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Asthma: recent advances

Gianni Marone

Asthma represents an increasing source of morbidity and significant mortality in westernized societies. A recent meeting discussed progress in understanding the genetic, molecular and immunological basis of this allergic disorder.*

The prevalence of bronchial asthma and allergic disorders has risen steadily this century in westernized societies, doubling in the past 20 years¹. Asthma, a chronic disease that can be fatal, now affects approximately one child in seven in Great Britain, and in the United States it causes about a third of paediatric emergency room visits. What changes have occurred since 1960 that could explain the asthma 'epidemic'? The finger has been pointed at a variety of factors: changes in houses (warmer, less ventilation), the introduction of broad-spectrum antibiotics or programmes of vaccination with bacille Calmette-Guérin (BCG) that might have changed bacterial infections in humans², viral infections, diet (more calories/fat, less fish), and indoor entertainment (more time spent indoors and less outdoor exercise)³. However, none of these is sufficient to explain the increase in morbidity and mortality that has been

recorded in several countries. At the recent conference 'Asthma V', specialists in various aspects of allergic disorders discussed the results of their research.

Genetic and environmental factors in the development of atopy

Asthma is familial, and genome-wide searches have shown that many genetic loci predispose to the disease⁴. Like most common human diseases, allergy and bronchial asthma are 'complex' - they are multifactorial in that they are influenced by genetic and environmental factors. Cookson and his collaborators were the first to suggest

linkage of an atopy gene to chromosome 11q13 (Ref. 4). At the conference, they reported linkage of atopy to various chromosomes (4, 6, 7, 11, 13 and 16) and that there is a strong maternal genetic influence on asthma development in children. Ongoing studies of the genetics of asthma will be of paramount importance to understand the pathophysiology of the disease, to define subgroups of patients and to identify individuals at genetic risk, and eventually to prevent development of the disease.

In a multicentre study of atopy and asthma, more than 7000 newborns recruited in five German cities were followed from the age of 1 month to 7 years. It was found that early induction of sensitization to indoor allergen during infancy, regardless of a family history of atopy, is related to domestic allergen (cat and mite allergens) exposure in a dose-response relationship. In particular, exposure to less than 750 ng of mite allergen per gram of dust sample in the group with a

positive family history resulted in a 3% cumulative rate of sensitization (U. Wahn, Berlin). These results reinforce the importance of early exposure to allergens in the development of asthma and the relevance of allergen-elimination strategies, which may ultimately reduce the asthma epidemic.

Signal transduction in immune and inflammatory cells

IgE is central to the atopic state. In sensitized individuals, disease is initiated by the interaction of antigens with specific IgE bound to high-affinity IgE receptors (FcεRI) ($K_a \sim 10^{10} \text{ M}^{-1}$) on mast cells and basophils. There are two forms of FcεRI: a tetrameric complex ($\alpha\beta\gamma_2$) on basophils and mast cells; and a trimeric complex ($\alpha\gamma_2$) on monocytes, dendritic cells and Langerhans cells. Monomeric IgE can increase the expression of FcεRI, up-regulating cell reactivity⁵. Gene disruption models demonstrate that the amplification function of the β -chain is associated with a tyrosine kinase (Lyn), which upon receptor activation results in phosphorylation of 'self' (β -chain) as well as activation of Syc through association with the γ chain (J-P. Kinet, Boston, MA). It is thought that variants of the FcεRβ gene on chromosome 11 might be associated with atopy.

There are at least three classes of immunoreceptor tyrosine-based activation motif (ITAM)-bearing negative co-receptors. Gp49 B1 belongs to an expanding inhibitory receptor family primarily expressed on mast cells. Co-ligation of FcεRI and Gp49 B1 results in inhibitory signals on mast cells (H.R. Katz, Boston, MA). Gp49 B1 has a significant amino acid sequence homology with a family of receptors expressed on human natural killer (NK) cells termed killer-cell inhibitory receptors (KIRs) and certain T cells that inhibit their cytotoxicity. The discovery that Gp49 B1 inhibits the activation of mast cells that also possess an FcγRIIB inhibitory motif suggests that negative regulation plays a fundamental role in mast cell homeostasis⁶. Inappropriate activation of mast cells in allergic responses may reflect an imbalance of activating and homeostatic inhibitory control mechanisms, rather than just the presence of activating signals.

Cytokines and chemokines

Atopy represents a unique situation, in that increased interleukin 4 (IL-4) production seems to result from genetic predisposition. This is supported by linkage between markers surrounding the IL-4 gene and elevated serum IgE levels. The mechanisms regulating IL-4 expression, and hence T helper 2 (Th2)-cell differentiation, have been intensively studied. Several nuclear factors affecting IL-4 transcription and their interactions on crucial DNA elements within the IL-4 promoter have been identified. The AP-1-related protooncogene product c-Maf is a key player in IL-4 transcription in T cells. A crucial role of STAT-6 in IL-4 expression and Th2 responses emerges from studies in STAT-6-deficient mice showing a profound reduction of IgE and IgG1 responses and of Th2 cytokine production⁷. Overexpression of the *Drosophila*-related factor CP-2 results in a 3–9-fold increase of IL-4 promoter activity, but downregulates IL-2 transcription. Overexpression of a CP-2 dominant-negative variant, known to interfere specifically with CP-2 binding and function, represses both constitutive and induced IL-4 promoter activity, suggesting this factor plays an important role in IL-4 expression (V. Casolaro, Baltimore, MD).

Although T cells are the best-studied IL-4 source, FcεRI⁺ cells – i.e. basophils and mast cells – can produce IL-4 and other Th2-related cytokines⁸. IL-4 and IL-13, which share the capacity to increase IgE biosynthesis, to switch Th0 cells to Th2 cells and to mediate eosinophil and basophil adhesion through upregulation of vascular cell adhesion molecule 1, are immunologically released by basophils, representing a major and rapid source of cytokines in allergic inflammation (L.M. Lichtenstein, Baltimore, MD). Little is known about the molecular mechanisms mediating cytokine expression in FcεRI⁺ cells. Identification of important factors mediating IL-4 gene activation in response to antigen exposure in T cells and in FcεRI⁺ cells is of central importance to our understanding of atopic conditions. This will provide novel targets for immunological or genetic interventions aimed at preventing atopic disease in predisposed subjects.

Many cytokine genes are overexpressed by inflammatory cells in atopic disease.

Granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, IL-4, IL-5 and IL-13 are encoded in a small segment (5q23-31) on the long arm of human chromosome 5. IL-5 plays an important role in allergic disorders, but transcription regulation of human IL-5 is still under scrutiny (T.H. Lee, London). Altered responsiveness of asthmatic airway smooth muscle has been attributed to autocrine action of IL-1β (Ref. 9). IL-1 interacts with at least three surface receptors (IL-1RI, IL-1RII and IL-1RIII). IL-1RII has no signalling function and is shed in a soluble form¹⁰, suggesting it could inhibit IL-1 function by sequestering it and thus preventing it from binding to IL-1RI, the only IL-1R with a cell-signalling function (A. Mantovani, Milan).

Two subfamilies of chemokines are distinguished according to the position of the first two cysteines (CXC and CC chemokines), which are adjacent or separated by one amino acid¹¹. Nearly 40 chemokines act in a similar fashion on leukocytes, inducing adhesion, migration, chemotaxis and release of mediators. Chemokines act on at least eight different receptors also expressed on human eosinophils and basophils. In particular, monocyte chemotactic factor 1 (MCP-1), MCP-2, MCP-4 and macrophage inflammatory protein 1α (MIP-1α) (with a potency decreasing in this order) induce histamine release from human basophils. CCR1 and CCR3 are the main chemokine receptors of eosinophils. CCR3 binds eotaxin, and eotaxin 2 is expressed in human eosinophils and basophils. Eotaxin 2 induces chemotaxis of eosinophils and basophils and the release of histamine and leukotriene C₄ (LTC₄) from basophils primed with IL-3. The demonstration that CCR3 is expressed on eosinophils and basophils, and that it mediates chemotaxis and mediator release, clearly indicates that this receptor is of importance for allergic reactions (M. Baggiolini, Berne).

Integrated T-cell and mast-cell/basophil hypothesis of allergic disorders

Cells from the asthmatic lung and from bronchoalveolar lavage fluid, especially in

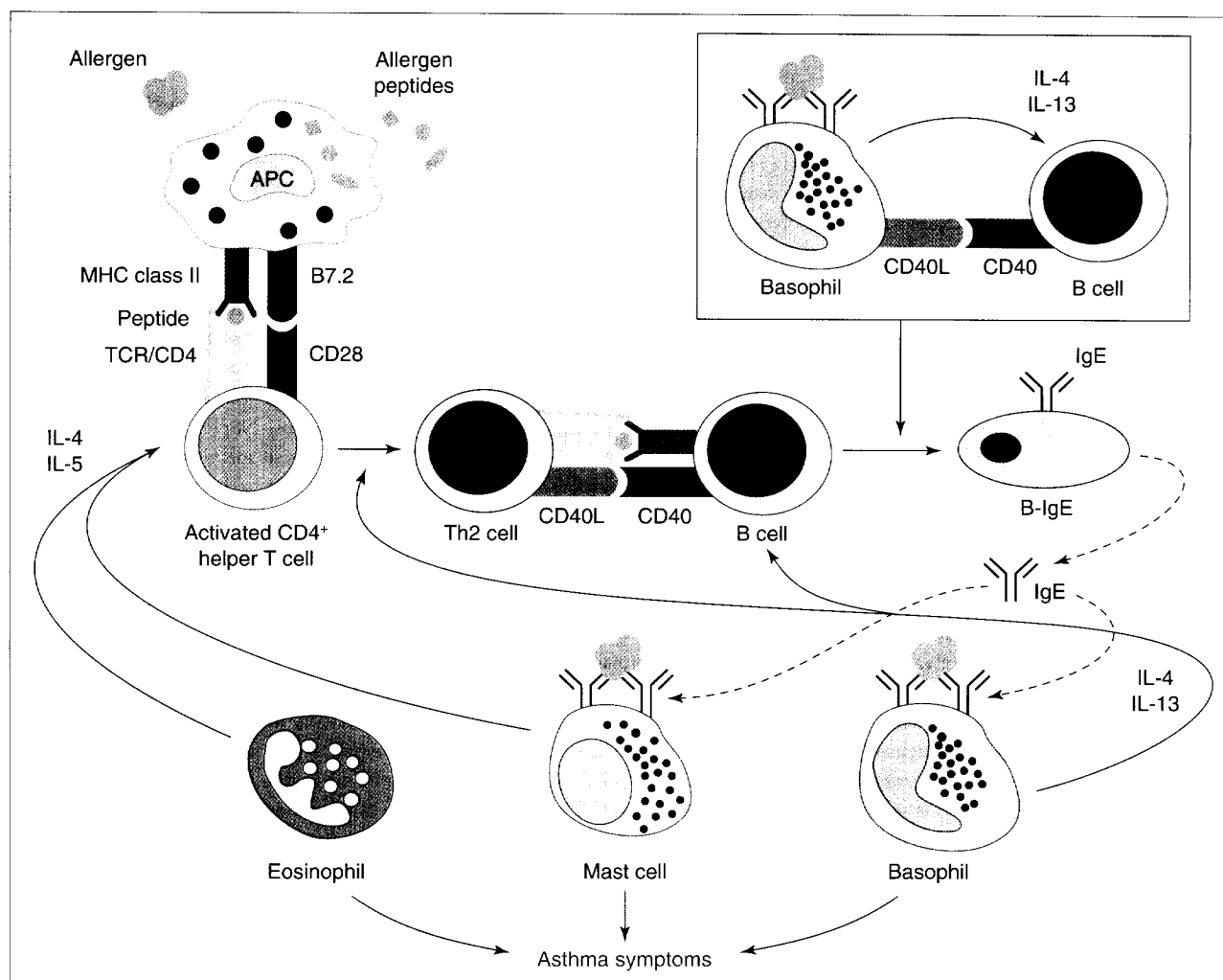


Fig. 1. Integrated T-cell and mast-cell/basophil hypothesis of bronchial asthma. Processing of the allergen by APCs leads to formation of allergen peptide that is presented to the TCR of CD4⁺ helper T cells in association with MHC class II molecules. IL-4 released by eosinophils, basophils and mast cells facilitates the differentiation of Th cells into Th2 cells that secrete IL-4, IL-5, IL-10 and IL-13 after antigen stimulation. Activated Th2 cells interact through the TCR with the peptide-MHC complex on B cells. Adhesive interactions between Th2 and B cells are also mediated by the surface expression of CD40L on Th2 cells and CD40 on B cells. IL-4 and IL-13, secreted to a varied extent by Th2 cells, basophils, mast cells and eosinophils, activate ϵ germ-line transcription in B cells, resulting in deletional switch recombination and synthesis of IgE. IgE binds with high affinity to IgE receptors (Fc ϵ RI) on mast cells and basophils. Activated human basophils and mast cells also express CD40L (see box), which mediates engagement of CD40 on B cells. Thus, human basophils, mast cells and eosinophils play a dual role as immunoregulatory cells and as effectors of allergic inflammation through the release of pro-inflammatory, vasoactive and fibrogenic factors (histamine, peptide leukotrienes, PAF, tryptase, chymase, and so on; see text) that are responsible for the symptoms of bronchial asthma. Abbreviations: APC, antigen-presenting cell; B, B cell; CD40L, CD40 ligand; IL, interleukin; MHC, major histocompatibility complex; PAF, platelet-activating factor; TCR, T-cell receptor; Th2, T helper 2 cell.

the late-phase response, contain IL-5 and IL-4 mRNA (Ref. 12). CD4⁺ cells are the primary producers of IL-5, although eosinophils and mast cells also contribute to the overall cytokine profile. This could explain the cyclosporin A (CsA) activity in asthma, although CsA also inhibits the release of mediators from human mast cells and basophils¹³. The T-cell hypothesis of asthma is supported by the beneficial effects of infusion of a chimeric monoclonal antibody

targeting CD4⁺ cells in corticosteroid-dependent asthmatics by depleting CD4⁺ T cells (A.B. Kay, London).

The mast-cell/basophil hypothesis of asthma (Fig. 1) is supported by the finding that human Fc ϵ RI⁺ cells express and release various cytokines. In addition, different cytokines play a role in human mast cell differentiation. Stem cell factor (SCF), the principal growth, differentiating and activating factor of human mast cells, is also stored in human

mast cells¹⁴. Tryptase accounts for most of the trypsin-like activity in human mast cells. Two genes encode α - and β -tryptase on human chromosome 16. β -tryptase is stored in secretory granules, whereas α -tryptase is constitutively secreted. Levels of β -tryptase in blood or other biological fluids generally correspond to levels of mast cell activation, whereas levels of α -tryptase correspond to total body number of mast cells¹⁵. L.B. Schwartz (Richmond, VI) reported that a

monoclonal 3D7 antibody recognizes a newly described secretory granule protein of human basophils and may be used to evaluate basophil involvement in allergic disorders.

G. Marone and colleagues (Naples) presented evidence that cardiac mast cells play a role in the cardiovascular derangements associated with severe allergic disorders. Cardiac mast cells were found around coronary vessels and in the intima. Isolated human heart mast cells can be activated by IgE-mediated stimuli, C5a, eosinophil cationic protein (ECP) and major basic protein (MBP)¹⁶. Peptide LTs and histamine released by these cells can result in coronary artery spasm and arrhythmias. Thus, cardiac mast cells can be the site of local or systemic anaphylaxis. Cardiac mast cells also contain SCF, stored in secretory granules, which is rapidly released on activation but is also degraded. Cardiac mast cell density is increased in patients with coronary disease or dilated cardiomyopathy, suggesting that anaphylaxis in these patients may be especially dangerous both from the view of tolerance of hypotension and hypoxia and because of the cardiac anaphylaxis.

Preformed mediators of allergic disorders

The cleavage of peptides and proteins by proteases is crucial for homeostasis, but uncontrolled proteolysis in tissues can have serious consequences. Proteases are the major secretory products of mast cells on a weight basis. These comprise tryptase, the chemotryptic protease chymase, and the unique carboxypeptidase, all of which have been isolated from human mast cells and had their cDNA sequenced. Tryptase induces eosinophil and neutrophil chemotaxis, epithelial cell and eosinophil activation, and collagen type I synthesis by lung fibroblasts¹⁷. Chymase is abundant in human skin and heart mast cells but virtually absent from human lung mast cells. Chymase participates in inflammatory processes also by cleaving certain cytokines – e.g. it converts IL-1 β into an active form and degrades IL-4 (Ref. 18). Proteases could be targets for therapeutic interventions in allergic disorders. For instance, the tryptase inhibitor APC 366 is active in inhibiting both

the early and late phase of bronchoconstriction in a model of allergic inflammation.

Bradykinin and lysylbradykinin are natural vasoactive peptides generated by proteolytic cleavage of α_2 -globulin precursors ('kininogenes') by the actions of proteolytic enzymes known as 'kininogenases'. Once produced, these peptides interact with specific receptors to induce a spectrum of biological effects. Two subtypes of kinin receptors – B₁ and B₂ – have been cloned¹⁹. *In vivo*-administered kinins affect all levels of human airways, via B₂ receptors, but the magnitude of the response depends on whether the airways are inflamed or not. Bronchoconstriction induced by bradykinin inhalation in humans is exacerbated by a nitric oxide (NO) synthase inhibitor, indicating that the effects of bradykinin are modulated by NO formation in the airways²⁰. D. Proud (Baltimore, MD) predicted that the development of third-generation, orally active, kinin receptor antagonists will provide opportunities for unravelling the precise role of bradykinins in asthma.

Arachidonic acid metabolism

The cysteinyl LTs C₄, D₄ and E₄, produced by resident mast cells and by infiltrating eosinophils and basophils, are implicated in bronchial constriction and submucosal oedema of airways in asthmatics. The biosynthesis of LTs is initiated by activation signals for Ca²⁺ influx, which then activates and translocates cytosolic phospholipase A₂ to the nuclear membrane where it catalyses the release of arachidonic acid from phospholipids. Arachidonic acid is subsequently presented by an 18 kDa integral perinuclear membrane protein, 5-lipoxygenase (5-LO)-activating protein (FLAP), to 5-LO, which is also translocated to the nuclear membrane. 5-LO catalyses the sequential formation of 5-HPETE and LTA₄. LTA₄ is then conjugated with reduced glutathione by LTC₄ synthase, the only enzyme committed to the biosynthesis of LTC₄. Human LTC₄ synthase has been cloned and mapped on human chromosome 5 (5q35) distal to genes relevant to allergic diseases, such as IL-4 and IL-5 (K.F. Austen, Boston, MA). The LTC₄ synthase gene consists of five exons ranging from 71 to 257 bp in length and four introns, and

spans about 2.5 kb. The mechanism controlling the cell-specific expression of LTC₄ synthase is still unknown. Human LTC₄ synthase and 5-LO have approximately 30% homology and define a new gene family.

Cell activation by cytokines modulates the dynamics of arachidonic acid pools, causing redistribution of these fatty acids, which in turn is largely responsible for the amount and type of eicosanoids immunologically produced by inflammatory cells (M. Triggiani, Naples). This remodelling process consists mainly of the accumulation of arachidonic acid into selected pools, which are preferential substrates for phospholipases. This peculiar distribution profile is detectable in eosinophils obtained *ex vivo* from asthmatic airways²¹.

Adhesion molecules and viral infections in allergic inflammation

Respiratory syncytial virus (RSV), parainfluenza virus (PIV), rhinovirus (RV) and (less often) adenovirus (AD) can exacerbate asthma via complex multimechanistic processes²². RV replicates in bronchial epithelial cells and induces the release of RANTES and GM-CSF, which in turn may attract leukocytes. Airway macrophages express intercellular adhesion molecule 1 (ICAM-1), which binds RV, and secrete cytokines with antiviral (interferon α) and proinflammatory (IL-1, tumour necrosis factor α) effects. Intriguingly, the cytokine response of human T-cell clones to two RV serotypes (RV16 and RV49) is Th1-like (W.W. Busse, Madison, WI).

Epithelial cells from conjunctiva express β_2 integrins. In particular, they appear to express the α_1 molecule, which so far has been considered restricted to cells of haematopoietic origin (G.W. Canonica, Genoa). Data were presented showing that *in vivo* administration of cetirizine was associated with decreased ICAM-1 expression.

Studies presented by J.C. Hogg (Vancouver) focused on latent viral infections in lungs from patients with asthma and other pulmonary diseases. Polymerase chain reaction screening for common respiratory viruses [RSV, human rhinovirus (HRV), influenza A, B and C, PIV and AD] demonstrated a widespread prevalence of

common respiratory viral nucleic acid in lung tissue, suggesting that the lung may serve as a reservoir of residual respiratory virus infection.

Prospectives in immunotherapy of allergic disorders

Conventional immunotherapy for allergic diseases requires an optimal dose of allergen, should be prolonged for a sufficient time and is efficacious in allergic rhinitis (P.S. Creticos, Baltimore, MD). Alternative immunotherapy using immunogenic peptides downregulates T-cell responses. T-cell peptide immunotherapy with synthetic peptides of the ragweed allergen Amb a 1 and the cat allergen Fel d 1 was given in two multicentre trials (Creticos). Peptide treatment was well tolerated and there was a mean 30% clinical improvement, but this was not different from the effect of placebo, suggesting that the placebo effect should not be overlooked. A newer strategy is the immune deviation of the allergic response by DNA immunization (E. Ratz, La Jolla, CA) through the injection of plasmid DNA encoding a specific antigen. This approach has been successfully applied in animal models²³.

Adenosine is a natural nucleoside involved in bronchial constriction in asthmatics whose effects are mediated through four receptor subtypes: the A₁, A_{2a}, A_{2b} and A₃ receptors. When an aerosolized phosphorothioate antisense oligonucleotide to the adenosine A₁ receptor was given to allergic rabbits, the isolated muscle response to both adenosine and the house dust mite allergen was blocked²⁴. This fascinating approach may not only enable definition of the contribution of adenosine to allergic disease but may also lead to a novel therapeutic strategy (W.J. Metzger, Greenville, NC).

Concluding remarks

Despite new insights into the nature of asthma, evidence shows that it is increasing in prevalence and severity, especially in westernized societies. Moreover, asthma continues to be a source of significant mortality notwithstanding the larger and apparently improved pharmacopoeia available to physicians.

Clinicians have long recognized the existence of at least two forms of asthma (extrinsic and intrinsic). Indeed, asthma is not a single disease, and different genes or their combination are responsible for the various forms. Allergic inflammation sustained by the complex network of different immune and inflammatory cells underlies bronchial asthma. In particular, basophils and mast cells play a dual role as proinflammatory and immunoregulatory cells, although in certain experimental models neither FcεRI⁺ cells²⁵ nor IgE are essential for airway inflammation²⁶. It is evident that we are just starting to understand the imbalance of positive and negative receptors on effector cells of allergic inflammation, and molecular events underlying the dysregulation of cytokine production and IgE synthesis in asthma.

Nevertheless, a number of possible therapeutic strategies are evident. A better genetic and molecular characterization of asthmatics could define subgroups of patients for whom immunological and pharmacological therapy could be tailored. For example, there is some evidence that fatal asthma is familial and it is possible that genes predisposing to this form are different, or their combination is different, from those associated with less severe asthma.

Thus far, treatment of asthma has been based on conventional immunotherapy, corticosteroids (inhaled and systemic) and symptomatic treatment. Among the new immunological strategies envisaged is immunization through the injection of plasmid DNA encoding a specific allergen, as well as the use of cytokines (e.g. IL-12, IL-10), anti-cytokines (e.g. anti-IL-4), chemokine or cytokine receptor antagonists (e.g. anti-CCR3, anti-IL-5 receptor), anti-CD4, anti-IgE and immunosuppressive drugs (e.g. CsA, FK-506).

Despite intense research worldwide, asthma and allergic disorders remain elusive from an immunological viewpoint. The conference ended with a call for more international and institutional support for research into the immunology of these disorders.

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