Asthma: an inherited dysfunction of bone marrow cells?

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The pathogenic mechanisms in bronchial asthma are complex, and the many inflammatory mediator cascades [1-4] fail to explain all the characteristics of the disease. Notably, they do not encompass familial inheritance, development of immediate hypersensitivity and airway inflammation. However, over the last year detailed epidemiological, genetic and molecular biological studies have begun to point to a unitary hypothesis which involves immunoglobulin E (IgE) hyperresponsiveness.

Using skin tests and radioallergosorbent tests (RAST) for specific IgE to define atopy, Cookson and Hornek [5] demonstrated that atopic status is an autosomally dominant inherited trait. Ninety percent of atopic asthmatics had at least one atopic parent. By use of modern genetic linkage analysis, these workers [6] identified a gene locus on chromosome 11q in individuals who have decisive IgE hyperresponsiveness. Thus, 85% of those with this gene had symptoms of atopy, 60% had wheeze and 20% had been diagnosed as asthmatic. To provide a clue to the role of this gene, chromosome 11q is known to carry a number of genes for cell surface antigens, some of which occur on T-lymphocytes.

This tendency to IgE hyperresponsiveness and to asthma can be transmitted in bone marrow transplants. Agostri et al. [7] showed that positive skin tests to specific allergens can be transmitted from donors to recipients of allogenic bone marrow transplants as can asthma itself. The effect extended beyond one year, suggesting that proliferating cells from the donor bone marrow were responsible for specific IgE hyperresponsiveness and asthma in the recipient.

These observations on atopic asthma are important because it has recently been realized that there may be no distinction between extrinsic (atopic) and intrinsic asthma [8]. In a large scale epidemiological study, Burrows et al. [8] showed that the tendency to asthma is correlated with a high IgE level, whilst rhinitis is associated with positive skin tests. They therefore questioned the need to distinguish between intrinsic and extrinsic asthma, arguing that both have a common mechanism associated with IgE hyperresponsiveness.

IgE production by B-lymphocytes appears to be controlled by a cytokine (leucocyte regulatory peptide) called interleukin-4 (IL-4), which may be elaborated and released by a subset of T-lymphocyte helper cells [9]. In addition to regulatory IgE production, IL-4 may play an important role in locating mast cells within the mucosa.

The final element in this unitary hypothesis of asthma, is the role of the mast cell in regulating the development of airway inflammation. Inflammation is considered by many [10] to be important in causing the manifestation of airway narrowing and bronchial hyperresponsiveness. When the specific allergen reacts with its high affinity IgE receptor on a mast cell, a number of powerful haemopoietic growth factors are released. They include granulocyte/macrophage colony stimulating factor (GM-CSF) and IL-3 [11], which appear able to recruit, prime and activate inflammatory cells such as neutrophils, macrophages and eosinophils as well as to stimulate bone marrow production.

From these observations, we can perhaps conclude that asthma may not specifically be a disease of the lungs. Instead, it could be a dysfunction of a bone marrow cell, probably of a lymphocyte subset. This dysfunction is an autosomally dominant inherited trait and can lead to IgE hyperresponsiveness. Much still remains unexplained, but a unitary theory encompassing many of the important characteristics of asthma is now available. This could not only revolutionize our understanding, but could also lead to new therapeutic approaches which do not rely on antagonizing secondary mediators [12].

References

7. Agostri JM, Sprenger JD, Lum LG, et al. - Transfer of allergen-specific IgE-mediated hypersensitivity with allogenic


