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Commentary

Childhood infections and asthma: at the crossroads of the hygiene and Barker hypotheses

Kelan G Tantisira and Scott T Weiss

Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Kelan G Tantisira, MD, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115, USA. Tel: +1 617 525 0863; fax: +1 617 525 0958; e-mail: rekgt@channing.harvard.edu

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Abstract

The hygiene hypothesis states that childhood asthma develops as a result of decreased exposure to infectious agents during infancy and early childhood. This results in the persistence of the neonatal T helper lymphocyte 2 immunophenotype, thereby predisposing the child to atopic disease. While multiple studies support the hygiene hypothesis in asthma ontogeny, the evidence remains inconclusive; multiple other environmental exposures in early childhood also alter predisposition to asthma. Moreover, the current paradigm for asthma development extends far beyond simple childhood environmental exposures to include fetal development, genetic predisposition, and interactions of the developmental state and genetics with the environment.

Keywords: asthma, child, fetal programming, gene by environment, infection

Introduction

In 1989, David Strachan described decreases in the prevalence of childhood hay fever and atopic dermatitis in association with the presence of older siblings [1]. He concluded that "declining family size, improved household amenities, and higher standards of personal cleanliness have reduced the opportunities for cross-infection in young families. This may have resulted in more widespread clinical expression of atopic disease" [1]. This, and subsequent observations, led to the formulation of the 'hygiene hypothesis'. The biological basis for the hygiene hypothesis lies in the induction of a T helper lymphocyte 1 (Th1) population by bacterial and viral infections, and the resultant deviation from the T helper lymphocyte 2 (Th2) immune responses involved in IgE-mediated allergy [2].

Asthma can be defined as a combination of airway inflammation, often as a result of allergic sensitization, and airway hyperresponsiveness. While family size and childhood infections have generally not been associated with airway responsiveness, because of its close relationship with atopy the risk for childhood asthma has also been hypothesized to relate to these factors. Family size and/or attendance at daycare have consistently been associated with decrements in the relative risk of asthma [3–5], although a few studies have demonstrated increased asthma risk with daycare, probably due to an increased prevalence of lower respiratory tract infections [6]. Lower respiratory tract infections in early childhood have uniformly been associated with an increased risk of subsequent asthma [3,5,7]. While the association of non-respiratory childhood infections and the risk of asthma have been generally supportive of a protective effect, the evidence remains inconclusive. In a case–control study of 1659 Italian military cadets, the relative risk of atopy decreased with exposure to orofecal microbes, including *Helicobacter pylori*, *Toxoplasma gondii*, and hepatitis A virus, as diagnosed by serology [8]. Allergic asthma was

CI = confidence interval; IL = interleukin; OR = odds ratio; Th1 = T helper lymphocyte 1; Th2 = T helper lymphocyte 2.

present in only one of the 245 cadets positive for at least two of these serologies. A decreased risk of atopy was not noted in relation to the airborne respiratory viral serologies evaluated. While exposure to measles [4] and *Mycobacterium tuberculosis* [9] have also been reported to protect against asthma development, no specific infection to date has consistently been demonstrated to support the tenets of the hygiene hypothesis.

The focus article

The article by Illi *et al* [10] provides convincing data in support of the hygiene hypothesis. In a longitudinal birth cohort of 1314 children followed to the age of 7 years, Illi *et al* compared the prevalence of doctor-diagnosed asthma, current wheeze, and airway hyperresponsiveness with the occurrence of various categories of infection during the first 3 years of life. As expected, lower respiratory tract infections were positively associated with asthma (odds ratio [OR] = 4.46, 95% confidence interval [CI] = 2.07–9.64 for four or more infections versus one or no infection), wheeze (OR = 3.97, 95% CI = 2.06–7.64), and airway responsiveness (OR = 2.14, 95% CI = 1.03–4.43). As a group, however, non-lower respiratory viral infections demonstrated a strong protective effect against the same outcomes (i.e. asthma [OR = 0.16, 95% CI = 0.05–0.54 for eight or more infections versus one or no infection], wheeze [OR = 0.46, 95% CI = 0.14–1.49], and airway responsiveness [OR = 0.24, 95% CI = 0.09–0.68]). The effect was strongest for rhinorrhea and herpetic infections, and was not noted with bacterial, fungal, or gastrointestinal infections. The limitations of this study included follow-up of only 71% of infants (allowing for potential bias) and no direct measures of infectious burden. Additionally, the cohort's primary study design was to evaluate infants at high risk for atopy, potentially limiting the generalizability of the results. Nevertheless, this was a well-designed study, the particular strengths of which included consistency of associations across several asthma phenotypes, including airway hyperresponsiveness. Moreover, the associations noted were strong and there appeared to be a dose–response effect between the number of infections and the outcome. For instance, the relative odds for airway responsiveness were 0.50 for two to four viral infections versus one or no infections, 0.34 for five to seven infections, and 0.24 for eight or more infections.

A broader paradigm for asthma development

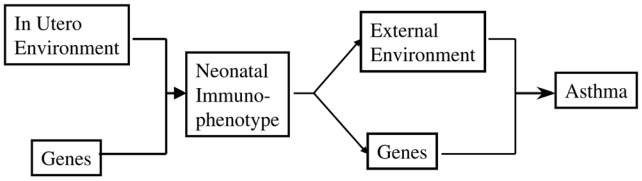
While early exposure to infectious burden may affect the Th1/Th2 balance in the developing neonate, other environmental risk factors for the development of childhood asthma may also affect immune system ontogeny. These risk factors include the protective effect of early exposures to farm animals (via endotoxin) [11] and to household pets (via immune tolerance) [12], and the increased asthma risk associated with antibiotic usage (via suppression of the gut flora) [13]. However, other early childhood exposures increasing risk for the development of asthma, such as household polyvinylchloride exposure and environmental tobacco smoke, do not have readily apparent effects on the immune system. Overall, it is clear that variations in early life environment are significant risk factors for the development of childhood asthma, but that these variations are not sufficient to cause asthma by themselves. The evolving paradigm supports a combination of genetics, *in utero* development, and early life environment in the origin of asthma (Fig. 1).

The idea that fetal programming can affect the subsequent development of chronic disease was popularized by Barker and colleagues [14], and it is often referred to as the Barker hypothesis. This hypothesis of fetal origins proposes that these diseases originate through adaptations that the fetus makes when it is undernourished. Such diseases may be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period of early life results in long-term changes in physiology or metabolism [15]. A prominent example of this is the increased risk of asthma in low birth weight infants [7,16]. While the Barker hypothesis focuses on alterations in the developing fetus due to nutrition, there is evolving evidence that many other factors involving the *in utero* environment and fetal gene by environment interactions can affect fetal programming and the subsequent development of disease.

The maternal–fetal interface appears to play a particularly prominent role in the subsequent development of asthma; risk of childhood asthma is greater for infants with a maternal history of asthma than those with a paternal history of asthma [17]. Whether this maternal influence is primarily genetic, environmental, or both has yet to be fully elucidated. Maternal imprinting, a phenomenon whereby the maternal genes are preferentially expressed in the fetus, has been noted in linkage studies of atopy [18] and asthma [19], and probably explains the familial aggregation pattern of pulmonary function noted within asthmatics [20]. Maternal environmental characteristics, as they relate to the fetus, including smoking [21] and infections [22] during pregnancy, have also been strongly associated with subsequent asthma development.

Within the developing fetus, a weak Th2 response normally develops as a result of fetal priming to help maintain pregnancy. *In utero* exposure to allergens may significantly enhance the Th2 response [23,24]. The critical period for this programmed response of the fetus to allergens is thought to be from 5 to 7 months of gestation [25]. The fetal response to allergens may also vary according to genetic predisposition. In a recent study of fetal IgE production, endogenous production of IgE was noted at as early as 8 weeks' gestation, but only in those fetuses with at least one *IL4RA*A1902G* allele [26]. This genotype

Figure 1



Overview of the development of childhood asthma. Fetal environmental and genetic influences lead to a specific immunophenotype in the newborn. Subsequent interactions with external environmental exposures (including infections), in conjunction with genetic predisposition, lead to the development of asthma. It is probable that all three components (developmental, genetic, and environmental) are necessary for asthma to occur.

Table 1

Environmental risk factors in the development of asthma

In utero environmental factors	Postnatal environmental factors
Maternal diet	Infant diet (breast versus bottle)
Maternal/fetal infections	Maternal smoking
Bacterial	Allergens
Viral	Endotoxin
Parasitic	Daycare
Maternal smoking	Farm animals
Allergens	Antibiotics
Endotoxin	

would predispose to early elevations of IgE levels, which have been correlated with asthma and atopy risk [27].

The result of interactions between genetics and the *in utero* environment is a Th2 skewed immunophenotype in the neonate. Those infants with IL-13 producing Th2 lymphocytes may be particularly predisposed to develop asthma [28]. The risk of atopy and asthma is related to failure of the neonate to generate interferon-γ and the resultant failure to transition from the Th2 to the Th1 immunophenotype [29,30]. This failure to transition probably occurs only within genetically susceptible individuals [29], under environmental influences from both the *in utero* and postnatal state (Table 1). One common hypothesis to support this gene by environment interaction in the neonate has been the role of endotoxin and polymorphisms of the CD14 gene. Endotoxin is a component of Gram-negative bacterial cell walls, is fairly ubiquitous in nature, and is an accurate indicator of the cleanliness of indoor environments in urban areas. CD14 recognizes and binds to the endotoxin. A C → T polymorphism at position 159 of the 5′ flanking region of the CD14 gene has been identified. The homozygous TT genotype has been associated with increases in the serum CD14 level, decreases in serum IgE concentrations, and decreases in the number of positive skin tests in atopic individuals [31]. Whether this association is also true in the development of asthma is under active investigation.

Conclusion

Overall, there appears to be supportive evidence for the role of early exposure to non-respiratory infections as a protective factor against the development of childhood asthma. However, this is likely to be only one of several independent environmental risk factors for asthma in the neonate. Moreover, these postnatal environmental risk factors are themselves only part of a greater scheme that includes fetal development and genetic predisposition. Together, these three broad influences (developmental, genetic, and environmental), along with their complex interactions, are currently the most important factors in the ontogeny of childhood asthma.

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