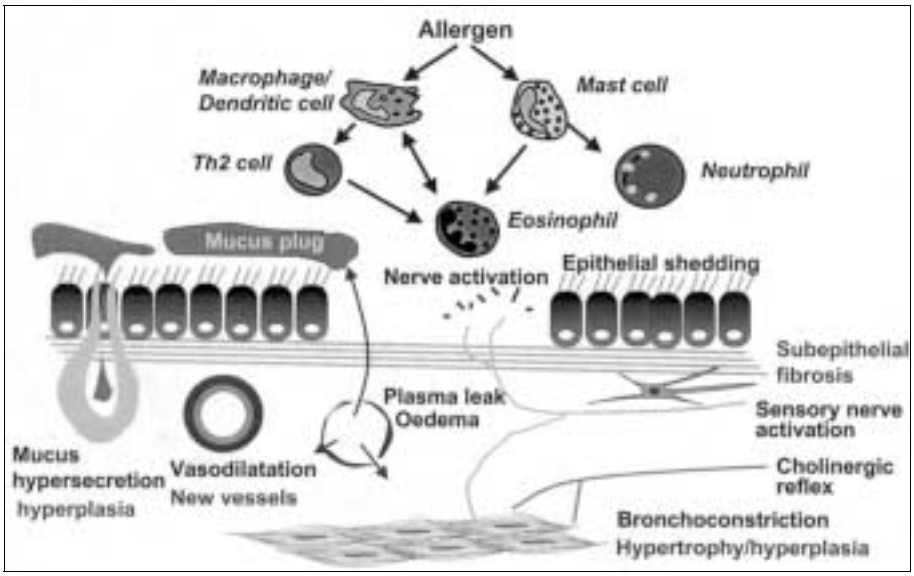

Figure 1. Multiple inflammatory cells in asthma produce chronic inflammatory changes in the airway wall.

Asthma as an inflammatory disease

Asthma is a complex chronic inflammatory disease that involves many cells, mediators and inflammatory effects [11] [Figure 1]. This inflammation is present even in patients with very mild episodic disease. The inflammation in asthma is characterized by the activation of mast cells and Th2 lymphocytes and an infiltration of activated eosinophils. It is found in airways of all sizes – from trachea down to terminal bronchioles. Indeed, the presence of inflammation in small airways has raised concern that we may not be treating these peripheral airways adequately with inhaled drugs that possibly do not penetrate to the lung periphery in severe disease [12]. Many mediators are involved in asthma and almost 100 have been implicated [13], including multiple cytokines, chemokines and growth factors [14]. Blocking a single mediator is therefore unlikely to be very effective in this complex disease, thus mediator antagonists have so far not proved to be very effective compared with drugs having a broad spectrum of anti-inflammatory effects, such as corticosteroids.

An important new concept is that structural cells of the airways become mediator-producing cells. Thus, airway epithelial cells, endothelial cells, fibroblasts and even airway smooth muscle cells show an altered phenotype and express multiple inflammatory mediators, including cytokines, chemokines and peptides. Indeed, these cells then become key targets for asthma therapy. There is increasing evidence that airway epithelial cells are major targets for inhaled corticosteroids [15].

Chronic inflammation in asthma may lead to structural changes in the airway, including fibrosis under the epithelium, increased thickness of airway smooth muscle, increased numbers of blood vessels (angiogenesis) and increased-mucus secreting cells [16]. These changes, referred to as remodeling, may not be reversible with current treatments and explain why there is an irreversible component of airway obstruction in some patients with severe disease. This may also explain why there is an accelerated decline in lung function in asthmatic patients [17]. Why some patients develop these irreversible changes while others do not may be determined by genetic factors that are currently unknown.

Airway hyper-responsiveness

The relationship between inflammation and clinical symptoms of asthma is not clear. There is evidence that the degree of inflammation is loosely related to airway hyper-responsiveness, as measured by histamine or methacholine challenge. However, the degree of inflammation does not clearly correspond to asthma severity. This suggests that other factors, such as structural changes in the airway wall, are important. The airway hyper-responsiveness in asthma is a striking physiologic abnormality that is present even when airway function is normal. It is likely that several factors underlie this increased responsiveness to constrictor agents, particularly those that act indirectly by releasing bronchoconstrictor mediators from airway cells. Airway hyper-responsiveness may be due to increased release of mediators (such as histamine and leukotrienes from mast cells), increased contractility of airway smooth muscle, and thickening of the airway wall by elements that are reversible (edema) and irreversible (airway smooth muscle thickening, fibrosis). Increased sensitivity of airway sensory nerves may also be a major contributing factor to airway hyper-responsiveness since the nerves become sensitized by the chronic inflammation in the airways.

In hyper-responsive airways, triggers that would not normally narrow the airways, such as exercise, have a bronchoconstrictor effect. There is reason to believe that products of the inflammatory

IL = interleukin

response may directly lead to an increase in asthma symptoms such as cough and chest tightness. These sensory symptoms, which are the equivalent of pain in other inflammatory diseases, may be mediated by sensitization and activation of airway sensory nerve endings.

Anti-inflammatory mechanisms

Although emphasis has been placed on inflammatory mechanisms, there may be endogenous anti-inflammatory mechanisms that are defective in asthma, resulting in increased inflammatory responses in the airways [18]. Various cytokines have anti-inflammatory actions, the most extensively investigated of which is IL-10, a cytokine with a broad spectrum of anti-inflammatory actions [19]. There is evidence that IL-10 secretion and gene transcription are defective in macrophages and monocytes from asthmatic patients, particularly in patients with severe disease [20]. This may lead to enhancement of inflammatory effects in asthma and may be a determinant of asthma severity.

Modern asthma management

The management of asthma has been revolutionized by the use of inhaled corticosteroid for all patients with persistent asthma, including children. This is by far the most effective therapy for managing asthma, with control of symptoms, improvement in health status and prevention of exacerbations [21]. There is also evidence that early use of inhaled corticosteroid may prevent irreversible airway obstruction and that regular treatment with inhaled corticosteroid markedly reduces asthma mortality [22]. Inhaled corticosteroids have therefore become first-line treatment for asthma and are now recommended as the controller treatment of choice in all patients. Side effects have been carefully evaluated, especially in children, and there is no evidence that the low doses required by most patients cause any clinically important effects on growth in children or bone density in adults [21].

It has recently become clear that the dose-response curve for the effectiveness of inhaled corticosteroids in asthma is relatively flat for most patients, so that most of the benefit is seen at doses of 400–800 g beclomethasome dipropionate or its equivalent per day [23]. In patients not controlled on these doses it is more effective to then add another class of drug rather than increasing the dose of inhaled steroids. The most effective add-on therapy is a long-acting inhaled beta-2 agonist (salmeterol or formoterol) and there are now a significant number of studies demonstrating this advantage. Hence, the rationale for the introduction of fixed combination inhalers containing a corticosteroid and LABA. These combination inhalers are more convenient for patients, more cost-effective, and patients are more compliant [24].

The other add-on therapies are theophylline and anti-leukotrienes. Low dose theophylline has an anti-inflammatory effect [25] and is more effective than increasing the doses of inhaled corticosteroids in patients not controlled on low doses [26]. Recent molecular studies have demonstrated that low concentrations of theophylline may enhance the anti-inflammatory action of corticosteroids. However, theophylline is less effective than LABAs as an add-on therapy [27].

Anti-leukotrienes have attracted much attention as they are the first new class of treatment for asthma in over 30 years [28]. They have the advantage of being taken as a tablet once a day, but are expensive and considerably less effective than low doses of inhaled corticosteroids, as demonstrated in all the studies that compared these two drugs directly. As add-on therapy they are less effective than LABAs and are more expensive [29]. In patients with severe asthma, anti-leukotrienes do not seem to have any beneficial effect [30], whereas LABAs are effective [31].

New treatments for asthma

Most patients with asthma are well controlled with inhaled corticosteroids and a beta-2 agonist, yet many patients remain undertreated and are poorly compliant with regular preventive treatment [1]. Compliance with inhaled corticosteroids is very poor, particularly in patients with mild and moderate asthma. This is partly because patients forget to take regular treatment when their symptoms are controlled and partly because they are afraid of systemic side effects of inhaled corticosteroids. Preferable therefore are the new treatments that are as effective as inhaled corticosteroids and could be taken as a once-daily tablet or even as a weekly or monthly injection. At the other end of the spectrum are patients with severe asthma who are difficult to control with existing treatments, including high doses of inhaled corticosteroids. New classes of treatment are needed for these patients, who constitute only about 5% of patients but account for more than half of the healthcare costs of asthma [32]

It has proved very difficult to develop new effective treatment for asthma, although much research is underway [33]. There has been a particular emphasis on treatments that block the eosinophilic inflammatory process by blocking cytokines, chemokines or adhesion molecules that are involved in the recruitment of eosinophils to the airways. Monoclonal antibodies to IL-5 have been shown to be remarkably effective in reducing blood and sputum eosinophils in asthmatic patients, yet have no effect on airway responses to allergen, on airway hyper-responsiveness or on asthma symptoms [34]. This has questioned whether inhibition of eosinophils is sufficient for the clinical control of asthma and implies that corticosteroids act in asthma by blocking multiple inflammatory mechanisms. Other cytokine-based approaches include inhibitors of IL-4 and IL-13, or anti-inflammatory cytokines (IL-10, IL-12 and IFNγ), but so far they have not proved effective [35]. Perhaps the most promising new therapy is an antibody that blocks immunoglobulin E (omalizumab) and appears to be most effective in patients with more severe asthma and reduces the requirement for oral and inhaled corticosteroids [36]. This treatment may be complementary to inhaled corticosteroid in patients with severe asthma, as corticosteroids alone do not reduce IgE. Several other new classes of drug are in development, including phosphodiesterase-4 inhibitors, p38 mitogen-activated protein kinase inhibitors, and inhibitors of nuclear factor-kappa B, but it is unlikely that these

LABA = long-acting inhaled beta-2 agonist

IFNγ = interferon gamma

treatments will be more effective than corticosteroids and are more likely to cause side effects.

Even corticosteroids do not cure asthma, because when they are withdrawn asthma deteriorates and airway inflammation increases. The prospects for a curative treatment are dim at present since the underlying molecular causes of asthma remain unknown. Perhaps the most hopeful approach is vaccination with bacterial products to prevent the immune deviation from Th1 to Th2 cells. This strategy may have risks since Th1-dominated disease, such as diabetes and autoimmune diseases, might increase. Another problem is that to be effective vaccination must be administered in infancy.

Non-invasive monitoring of inflammation

Since inflammation underlies asthma it is important that this be measured in the clinical setting. Airway inflammation has traditionally been measured by fiberoptic bronchial biopsies and bronchoalveolar lavage, but these invasive approaches are not practical in the ambulatory clinic setting and cannot be repeated or used in children or patients with severe disease. Nonetheless, several less invasive approaches have been developed. Induced sputum has provided important information on eosinophils and other inflammatory cells as well as on mediators [37], but this procedure is relatively invasive, is unsuitable for young children, requires considerable expertise, and therefore is not suitable as a routine clinical measurement. Nitric oxide is formed in increased amounts at inflammatory sites due to the induction of inducible NO synthase. This accounts for the increase in NO concentrations in exhaled breath of patients with asthma. Evidence is accumulating that this simple non-invasive measurement may be useful in monitoring inflammation in asthma and its control by corticosteroids [38]. This technique may also be applied in infants and may therefore be useful in deciding whether wheezing is due to asthma or a non-asthmatic condition [39]. At present exhaled NO can only be measured by expensive analyzers, but in all likelihood small and inexpensive detectors will become available that will allow patients to monitor exhaled NO at home.

Several other non-invasive measurements are currently being explored, including exhaled carbon monoxide and hydrocarbons and exhaled breath condensate in which several mediators may be detected [40]. For example, patients with asthma have increased concentrations of leukotrienes in exhaled breath condensate and this might be used to predict the patients who can benefit from anti-leukotriene treatment. This technique can also detect cytokines, and in asthmatic children there is an increase in the IL-4:IFNγ ratio in exhaled breath condensate. In the future it may be possible to measure a number of biomarkers in exhaled breath condensate (a "breathogram") in order to aid diagnosis of asthma and to predict and monitor responses to treatment.

Future developments

It is clear that the future will provide a better understanding of the molecular and cellular mechanisms that cause asthma. This will enable us to understand differences in asthma severity and outcome between patients in terms of differences in single nucleotide polymorphisms. Detection of panels of single nucleotide polymorphisms using gene chip arrays or patterns of protein expression may then predict the outcome in individual patients and their responses to more specific therapies. It is possible that each patient will be treated with a specific and highly effective therapy based on these individual differences. Furthermore, we may be able to prevent the development of asthma in predisposed individuals using some form of vaccination to prevent the development of atopy. However, it is possible that atopy confers some benefits that are not yet apparent and there may be long-term disadvantages in its prevention.

NO = nitric oxide

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