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Asthma is recognized as the most common treatable chronic disease of the lung, afflicting over 100 million people of all age groups yet, despite therapeutic advances, there has been little impact on the rising morbidity and mortality from the disease. This article discusses ways in which molecular medicine can inform public health policy and clinical practice in the management of asthma. It focuses on the recognition that asthma is an inflammatory disorder, and that the public health burden of the disease can be reduced by identifying environmental factors that may trigger asthma in genetically susceptible individuals.

William Osier first alluded to the importance of airway inflammation in asthma in 1892, yet it has taken us over 100 years to gain an insight into the pathogenesis of asthma, primarily because of the difficulty in obtaining access to ‘airway tissue’ in living patients. With the introduction of fibre-optic bronchoscopy and also advances in molecular medicine, the past decade has seen a major change in how asthma is perceived: as a disease of airway inflammation rather than solely in terms of disordered smooth muscle function. The disease process is now accepted to involve the action of several types of immune response and a number of different cell types, including eosinophils, mast cells and T cells, acting in an orchestrated fashion. This knowledge of the molecular mechanisms in asthma has changed the emphasis of the clinical management of asthma towards the recognition of the central role of allergen-provoked inflammation, and has mirrored the development of more selective and more potent drugs specific for the mediators of inflammation. This shift in emphasis has public health implications for the prevention of asthma; these will be discussed in this short article.

Allergic airway inflammation in asthma
The clinical expression of asthma spans a wide spectrum, from mild seasonal symptoms to severe, intractable and debilitating disease. There has been an explosion in knowledge over the past decade in the understanding of the complex interactions of cytokines and their effects on the differentiation, maturation and activation of different cell types and subsets. Modern molecular techniques, such as immunohistochemistry, in situ hybridization and PCR, have been applied to the examination of biopsies of bronchial tissue and cells obtained by washing out sections of the airways (bronchial lavage) of mild to moderate asthmatics. These studies have led to the recognition that there is a characteristic repertoire of cytokines produced by the Th2 subset of CD4+ helper T cells in asthma. From this understanding, a cohesive explanation of the role of cytokines in asthma can be derived (Fig. 1).

Acute airway inflammation
The airways of asthmatic patients respond to inhaled allergen by producing an acute phase of bronchoconstriction (early asthmatic
response, EAR) followed by further bronchoconstriction (late asthmatic response; LAR) (Fig. 2). After recovery there is an increase in acquired bronchial hyperresponsiveness (BHR) to agents such as methacholine and histamine; this can persist for several days after the resolution of the LAR. In the short term, this 'acute model' of allergen provocation has helped to explain why some of the currently used drugs are effective for the management of asthma. Both nedocromil sodium and sodium cromoglycate inhibit the EAR, LAR and BHR by inhibiting the release of mast-cell-derived mediators (see Fig. 2). Corticosteroids reduce the LAR, probably by inhibiting the cytokine-mediated upregulation of adhesion molecules on the pulmonary microvasculature that is responsible for leukocyte recruitment in the airways. They also reduce the secretion of cytokines from mast cells and T cells. These are suppressive effects that are thought to result from the corticosteroid binding to a cytoplasmic receptor, formation of a complex that binds to specific sites on DNA, and activation or repression of

Figure 1. The role of cytokines in inflammatory responses in asthma. In asthma, cytokines are produced as a result of the upregulation of the interleukin 4 (IL-4) gene cluster (IL-3, IL-4, IL-5, IL-6, IL-9, IL-13 and granulocyte-macrophage colony-stimulating factor (GM-CSF)) in leucocytes in response to allergen provocation. These cytokines are of fundamental importance to the initiation and maintenance of the allergic inflammatory response. The inflammatory events seen in asthma, including T-cell activation and release of pro-inflammatory mediators by mast cells, occurs after the switching of the isotype of antibody produced by B cells to immunoglobulin E (IgE), which is mediated/regulated by the cytokines IL-4 and IL-13 produced by T helper (Th) cells and follows the presentation of allergen to B and T cells by dendritic cells and macrophages. The Th2 T-cell subset matures and expands under the influence of IL-4 produced by both Th cells and mast cells, IL-3, IL-5 and GM-CSF induce the maturation and activation of eosinophils and basophils, resulting in eosinophil recruitment to the airways from pulmonary vasculature; and IL-6 and IL-9 are important in mast-cell maturation and upregulation of IgE secretion from B cells. The production of other cytokines that would suppress this characteristic response in asthma is reduced; these 'anti-asthmatic' cytokines are: interferon γ (IFN-γ), produced by Th1 cells; and IL-12, produced by monocytes and macrophages. The bronchial epithelium (IL-6, IL-8, GM-CSF) and fibroblasts (IL-8, GM-CSF, stem-cell factor (SCF)) are also important cytokine producers, and these cells have a role in severe asthma, where continuous T-cell activation and leukocyte recruitment persist even after the stimulus of allergen provocation has ceased (not shown). FcR, Fc receptors; HLA class II, class II human leucocyte antigen receptors; TCR, T-cell receptor; TNF, tumour necrosis factor.
Specific genes coding for cytokines. Similar transcription-factor-mediated downregulation of both cytokine production and pro-inflammatory pathways is likely to account for the efficacy of most anti-asthma drugs in current use.

**Chronic airway inflammation and repair**

Statistics of the 'cost of illness' for adult asthma, according to disease severity, reveal a disproportionate use of medical resources by patients with severe disease. In North America, 10% of asthmatics have severe asthma, yet this minority accounts for over 54% of the total resources allocated to the control and management of the disease. Similar data from other countries confirm that severe asthmatics are more likely to consult asthma specialists, use emergency room services and require hospitalization. On the grounds of public health costs alone, there is a clear case for focusing scientific research on this group of asthmatics, particularly in identifying factors that contribute to the chronicity and severity of the disease. While it is recognized that airway inflammation underlies the pathophysiology of asthma, its relationship to disease severity is less clear. Although 'biomarkers', such as the presence of eosinophils in the sputum and a persistent blood eosinophilia, relate to disease severity, these measures are too variable to provide clinically useful markers to predict the level of airway inflammation. Furthermore, the observation that patients with asthma have persistent airway inflammation, even in the absence of provoking allergens, suggests complex cellular and mediator mechanisms in maintaining the inflammatory response beyond allergen provocation. It is the continued allergen-specific production of immunoglobulin E (IgE) in severe disease that provides the rationale for allergen avoidance in asthma. Recent epidemiological studies have linked the level of total serum IgE to disease progression, although there have been few long-term studies on airway inflammation and long-term prognosis. The evidence that does exist suggests that severe and poorly controlled asthma progresses to an increasing, irreversible condition. Severe and prolonged inflammation in most tissues is almost always accompanied by tissue remodelling, and the airways are no exception, although the mechanisms involved and their contribution to the overall pathophysiology of severe and chronic asthma have not been fully evaluated.
It follows that the severity and chronicity of asthma result from the
dysregulation of cytokine networks, leading to persistent inflammation,
which becomes refractory to treatment, in structurally altered airways.
The responsibility for disease progression does not lie with any single
cellular element but embraces T and B cells, mast cells, eosinophils,
endothelial cells, epithelial cells and myofibroblasts acting cooperatively
with each other and with formed elements of the airways,
including smooth muscle and nerves, leading to the variable phenotype
that is characteristic of severe disease. This provides an integrated
view of asthma as a chronic disease of ongoing inflammation and repair.

Nitric oxide and asthma – a new non-invasive test

One of the persisting difficulties in the management of moderate
to severe asthma is the inability to monitor airway inflammation
without the use of invasive investigations. Recently, it has been rec-
ognized that nitric oxide (NO) is important in asthma as a vasodilator,
neurotransmitter and inflammatory mediator. NO is generated from
l-arginine by the enzyme NO synthase, which can exist in constitutive
and inducible isoforms (cNOS and iNOS, respectively). Our group
has recently shown, using immunological techniques, that iNOS is pres-
ent in large amounts in the bronchial epithelium of mild asthmatics,
but only rarely in people unaffected by asthma. Consistent with the
hypothesis that there is an increase in NO generation associated with
airway inflammation is the increase in NO detected in exhaled air in
people with symptomatic asthma or rhinitis. This production of NO
by human airway epithelial cells has been shown to be inhibited by
the addition of corticosteroids to cells in vitro. Further evidence indi-
cates that iNOS is downregulated (possibly by blocking NF-kB) in
those people with asthma that responds to corticosteroids, and this
response to the corticosteroids is associated with a reduction in NO

Environmental factors, particularly inhaled allergens such as house
dust mite (HDM), pollen and fungal spores, are important in the
development of asthma. Studies have shown a link between the
prevalence of asthma and the long-term exposure to allergens; and if
the exposure to allergens is reduced, the symptoms of asthma tend to
improve. These observations strongly suggest that allergens induce
the onset of asthma by stimulating a chronic, allergic inflammation in
the airways. Identifying ways to reduce allergen exposure, or modu-
late the factors that may reduce ‘sensitization’, are important research
priorities with implications for public health. One factor known to
influence airway sensitization is the quality of air we breathe. It is
recognized that air pollutants such as ozone, nitrogen dioxide and
sulphur dioxide can trigger asthma exacerbations, but the interac-
tion of susceptible people with environmental allergens may be more
important than the control of the gases in their environment. Studies
in which people have been kept in controlled chambers have shown
that exposure to certain pollutants, or a combination of them, can
enhance the response of the airway to allergens. Thus, the environ-
ment in which susceptible people live and work could provide impor-
tant targets for the prevention of asthma; further investigations will
be needed before such approaches can be implemented effectively.

Coexistent virus infection has also been implicated as a factor that
affects the inflammatory events in individuals with asthma. There is
evidence that first-born children are at greater risk of developing
asthma than siblings that follow. Although the mechanisms are
unknown, one explanation is that younger children of the family are
in some way protected by early exposure to infectious agents, such as
the measles virus. Early in life, viruses and other infections may pro-
protect the children rather than make them more liable to illness. In later
childhood, viruses clearly have the capacity to exacerbate asthma.
Using PCR, we have recently shown that common respiratory viruses,
particularly rhinovirus and coronavirus, are associated with exacer-
bations of asthma in children, and hospital admissions for asthma
in adults. However, although viruses are important in short-term
exacerbations of asthma in children, continued exposure to allergens
remains the main drive behind the persistence of asthma symptoms
into adulthood in susceptible individuals.
Glossary

Atopy – The genetic predisposition for mounting an immunoglobulin (predominantly IgE) response to common allergens. It is associated with increased levels of IgE in the circulation and tissues and is the major risk factor for developing asthma.

Bronchial hyperresponsiveness – Describes airways that narrow too readily or too much in response to a provoking stimulus. In asthmatic patients, the airways can be hyperresponsive to many different stimuli. The airways of people without asthma are not hyperresponsive.

Nuclear factor κB (NF-κB) – A transcription factor involved in the upregulation of adhesion molecules that are important in leukocyte recruitment from the peripheral circulation. By binding to specific promoter sites on genes coding for adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), NF-κB can activate or suppress the target genes.

Stem-cell factor (SCF) – A growth factor necessary for mast cells; produced by fibroblasts. Also known as c-Kit ligand or Steel factor.

Early exposure to allergens

Factors in early life, such as atopy, low birthweight and maternal smoking during pregnancy, are known to increase the frequency and severity of ‘wheezing illnesses’ (or asthma) in infancy, yet less is known about the factors that predict wheezing in adolescence. This suggests that, whilst the symptoms of asthma in adults are caused by airway inflammation, wheezing symptoms in infancy are related to the size of the airways in utero and during the first year of life, which, in turn, are susceptible to environmental insults. The MRC Environmental Epidemiology Unit (Southampton, UK) has shown that obstructive lung disease, such as asthma and allergies, in late adulthood is associated with disproportionate growth as a foetus. An enlarged head size at birth in relation to body size is strongly associated with elevated serum IgE in adulthood, and it is possible that this is related to thymic maturation. The size of the brain, and consequently the head circumference, is related to the growth of the thymus gland. In some foetuses, undernutrition results in growth retardation and, as a result, a ‘brain-sparing’ reflex redistributes blood and nutrients to the brain at the expense of the trunk and limbs, including the thymus gland. Animal studies indicate that this would alter the Th1/Th2 lymphocyte population in the thymus, resulting in Th2 dominance and an immune response characteristic of that in asthma and allergy. Furthermore, T cells can be isolated from the foetal blood in the umbilical cord of babies born to parents who are atopic; if these cells are stimulated in vitro with a specific allergen, they show impaired production of the ‘allergy-suppressing’ cytokine interferon γ (IFN-γ) and enhanced IL-4 production. These observations suggest that the Th2 response to allergens that is characteristic of asthma might already be programmed in utero, and has given rise to the concept of ‘foetal programming’, whereby lung development in foetal and early life determines the expression of respiratory illness (including asthma and chronic bronchiitis) and allergy in adulthood. Exposure to house dust mite (HDM) allergen in the first year of life has also been shown to determine whether or not an atopic child will develop asthma, measured at the age of 11. The age of onset of the first episode of wheezing in these children also correlates with the quantity of HDM exposure at the age of one year.
Questions arising for molecular medicine

- Why do patients with even the mildest forms of asthma still have evidence of airway inflammation? Will the prevention of this inflammation lead to improvement in prognosis?
- How important is the bronchial epithelium in maintaining airway inflammation? What significance could this have for treatment?
- If viruses have the potential to protect against childhood wheezing illnesses, could the vaccination of children against common childhood infections in developed countries account for the rising prevalence of asthma?
- Is the mixture of air pollutants in the air we breathe likely to be more toxic than any single pollutant?

Using risk factors to prevent asthma

When the genetic, environmental and 'early life' risk factors are better understood, it should be possible to identify individuals at risk of asthma and, perhaps through dietary regulation and allergen avoidance, asthma might be prevented in those most at risk. At least one study has already attempted to prevent the development of asthma. The early avoidance of dietary allergens (cows' milk and eggs) and measures to reduce HDM exposure have been applied to babies born to atopic mothers in a study on the Isle of Wight (UK). These seemingly simple measures resulted in a marked reduction in wheezing, eczema, food intolerance, rhinitis and skin-test responses to common allergens measured at two years of age. Other studies have shown that public health measures can prevent asthma in the general population, including adults. Two of the most quoted studies have been carried out in Barcelona (Spain) and Papua New Guinea; epidemics of asthma had been recorded in both places, and further outbreaks were prevented by reducing the exposure of the general population to soya bean dust (Spain) and HDM allergens (Papua New Guinea). A preventive strategy such as this could be applied to patients with mild to moderately severe asthma in developed countries, although it might be less useful in patients with severe asthma, who are the major public health burden.

Guidelines

Public health professionals often comment, with reference to asthma, that there is little value in developing effective therapies if they are not used. Current evidence shows that there are problems of under-diagnosis and, even if the correct diagnosis of asthma is made, many patients receive insufficient prophylactic therapy. Consequently, the past ten years have seen the increasing use of national and international guidelines aimed at identifying and recommending 'the ideal multidisciplinary treatment of asthma'. Typical guidelines include: the education of patients and health professionals; advice on plans for self management by patients; and logical step-by-step drug treatment plans that emphasize early treatment with anti-inflammatory agents, particularly corticosteroids. Evidence from the USA, Europe and Australia suggests that such approaches may reduce hospital admissions for asthma, and improve compliance, inhaler techniques and symptom control.

The most recent, and perhaps most ambitious, initiative has been the Global Initiative for Asthma (GINA. 1995), a joint US National Institutes of Health (NIH) and World Health Organization (WHO) project. Under the aegis of GINA, an international panel of experts has identified priorities in the treatment of asthma and suggested measures to implement them. With an emphasis on recognizing the importance of airway inflammation and improving patient and health-professional education, the long-term goal is to form a consensus, that is common to countries across the world, on how the disease should be treated.

These guidelines assume that the degree of inflammation is mirrored by the severity of symptoms. The observation that the airways of asthmatics with only intermittent or mild symptoms are inflamed raises the question as to whether all asthmatics should be treated with anti-inflammatory agents, irrespective of the clinical severity. To assess whether such early intervention can affect the progression of intermittent asthma to a more severe or chronic condition requires long-term studies of the effects of treatment; these studies will also require careful monitoring of the side effects from the therapy. Whether national and international guidelines will have any lasting effect on the morbidity and mortality of asthma remains to be proven.

Prospects for the future

Our knowledge of the underlying mechanisms of asthma has been revolutionized by advances in molecular medicine coupled with studies of the environmental and genetic factors that affect asthma. These have successfully crossed the boundaries between basic and clinical science. We are now more confident that the application of the most recent tools of molecular and cellular biology will, over the next decade, produce new insights into asthma and provide strategies for public health, directed primarily towards prevention in the face of the rising prevalence of the disease.