

ORIGINAL ARTICLE

The influence of early environmental exposures on immune development and subsequent risk of allergic disease

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Abstract

Environmental exposures in pregnancy and the early postnatal period affect early immune development. Early immune function and future allergy susceptibility appear to result from a combination of maternal phenotype, infant genotype, and environmental exposures *in utero* that affect early gene expression. Furthermore, epigenetic changes in gene expression in one generation can also be inherited across subsequent generations, potentially amplifying heritable allergy risk.

Early events have a defining influence on immune development and allergic susceptibility.

In the context of asthma and allergic disease, a substantial body of work suggests a link between epigenetic gene regulation, immunity, and physiological development. Histone modifications (methylation and acetylation) and DNA methylation patterns epigenetically control cellular immune development and play a central role in T-cell development (1).

A new study on postnatal innate immune development

Children with allergic disease show distinct differences in immune development from nonallergic children. In a 1999 study (2), we mapped the postnatal development of Th1 responses demonstrating relative deficiencies in allergic infants. This may be related to inadequate suppression of the Th2 responses that dominate in early life. Our results highlighted the likely importance of postnatal exposure to microbes in postnatal immune maturation. This is because the innate immune compartment is critical in the programming, maturation, and patterns of T-cell development. This highlighted the urgent need to characterize the normal development of innate microbial responses and possible differences in allergic children.

We examined the effects of postnatal microbial exposure on T-cell ontogeny in a longitudinal cohort study of 739 infants followed from birth and at 1, 2.5, and 5 years of age (3, 4). In a case-control design, we compared allergic children

($n = 35$) with nonallergic children ($n = 35$) randomly selected on the basis of their clinical phenotype and if they had available blood samples from each age time-point. Nonallergic children had no evidence of allergy or sensitization at any age. The allergic children had diagnosed allergic disease (eczema and/or food allergy) with evidence of sensitization within the first year, and many subsequently developed asthma and aeroallergen disease (Fig. 1).

Microbial recognition by the innate immune system relies on toll-like receptors (TLRs), which may be important in regulatory pathways that inhibit allergic responses. Mononuclear cells from the children were cultured with a broad range of microbial TLR ligands and responses detected by the production of inflammatory cytokines such as interleukin (IL)-1 β . Nonallergic children showed significantly attenuated innate responses to virtually all TLR ligands compared with adults at birth, and with age, we saw gradual maturation of these innate inflammatory responses.

In contrast, allergic children had excessive perinatal inflammatory responses to all TLR ligands compared with nonallergic children, in many cases comparable or greater than adults. With age, the allergic children showed the opposite pattern to the nonallergic group, with significant age-related attenuation. By 5 years, the innate inflammatory response was significantly attenuated compared with nonallergic children for all measured inflammatory cytokines including tumor necrosis factor (TNF)- α , IL-6, and IL-12.

Allergy: initial “hyper-responsiveness” gives rise to a deficiency

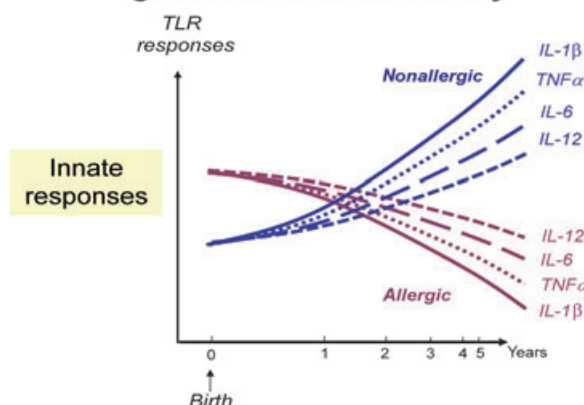


Figure 1 Allergy: initial ‘hyper-responsiveness’ gives rise to a deficiency. Reprinted from (3), with permission from Elsevier.

We also examined the T-effector cell compartment in the same cohort. Nonallergic children showed a substantial interferon (IFN)- γ Th1 response to ovalbumin and house dust mite that increased with age. Th2 and IL-13 responses remained low as expected. The increase in Th1 paralleled the increase in innate immune function. In allergic children, attenuation was seen in IFN- γ Th1 maturation with age. Th2 responses were already significantly elevated at birth and amplified with age.

In summary, nonallergic children show a parallel response between innate microbial responses and the T-effector cell compartment, with high, significant correlations between innate and adaptive responses. Allergic children show no consistent correlations, suggesting dissociation in interactions between antigen-presenting cells and T cells. Allergic children show a propensity for inflammatory cytokine reduction in the perinatal period that directly correlates with the Th2 trends and continues with age.

In support is a 1999 study (5) suggesting that, if exaggerated, inflammatory cytokine production in the microbial response may tip the balance toward Th2 differentiation, and Th2 cytokine production is induced as part of the microbial response and serves to downregulate the inflammatory response as part of a negative feedback mechanism. This may have a role in initiating the Th2 immune deviation we see in allergic children, and the excessive Th2 response may be responsible for the suppression of innate response we see with age.

Generational effects from epigenetics

Immune development is clearly driven by environmental changes. However, the key agents and mechanisms for these changes are unclear. Nonetheless, they have their first influence in the antenatal period, exerting potential epigenetic effects that ultimately affect phenotype. This may affect both tissue and immune function, as well as immune deficiencies in the neonatal period that influence the evolving immune phenotype. Epigenetic agents can also exert transgenerational effects.

Epigenetics affect gene expression and silencing not through changes in DNA sequence, but through conformational changes in DNA packaging into chromatin. Environmental factors can exert control through modifications such as gene methylation for silencing and histone acetylation for activation. Epigenetic modifications are influenced by environment, as seen in animal models in which genetically identical individuals can show dramatic differences in phenotype from epigenetic modification induced by environment exposure *in utero*. This paradigm is fundamental to the new field of developmental origins of disease and relevant to models for individual treatment and prevention, as the results of gene and environment interactions vary with polymorphisms.

Three examples illustrate how the environment and genes interact in early development to result in epigenetic gene expression changes (6). First, inhaled pollutants have recognized epigenetic effects. Cigarette smoke is associated with histone acetylation and proinflammatory effects, and an impact on placental function (7). Diesel exhaust affects DNA methylation and has immune effects including increased asthma risk. Organic pollutants such as pesticides and industrial chemicals are persistent and lipid soluble, are detectable in cord blood, placenta, and breast milk, and have epigenetic and immunological effects, even at low doses. The transgenerational effects of environmental exposure mean that although environmental pollutant levels may fall, effects could still be seen because of exposure in previous generations.

A second environmental factor that may have long-term effects on early immune development is dietary methyl donors. In a mouse model, supplementing the maternal diet with folate had significant epigenetic effects on gene silencing through methylation in the offspring. These affected genes suppress the allergic phenotype, resulting in an increase in asthma in the offspring (8), and this epigenetic effect was transmitted to the second generation. Effects in humans are unknown. Until we have more data, changing recommendations on folate supplementation in pregnancy would be premature.

Third, bacteria may have epigenetic effects on early immune development. In animal models, microbial exposure *in utero* can be protective against allergy, through epigenetic effects on immunity (9). In humans, in Germany, a farming environment has a protective effect against allergy, traced to an increase in immune regulation associated with epigenetic effects on *FOXP3* methylation (10).

Immune function results from interactions of genotype, environment, and epigenetics

These examples highlight that we are born with a particular genotype and a preset epigenetic program for immune regulation, but this program can be modified by early environmental exposure. This system is somewhat adaptive, allowing changes in gene expression in preparation for the anticipated postnatal environment. This may explain some presymptomatic differences we see in immune function at birth. In the postnatal period, genetic and environment interactions con-

tribute to the ongoing modification of genetic factors, leading to a phenotype.

Allergic disease appears not to be the result of isolated defects in individuals, but from complex interactions in immune networks that result in shifting patterns of gene expression. Genetic polymorphisms influence not only disease susceptibility but also individual susceptibility to environmental factors. Environmental exposure is clearly a driving force that modifies gene expression patterns, and this effect can be transgenerational.

The developmental origins of health and disease are relevant to modern diseases, including allergy. We need to understand the complex interactions between factors and how their effects vary in individuals to address individual disease prevention. For this reason, attention must be given to emerging epigenetic paradigms in allergic disease, which are likely to provide novel insights into mechanisms and

pathways through which the early environment can be harnessed to modify immune development and prevent allergic disease. Effective prevention strategies are the ultimate goal in reversing the allergy epidemic, but require a better understanding of environmental drivers, target genes, and mechanisms of early immune programming. We must understand these interactions in very early life, as well as individual variation, if we hope to prevent allergic disease.

Conflict of interest

Susan Prescott has received a research grant from Probiomix (VRI), consultancy fees from Fonterra, Danone, Mead Johnson, and Nestle. She has received travel assistance and speaker fees from Nestle Nutrition, Nutricia, and ALK-Abelló

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