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Toxicology 181–182 (2002) 305–310

TOXICOLOGY

www.elsevier.com/locate/toxicol

Respiratory allergy: what are the uncertainties?

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Abstract

The prevalence of asthma is increasing worldwide. The increase has been found for both sexes, for all races and age groups. The factors responsible are unclear. The short period of increase makes it unlikely that a genetic change is responsible but rather suggests that either air pollutants or a behavioral change may be involved. Behavioral changes may include decreased exercise and outdoor activity due to, for example increased usage of television and computers. What is the role of allergy in the development of asthma? In allergic sensitization, allergens initiate the inflammation and IgE antibodies are typically present. Once asthma has developed, factors such as irritants, infections and exercise may result in acute symptomatology. Infancy is a high risk period for allergic sensitization since natural defense mechanisms are not fully developed. Epidemiologic evidence suggests that microbial stimuli during early childhood can influence induction of atopic diseases. In animal studies, pre-infection with respiratory virus has resulted in enhanced response to allergens. Another factor implicated in the surge of allergic disease is airborne particulates. Evidence has been obtained for an association of environmental tobacco smoke (ETS) with development of allergic sensitization. ETS enhances IgE production as does diesel and aluminum silicate, the latter a component of fly ash. What are the mechanisms responsible for the environmental influences on development of allergy? Th2 cytokine responses, with suppression of Th1 cytokines, are prominent in children. Th1 maturation appears to be promoted by microbial exposure. Increased understanding of the complex interactions of environmental factors with the developing immune system is essential to reverse the current upward trend in allergic respiratory disease.

Keywords: Asthma; Respiratory allergy; Lymphocyte subsets; Hygiene hypothesis; Air pollutants

1. Introduction

The occurrence of asthma in industrialized countries has been increasing for the past 30 years. In the same period, the asthma mortality rate has doubled. This increase in asthma has been found for all races and age groups, and for both sexes (IOM, 2000).

What is responsible for the recent increase in asthma? The short time frame over which the increase has occurred makes it unlikely that a genetic change is responsible. Both environmental and behavioral factors have been suggested as explanations for the increase. Environmental factors include changes in outdoor and indoor environments. Behavioral considerations include

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PII: S0300-483X(02)00298-6

increased immunizations resulting in fewer childhood infections, increased use of antibiotics leading to alterations in gut microbial flora, decreased exercise and decreased outdoor play because of increased usage of television and computers among other factors. Since individuals now spend approximately 90% of their time indoors, a change in the indoor environment may be a significant contributor to the increase in asthma prevalence.

2. The role of allergy in development of asthma

Asthma is a chronic disease of the airways characterized by inflammation involving several cell types. Mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells all appear to be involved in either the initiation or continuation of the inflammation. The disease is characterized by episodes of wheezing, breathlessness, chest tightness and coughing. The airways show heightened responsiveness to numerous stimuli including irritants, cold air, and exercise. Some agents may be responsible for the development of the asthma, whereas the same agents, or others, may be required for elicitation of symptoms. Chronic inflammation in the airway wall may result in structural and functional changes in the tissue, such changes contributing to asthmatic symptoms.

A distinction is made between two forms of asthma, allergic and nonallergic. The forms have the same symptomotology, but differ in factors initiating the inflammation. In allergic asthma, allergens initiate the inflammation and circulating IgE antibodies are usually present. In nonallergic (nonatopic) asthma, IgE antibodies are not detected. For both types of asthma, a variety of factors (irritants, infections, exercise) may elicit asthmatic symptoms.

Asthma has been called a 'disease of children'. The recent increase in asthma rate among children 0–4 yrs was 160%, whereas for those 5–14 yrs, it was 74% (Platt-Mills et al., 1995). Allergic sensitization typically occurs in early childhood, with progression from allergy to asthma occurring in a subset of individuals. The presence of allergic disease appears to be related to the nature of the underlying lymphocyte cytokine response.

3. T lymphocytes and allergic asthma

The T lymphocyte is the primary regulator of the inflammatory cascade (see Fig. 1). Asthmatics show increased T cell activation and increased numbers of CD4 + T cells in the bronchial mucosa following allergen challenge (Corrigan and Kay, 1990).

CD4 + T cell subsets are identified by their cytokine profile. Th1 cells produce interleukin (IL)-2, tumor necrosis factor (TNF)-β, and interferon (IFN)-γ. Th2 cells produce IL-4, IL-5, and IL-13. The Th subsets show cross-regulation, i.e., some Th1 cytokines down-regulate production of cytokines from Th2 cells, and vice versa.

The development of chronic allergic respiratory disease appears to be a multiphasic process. Allergic sensitization can occur during fetal life (Fig. 2). In utero sensitization is thought to occur during the first 6 months of pregnancy before immune suppression or tolerance occurs. Allergen-specific T cells of fetal origin have been identified in cord blood. These T cells express predominantly the Th2 cytokine phenotype. The placenta secretes PGE_2, progesterone, IL-4 and IL-10, that directs the immune response toward the Th2 phenotype (Holt and Sly, 2000). Th1 responsiveness is suppressed to protect the placenta from the toxic effects of Th1 cytokines. Thus, initial allergen priming is Th2 polarized.

After birth, environmental allergens influence the pattern of response that develops. During the next few months, responses tend to deviate towards the Th1 profile but the Th2 phenotype is found in families with a history of atopy (Holt, 1999). Immune function is not fully matured until around age five.

Exposure of the immune system to environmental allergens results in activation of Th2 cells. Persistent disease develops in only 1/4–1/3 of children and seems to be in those that have Th2 mediated airways inflammation. The upregulated Th2 cytokines induce IgE and several cardinal features of asthma including bronchial hyperresponsiveness and eosinophila. IL-4 is particularly important in this process being required for the differentiation and expansion of Th2 lymphocytes, the growth and differentiation of

mast cells, and inhibition of Th1 lymphocyte development. It is the principal cytokine that stimulates isotype switching of B cells to produce IgE and controls synthesis of both IgE and IgG4 antibodies. The *ratio* of allergen-specific IgG4/IgE, rather than the quantitative amounts of each, appears to be important in allergic asthma with a high ratio favoring *protection* against asthma. Environmental factors, such as endotoxin exposure, may modulate the cytokine response.

4. Genetics and asthma

Asthma results from the effects of multiple and interacting genes. It has long been recognized that asthma clusters in families. Twin studies have provided further evidence of a genetic component of asthma (Weisch et al., 1999).

Atopy is a prolonged increased production of IgE as a result of allergen exposure (Feijen et al., 2000). Chromosome regions have been linked with different atopic traits. Total serum IgE has been linked to chromosome 5q (Marsh et al., 1994), eosinophilia to chromosome 6, and linkage for asthma to chromosomes 1, 2, 3, 4, 5, 6, 9, 11–14, 17, 19 and 21 (Feijen et al., 2000) where genes for IFN-γ, and mast cell growth factor are located. The core promoter of 5-lipoxygenase gene is localized on chromosome 10q11.2. The level of activity of this gene determines the level of bronchoconstricter leukotrienes in the airways (Weisch et al., 1999).

5. Environmental and lifestyle factors

5.1. The hygiene hypothesis

Genetic factors alone cannot explain the widespread increased incidence in asthma because the increase has occurred only within one or two generations. Environmental and lifestyle factors are thought to be mainly responsible for the increase. The connection between allergic sensitization and lifestyle has been conceived in the *hygiene hypothesis* whereby improved hygiene is thought to have deprived the developing immune system of the environmental stimuli that would skew the immune system toward Th1 responses (Strachan, 2000).

The hypothesis proposes that sensitization may be prevented by infections occurring in early in-

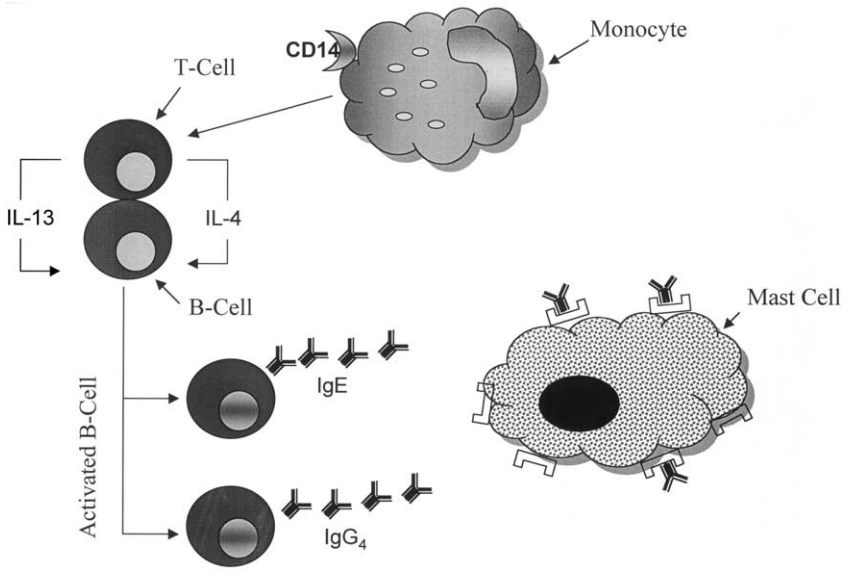

Fig. 1. Cytokines stimulation of lymphocyte subsets.

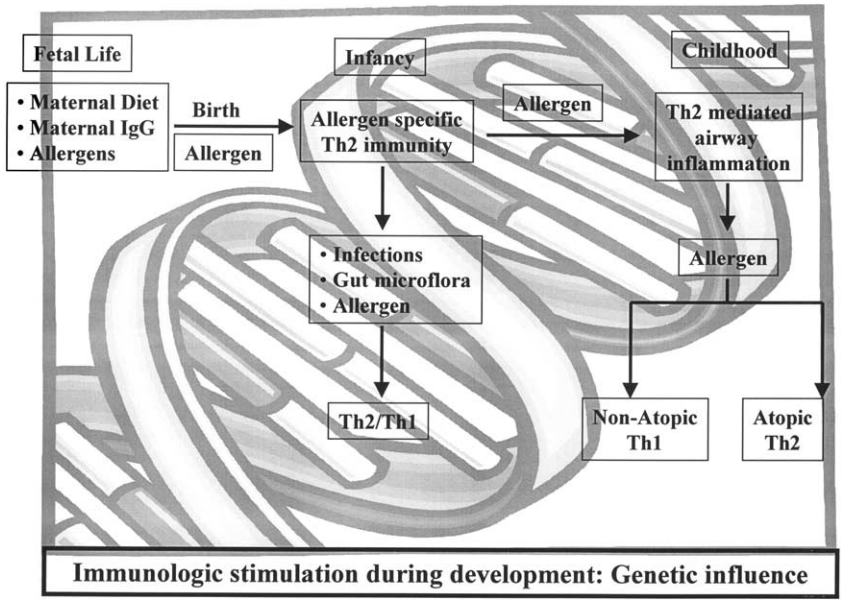

Fig. 2. Immunostimulatory events during developmental stages that impact on occurrence of asthma.

fancy. It is known that viral or bacterial infections at an early age tend to stimulate a Th1 response (Fig. 2) and will switch a Th2 response to a Th1 response. Epidemiological studies have suggested that childhood infections may 'protect' against the development of atopy. Such studies have indicated that expression of atopy is inversely related to social class, family size, and birth order (Busse and Lemanske, 2001). Each of these parameters can be a surrogate of infection frequency; i.e., low socio-economic status, large family size, and having a large number of elder siblings, likely maximize exposure to infectious respiratory agents during childhood.

The patterns of allergen-specific T-cell immunity that distinguish atopic from nonatopic adults appear to be established during early childhood. Th2 subjects (atopics) express allergen-specific IgE antibody in serum. Th1 maturation is thought to develop from contact with microbial agents. Vaccination against certain infections has been suggested to promote atopic sensitization by preventing the microbial stimulation that upregulates Th1-like immunity (Warner and Warner, 2000).

A related theory to explain the increase in childhood asthma is the 'gut microbial flora' theory. It is proposed that the early switch from Th2 to Th1 is the result of gut microbial exposure. It has been reported that allergic children are more likely to have low colonization with *Lactobacilli* and high counts of aerobic microorganisms such as coliforms and *Staphylococcus aureus*. The lower risk of asthma among farm children has been attributed to their consumption of unpasteurized milk that might contain a sizable microbial load, particularly of *Lactobacilli*, or may provide greater exposure to endotoxin (as in the hygiene hypothesis) (Nafstad et al., 2000).

6. Airborne particulates

Elevated particulate matter in ambient air can exacerbate existing asthma (Gavett and Koren, 2001). Particulates have been associated with increased emergency room visits and increased use of medication by asthmatics. In healthy human volunteers, particulate material has been associated with pulmonary inflammation and formation of oxidants. Since these effects correlated with the

transition metal content of the samples, it has been proposed that transition metals may promote the formation of reactive oxygen species.

Environmental tobacco smoke (ETS) has been associated with development of asthma in young children. There is concern that ETS may impair the normal development of the airways in the fetus, and may promote respiratory infections and wheezing. Tobacco smoke is also considered a cofactor in promoting IgE production, and has the inverse effect on IgG production. Animal studies have also demonstrated effects of airborne pollutants on IgE production. When instilled into the lungs of mice, diesel and aluminum silicate (found in fly ash) stimulated IgE to aerosolized allergens (van Zijverdin et al., 2000).

7. Indoor pollutants

A major change has occurred in the indoor climate during the past 30 years, and in the amount of time spent indoors. Modern building materials, decreased ventilation, increased temperature and increased insulation, can contribute to increased indoor air pollutants. Indoor sources of allergens include: pets, molds, dust mites, cockroaches, particles from cooking and heating, spray foams, cleaners, paints, and insulations, to name a few. A causal relationship between exposure to cat, cockroach, and house dust mites and *exacerbation* of asthma in sensitized individuals has been concluded (IOM, 2000), as well as between ETS and *exacerbation* of asthma in preschool-aged children in the USA (IOM, 2000).

Causal factors associated with the *development* of asthma are more difficult to establish. However, based on clinical and epidemiological studies, a casual relationship was concluded between dust mite exposure and development of asthma in *susceptible* children and between ETS and development of asthma in young children (IOM, 2000).

The interaction of environmental factors with genetic susceptibilities, as well as the diverse symptoms and severities that characterize asthma, makes it difficult to define exposure characteristics necessary for induction and exacerbation of the disease. However, it is clear that indoor exposures are a major contributor to the incidence of asthma.

8. Conclusions

Asthma is a complex chronic disease that occurs in susceptible populations. Genetic factors appear to play a significant role in predisposing to development of the disease with many genetic loci involved in initiation, progression and maintenance of the disease. Although gene frequencies will be stable, changes in the environment may have profound effects on the degree to which genetic risk becomes manifest. Prenatal exposure influences the development of sensitization by creating a Th2 atmosphere. Interaction of environmental factors with genetic background influences induction and exacerbation of asthma by modifying Th2 responses. Early life infections stimulate Th1 lymphocytes that may inhibit the expansion of allergen-specific Th2 lymphocytes and may limit the development of allergic diseases. In addition, a favorable ratio of allergen-specific IgG4/IgE may protect against development of allergy and asthma. Greater understanding must be gained of the contributions from early childhood respiratory infections, indoor and outdoor air pollutants, and continually changing socio-economic patterns, to reverse the current upward trend in asthma incidence and prevalence.

Acknowledgements

The author thanks Dr. Ranulfo Lemus for preparation of the figures.

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