An Analysis of the Hygiene Hypothesis in the Onset of Childhood Asthma

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Disclosures

Introduction
The concept of the hygiene hypothesis was first introduced by Strachan[1] in 1989, based on the observation that there was an inverse correlation between household size and allergic rhinitis. Strachan postulated that the incidence of infection was higher in households with more family members and that this increased incidence of infection reduced the subsequent development of allergic rhinitis. Recent studies have emphasized the critical importance of the first years of life in the development of the allergic phenotype. The potential role of the microbial burden on the development of the allergic phenotype during this initial period of immune maturation has gained considerable epidemiologic and experimental support, although not all studies support the hypothesis.

Immune Milieu of the Developing Fetus

During pregnancy, the developing fetus is exposed to the T-helper (Th) 2 environment of the placenta.[2] The production by placental trophoblasts of Th1 inhibitory mediators, including interleukin (IL)-4, IL-10, progesterone, and prostaglandin E-2, promotes the fetal development of Th2 responses. Fetal and cord blood cells respond to mitogen or antigen stimulation with a predominant Th2 cytokine pattern of response. [2] Patrick Holt, PhD,[3] of the Institute for Childhood Health Research and the Department of Medicine at the University of Western Australia in Perth, Australia, presented evidence that the slow maturation of the Th1 immune response that normally occurs over the first 12 to 18 months of life is what predisposes to the subsequent development of allergy and asthma.[4] Thus, failure of Th2 responses present at birth to deviate to Th1
responses with normal maturation of the immune system is what is postulated to drive the development of allergy and asthma. Studies by Holt and colleagues have shown that the Th1 cytokine interferon (IFN)-gamma promoter is methylated in cord blood mononuclear cells and that this promoter methylation inhibits transcription of IFN-gamma, explaining the low levels of Th1 cytokine responses in the fetus and neonate.

Childhood Infections and Risk of Subsequent Development of Allergy

Epidemiologic studies investigating the protective role of childhood infections on the subsequent development of allergy have produced conflicting results, with some studies supporting the hygiene hypothesis and other studies not showing a link. The nature of the infectious agent (bacteria vs virus and which specific bacteria or virus), the route of infection (airway vs gastrointestinal tract), the timing of the infections (first year of life vs later childhood infections), the length of follow up in terms of the subsequent development of allergy or asthma, and the retrospective nature of obtaining information regarding infections in childhood all contribute to the conflicting results in the literature.

Early Childhood Upper Respiratory Tract (URT) Viral Infections and the Development of Allergy and Asthma

The association of respiratory syncytial virus infection with the subsequent development of asthma has been noted in several studies. However, recent studies reviewed by Peter Ernst, MD,[5] of the Respiratory Epidemiology Unit at McGill University in Montreal, Canada, suggest a protective role for viruses on the subsequent development of allergy and asthma. A prospective study of a birth cohort suggests that frequent URT viral infections in the first year of life are associated with a reduced incidence of atopy at age 5 and asthma at age 7,[6] suggesting a protective role for URT viral infections. The weakness of this study is that no specific infectious agents were characterized in these self-reported URT viral infections. Further studies rigorously characterizing the viral pathogens causing URT infections in the first year of life will help to determine the role of individual viruses in the development of allergy and asthma.

An Animal Model of the Hygiene Hypothesis

Recent epidemiologic studies suggest that antibiotic use in infancy may be associated with an increased risk of the subsequent development of atopy. It is postulated that antibiotics deplete gastrointestinal tract bacteria, which normally suppress Th2 responses. Thus, antibiotics administered during a critical time in infancy (at the time of Th2 to Th1 immune deviation) are hypothesized to promote Th2 responses. In mouse models, the administration of the antibiotic kanamycin increases Th2 responses as evidenced by increased immunoglobulin E (IgE), increased IL-4, reduced IFN-gamma, and enhanced eosinophilic airway responses to inhaled allergen.[7,8] These results suggested
that antibiotic use during infancy may prevent postnatal Th-1 cell maturation thus resulting in a Th2-polarized immune deviation.

Orofically Transmitted Microbes and the Development of Atopy

The potential role of gastrointestinal bacteria in the development of atopy has been investigated in a retrospective study of military recruits in Italy in whom serologic analysis was used to document evidence of prior infection with orofically transmitted microbes, such as Toxoplasma gondii, Helicobacter pylori, and hepatitis A virus. [9] Respiratory allergy was infrequent in subjects exposed to these 3 orofically transmitted microbes. These studies support the hygiene hypothesis and suggest that increasing sanitation reduces the incidence of orofically transmitted infections, which had previously promoted Th1 immune responses.

Mycobacterial Infection, Bacillus Calmette-Guerin (BCG), and the Development of Asthma

The potential of mycobacterial infection or BCG to induce Th1 immune responses and prevent the development of allergy was suggested from studies of BCG vaccination given to Japanese schoolchildren at ages 6 and 12 years.[10] At age 12 years, children who had a strong delayed skin test response to tuberculin (interpreted as a strong Th1 response) had a low incidence of atopy (total and allergen-specific 19E).[1 0] However, not all subsequent studies of BCG[11 ] or mycobacterial infection[12] have supported this observation.

Early-Life Cat Exposure and the Subsequent Development of Atopy

The ability of cat allergen to provoke allergic symptoms is self-evident to cat-allergic subjects as well as physicians. However, recent studies have provoked controversy in suggesting that cats might inhibit the development of the atopic state. In a study performed--n- Sweden) children exposed to cats during the first year of life had a lower frequency of allergic rhinitis at 7 to 9 years of age, and a lower incidence of asthma at 12 to 13 years of age.[13] The lower prevalence of asthma at 12 to 13 years of age in children exposed to cats in their home during their first year of life was not explained by differences in parental history of allergy, the number of siblings, the number of infections during the first year of life, or by the gender of the child. Further studies are needed to confirm this intriguing but controversial observation.

Bacterial LPS: Friend or Foe

Lipopolysaccharide (LPS), or endotoxin, a component of Gram-negative bacterial cell walls, is present in household dust and in air pollution, assuring that asthmatic subjects are likely to be exposed to LPS.[14] The biologic effects
of LPS may have different consequences on the expression of asthma dependent upon whether the exposure to LPS occurs during the establishment of the atopic status, or whether the exposure to LPS occurs after the asthma phenotype is established. David A. Schwarz, Ma, MS,[15] of Duke University in Durham, North Carolina, presented evidence that inhaled LPS exacerbates airway inflammation and airway obstruction in asthmatics.[14] Prior allergen challenge significantly augments the inflammatory response to inhaled LPS.

The timing of exposure to LPS appears to be critical in determining whether LPS inhibits or induces expression of allergic inflammation and asthma. In animal models, LPS induces a strong Th1 immune response associated with the expression of IFN-gamma and IL-12.[14] Administration of LPS to mice prior to sensitization to allergen inhibits the development of sensitization to allergen as well as the subsequent eosinophilic airway response to inhaled allergen.[14] Support for the observation that LPS exposure can inhibit the development of atopy is also derived from human studies of infants ages 1 to 2 years, demonstrating that higher levels of indoor LPS exposure were associated with less allergen sensitization as assessed by skin testing.[16]

Harnessing the Hygiene Hypothesis in the Therapy of Allergy and Asthma

One bacterial product that may contribute to the prevention of allergic inflammation is CpG-containing motifs present in bacterial DNA.[17] In contrast to the high frequency of unmethylated CpG DNA in bacterial DNA, vertebrate DNA has a low frequency of CpG dinucleotides, and these are mostly methylated. Therefore, vertebrate DNA does not have immunostimulatory activity. CpG DNA induces a strong Th1 immune response and is able to inhibit the development of Th2-mediated eosinophilic inflammation and airway hyperreactivity in a mouse model of asthma.[14] The inhibition of eosinophilic inflammation by CpG is mediated by the inhibition of IL-5 and the bone marrow generation of eosinophils. The CpG motifs have no direct effects on inducing eosinophil apoptosis. The inhibition of Th2-mediated inflammation by CpG motifs is indirect as the CpG motifs are taken up by the innate immune system, which secretes cytokines that bias the T lymphocyte to generate a Th1 instead of a Th2 response. Cellular responses to CpG DNA are mediated by a cell surface Toll-like receptor, TLR 9.[18] Macrophages derived from TLR 9-deficient mice do not generate inflammatory cytokines when stimulated with CpG DNA, indicating a critical role for the TLR 9 receptor in CpG DNA-mediated signal transduction.[18] In vivo CpG-DNA-mediated Th-1 responses are abolished in TLR 9-deficient mice.[18] Thus, vertebrate immune systems appear to have evolved a specific Toll-like receptor that distinguishes bacterial DNA from self-DNA. Of note, another bacterial product that activates the innate immune response (LPS) binds to another Toll-like receptor (TLR 4). Mutations in TLR 4 are associated with hyporesponsiveness to inhaled LPS in
The hygiene hypothesis attempts to provide a biologic explanation for epidemiologic observations of decreased incidence of allergic disease in households with large numbers of siblings. Some, but not all, studies have suggested an inverse association between certain viral and bacterial infections and the subsequent development of allergy. In order to substantiate or refute such a link, prospective studies are needed that accurately document the specific nature of all bacterial or viral infections, especially in the critical first years of life when the developing immune system is maturing in its ability to generate Th1 immune responses to antigens. If further research confirms that aberrant immune deviation in the first few years of life is critical to the subsequent development of allergy and asthma, then interventions at this critical stage of immune development may determine whether we can prevent the subsequent development of allergy and asthma.

References

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