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REVIEW

The importance of environmental influences on pediatric asthma onset and prevention

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ABSTRACT

Complex interactions involving human genes, the immune system, and certain environmental factors may lead to asthma. The type and severity of airway inflammation and remodeling, as well as the asthma phenotype, are primarily determined by these interactions. Furthermore, it has been shown that exposure to environmental factors may either initiate asthma in those who are genetically predisposed, or *de novo* generate it in people who do not have a genetic background. This review examines the importance of the environment in asthma onset and prevention and delineates the possible mechanistic pathways underlying this effect.

IMPACT STATEMENT: This article describes the importance of gene-environmental interactions in asthma onset and persistence, and underpins the significance of epigenetics as a tool to modify asthma natural course.

KEY WORDS
Asthma; pathogenesis; genetics; epigenetics; environment.

INTRODUCTION

Asthma is a common chronic condition that affects both children and adults. It is characterized by recurrent respiratory symptoms and variable airflow limitation. The increased risk of asthma in children with asthmatic parents, provides evidence for the presence of a genetic component contributing to the development of this disease. On the other hand, since the human genome has not been changed, gene theory alone is unable either to justify the rise in asthma cases over the last decades or explain the development of the disease in individuals with an apparent atopy-free background (1, 2).

In a bid to demystify asthma pathogenesis, environmental factors attracted attention as a potential new variable. Current research indicates that asthma is the result of intricate interactions between the human genes, the immune system, and certain environmental factors. These interactions largely determine asthma phenotype as well as the type and severity of airway inflammation and remodeling. Moreover, environmental exposures have been demonstrated to either increase the prevalence of asthma in genetically sensitive individuals or cause the condition in others with no obvious genetic background (3, 4).

This review highlights current knowledge on the role of environmental factors in asthma onset and prevention.

THE ROLE OF GENETICS IN ASTHMA PATHOGENESIS: ARE GENES THE ANSWER TO EVERY QUESTION?

The implementation of Genome Wide Association Studies (GWAS) in clinical practice marked the importance of genetics in asthma pathogenesis. Through GWAS, it is estimated that almost 82% of the asthmatics have a genetic predisposition (5) and numerous genetic polymorphisms are found to be linked to asthma susceptibility, the level of lung function and the airway remodeling. Some of these polymorphisms may adversely affect the individual's lung function either pre- or post-natally and there are similarities between the genes implicated in lung function in both pediatric and adult populations. Strikingly, some genes responsible for the lung development at the beginning of life, seem to change their orientation during the life course and found to be involved in the development of chronic obstructive pulmonary disease (COPD) when lung ages (6, 7).

These data underpin the unquestionable significance of genes in the pathogenesis of asthma. The likelihood of asthma recurring in monozygotic twins is significantly greater than in dizygotic twins, emphasizing the influence of genetic risk factors in asthma. However, the observation that the concordance rate for asthma in monozygotic twins is not 100%, but rather about 75%, suggests that other factors may also have a significant impact (8).

Moreover, there has been a rise in asthma incidence since 1950s which cannot be explained by genetics alone. The human genome remained unaltered over this time despite the fast changes in our surrounding environment. So, it might be these environmental changes that are responsible for the asthma pandemic faced by the medical community the last decades.

THE ROLE OF THE ENVIRONMENT IN ASTHMA ONSET

Multiple sources provide evidence supporting the significance of environmental factors in determining asthma. The local ecosystem where a child is brought up, seems to affect the individuals' risk of developing asthma and is responsible for the diversity in asthma incidence between geographical areas. Research conducted on both adults and children, with careful attention to methodological details, confirms the clinical observation that there are genuine disparities in disease prevalence between countries. The more westernized a country, the higher the asthma risk (9, 10). Furthermore, there is substantial evidence indicating a rise in disease activity in both developed and developing countries which cannot be explained by genetic variables alone. For example, in Great Britain, it is estimated that one out of every seven children have asthma (11) and surprisingly, the sub-Saharan African countries where the disease did not exist in the 1960s, now have similar asthma rates to many developed countries (12).

One of the main culprits for the rising asthma prevalence is the change in lifestyle, the gradual abandonment of the "living in nature" for the "living in the modern world", that resulted in individuals' exposures to numerous unprecedent agents (*e.g.*, city air-pollution) with potential adverse effects in lung growth and development (13). It is well-established that exposure to allergens, air pollution, infectious agents, and tobacco smoke from conception to adulthood is associated with an elevated risk of asthma, rhinitis, and impaired lung function (14).

An Austrian cross-sectional study of 11,423 participants from the Lung, hEart, sociAl, boDy (LEAD) cohort, which included individuals aged 6 to 82 years, demonstrated that the adverse events associated with reduced lung function differ across different age groups and potentially geographical locations. Additionally, the frequency of adverse events tends to increase over time, and they exhibit substantial interactions with one another. It is crucial to note that the network of interactions becomes significantly more complex as individuals age. As a conclusion, the LEAD study posits that the development of asthma may be triggered by a sequence of adverse events that occur throughout an individual's lifetime (15). This assertion, which underscores the significance of environmental factors in the development of asthma, may be overly simplistic. The fact that not all fetuses exposed to nicotine during prenatal development exhibit reduced lung function and/or respiratory susceptibility in postnatal life, suggests the potential involvement of other variables in this process (16).

Furthermore, while most toddlers who attend nursery school experience recurrent upper respiratory tract infections, only a percentage of them develops prolonged and distressing lower respiratory tract symptoms including wheezing and dyspnea (17). It seems

that the exact same environmental exposures (tobacco smoke, viruses, aeroallergens *etc.*) that lead to asthma in some individuals, have no such an effect in others. So, the question is "what transforms a rather innocent environmental factor to an asthma-causing one"?

GENE-ENVIRONMENT INTERACTIONS IN ASTHMA PATHOGENESIS; IT TAKES TWO TO TANGO

By the early 1970s, a geneticist and physician, Dr. Knudson was internationally recognized for his "two-hit" theory of cancer causation, which explained the relationship between the hereditary and non-hereditary forms of a cancer. In later years, the theory gained great popularity and was adapted by other medical specialties to explain disease onset (18).

In line with this, the fact that asthma runs in families could be explained by an inherited-first hit (the carriage of a genetic variant) followed by a random-second hit (*e.g.*, viral infection, aeroallergen, and tobacco smoke exposure) that initiates the disease development (19). So, the exposure of a child who carries an asthma polymorphism (first hit), to viral infections or aeroallergens (second hit) may lead to a disorganized and prolonged inflammatory response that presents clinically as wheezing and bothersome cough. One potential explanation is that the effect of viruses on the airway epithelial cell (AEC) barrier is more pronounced and protracted in individuals with underlying or prior susceptibility to asthma than in those without asthma. It appears that their genetic background undermines their capacity to effectively combat the invading pathogen (20, 21). Furthermore, it is recognized that the cycle that commences with aeroallergen inhalation which penetrates the AEC barrier, maintains epithelial dysfunction and clinical symptoms in asthmatics but not in healthy individuals (22, 23). These data underscore the applicability of the "two-hit" hypothesis in asthma pathogenesis where the interplay between human genes and environmental factors is necessary and neither one of them (genes or environmental factors) can cause the disease unless they are concurrently present in the same individual.

Given that both genetic and environmental factors, as well as their interaction, significantly influence lung function and the susceptibility to asthma in children, it is puzzling why not all children of atopic families develop asthma and moreover, why children from non-atopic families might become asthmatics during their life course.

EPIGENETICS IN ASTHMA PATHOGENESIS

In 1859, Darwins' theory about the influence of the environment in the evolution of species was published, bringing the idea about a possible *cross-talk* between the environment and the genome. Darwin proposed that between unfavorable environmental conditions, the genetic makeup of all organisms, including humans, exhibits adaptability. The latter provides an organism with the necessary plasticity to adjust to changing environments and the ability to produce adaptive phenotypes from the original genetic genotype. Those species not capable to genetically adapt to the changing surroundings were doomed to extinction (24).

Today, more than 150 years after Darwin's publication, there is scientific data supporting possible cause-and-effect links between human genes and several environmental factors such as air pollution, obesity, diet, exposure to infections, antibiotics, and allergies, including exposures during early life (25).

These factors can activate or repress genes, leading to permanent changes in gene expression, without any change to the underlying gene sequence. This procedure is called *epigenetics* and affects the phenotype of an organism in a *positive* or a *negative* way (*e.g.*, causing initiation of, or preventing from a disease development, like asthma) through different mechanisms like DNA methylation, histone acetylation or deacetylation and microRNA regulation (26, 27). Maternal smoking during pregnancy has been among the most widely investigated epigenetic mechanisms in the epigenetic epidemiology field. As a result, it is now evident that fetal exposure to maternal smoking may lead, through epigenetic mechanisms, to decreased lung function after birth and later asthma development independent of the presence of a genetic asthma polymorphism. In other words, maternal smoking during pregnancy may, *de novo*, produce an asthmatic phenotype in the fetus, without changing the fetal DNA sequences (28-30).

ARE EPIGENETIC MODIFICATIONS HERITABLE?

Increasing data suggests that environmental exposures can lead to adverse health effects that can be

inherited across generations, even without direct exposure to the initial factor. Therefore, it is important to examine an individual's health considering the impact of cross-generational influences. Epigenetic transgenerational inheritance has been observed in both plants and animals. Animal experiments provide evidence that asthma risk can be passed down through generations following a single exposure to a noxious agent (31).

In humans, a growing body of work demonstrates that the parental and grandparental (transgenerational) exposome is associated with health outcomes in future generations, observable at a methylation level (32). For instance, grandchildren of maternal grandmothers who smoked during pregnancy are projected to have a poorer predicted FEV1/FVC% and a lower lung function overall. This effect impacts exclusively the male grandchildren and correlates with their increased asthma risk (33).

So, an individual's exposures from conception to senescence along with exposures of previous generations may impact lung health trajectory and create what we call an "epigenetic memory" which can be passed on to future generations (34).

THE USE OF EPIGENETICS AS AN ASTHMA MODIFICATION TOOL DURING PREGNANCY

The developing embryo is particularly susceptible to epigenetic alterations (*e.g.*, DNA methylation, histone modification, and microRNA expression) in response to the intrauterine environment, because the fetal DNA is hypomethylated at the onset of embryonic development (35).

For instance, there are numerous reports of altered DNA methylation at critical sites for metabolic processes following maternal dysglycemia and/or a high-fat diet during pregnancy (36, 37). Hence, pregnancy should be regarded as a window of opportunity where external interventions may alter fetal DNA expression and the resultant phenotype via epigenetic mechanisms.

In recent decades, clinical studies investigated the effect of mother's nutrition during pregnancy as a means of primary asthma prevention. Multiple observational studies suggest that administering vitamin D and long chain fatty acid (n3-LCPUFA) supplementation to pregnant women can alter the airway microbiota of infants, resulting in a reduction of bacteria levels linked to asthma and airway inflammation. It appears that the acetylation levels at immune regulatory genes, such as the CD14 gene, may be influenced by maternal fish and oil consumption, which could subsequently alter the immune responses of the offspring. The positive impact of LCPUFA appears to extend to both the transient early wheezing phenotype marked by airway infections and the asthma phenotype that persists into school age. On the other hand, the protective effect of vitamin D seems to be limited to the early transient wheezing phenotype. The benefits of supplementation have been examined in large randomized controlled trials (RCTs) and have demonstrated protective effects not just on early wheezing and asthma, but also on common early respiratory tract infections of the lower respiratory tract and croup. The beneficial effect of both LCPUFA and vitamin D on early asthma depends on the genetic risk profiles, which should be considered as a modifying epigenetic factor when implementing tailored preventative supplementation regimens during pregnancy (38).

Apart from the quality of maternal diet during pregnancy, maternal weight and fetal growth have attracted research attention due to their potential involvement in future lung pathology. The current literature offers compelling evidence that maternal obesity and intrauterine growth retardation (IUGR) are closely associated with a higher likelihood of lung disease. Insulin and leptin, as well as their respective downstream signaling cascades, are critical regulators in this mechanistic pathway. Although both hormones are necessary for physiological growth and development during pregnancy, the disruption of the concerted interaction and balance of these hormones, circulating cytokines, and growth factors during a critical window of development, can disrupt developmental processes and negatively impact the respiratory health of the child throughout their life. For instance, maternal obesity results in insulin- and leptin-insensitivity, as well as hyperinsulinemia and hyperleptinemia. IUGR, in contrast, is defined by a transient prenatal downregulation of insulin- and leptin signaling, which is followed by a postnatal upregulation during catch-up growth, resulting in the same disease progression as obesity. Subsequently, these two endocrine factors induce a cascade of pro-inflammatory programming, which results in the release of (adipo-) cytokines and can contribute to metabolic and pulmo-

nary diseases. These pulmonary sequelae range from aberrant alveolarization and angiogenesis to the remodeling of the extracellular matrix and, eventually, a reduction in lung function (39).

Furthermore, maternal immune system appears to be highly involved in the training and proper function of the fetal immune system. Maternal diet, illness, inflammation, smoking, and stress are all factors that might affect the evolution of the fetal immune system. Such in utero disturbances dysregulate the development of hematopoietic stem and progenitor cells in the fetus, through epigenetic mechanisms. As a result, the fetal immune cells undergo alterations in their composition or function. Disrupting the establishment or function of fetal-derived immune cells can have a significant influence on tissue-specific immunity and the risk of lung disease throughout a person's life (40). In line with this, maternal smoking during pregnancy is associated with increased proliferation of neonatal cord blood mononuclear cells in response to allergens. This may predispose to later development of allergic/eosinophilic asthma (41). Also, maternal smoking is linked to a downregulation of neonatal Toll-like receptor function and a reduction in cytokine secretion, increasing the risk for developing neutrophilic asthma in preschool years (42).

EPIGENETIC MODIFICATIONS OF ASTHMA RISK AFTER PREGNANCY: THE ROLE OF GUT MICROBIOME

It is evident that intrauterine environment represents a period of opportunity to manipulate the future fetal wellness or illness by interfering into the *fetal gene-womb environment* crosstalk. After birth, the infant DNA and immunity have been shaped through epigenetic mechanisms. So, at this point, the newborn is either programmed to enjoy a healthy lung lifespan or develop asthma later. Interestingly, the communication between the genome and the external environment continues after delivery offering a second and maybe last opportunity to prevent asthma development.

An increasing amount of evidence points to a major role for the external microbiome in asthma onset and persistence. Its potential for asthma prevention is highlighted by the extremely low prevalence of asthma in populations that are highly exposed to microbe-rich environments, such as the Russian Karelia communities and farm children. The likely explanation relies on the effect of the external microbiome on gut microbiome and the immune system maturation. At birth, the immune system is still immature and skewed towards type 2 responses. The newborn counts on its innate immunity and maternal antibodies to fight off invading bacteria and viruses. Type 1 immune response mechanism is under-developed, and so, the dendritic cells of a newborn exhibit a slow and impaired capacity to induce type 1 cytokine production, tumor necrosis factor-α, and type 1 interferons in response to pathogens. Also, at this stage, the adaptive immune responses are absent. For the newborn to survive, the immune system should quickly and properly evolve in the first few years of life. It is now evident that early life exposure to microbes is the most important inducing factor for the evolution of the immune system. This maturation progress should be properly set in to skew the immune system away from type 2 and towards type 1 responses, and a mature adaptive immunity. A proper maturation progress will result in a well-trained immune system being able to recognize "the good from the bad" and so, remain silent to harmless commensals and allergens but effectively kill pathogenic bacteria. Recent data support that this immune maturation will rapidly occur in microbe-rich environments, such as rural areas or farms. On the contrary, the development of the immune system is slowed and delayed in westernized societies due to the paucity of microbial exposure. The delayed immune maturation results in prolonged type 2 immune responses that increases the risk of atopic sensitization and ultimately childhood asthma, along with inadequate type 1 immune responses that increases the susceptibility to respiratory viruses (43).

The mechanisms underlying this protective effect in children living in a farm was investigated in the Protection against Allergy: Study in Rural Environments (PASTURE) birth cohort. The investigators modeled maturation using 16S rRNA sequence data of the human gut microbiome in infants from 2 to 12 months of age. The human gut microbiome undergoes significant changes during the first year of life and begins to stabilize shortly thereafter. Therefore, the authors posited that the first year of life is a period during which the human microbiome's development is influenced by the external en-

vironment, potentially with long-term repercussions. They found that the gut microbiome may contribute to asthma protection through metabolites like butyrate (a type of short chain fatty acid, SCFA), supporting the concept of a gut-lung axis in humans. Butyrate is the main source of energy for colonic epithelial cells, contributes to the maintenance of the epithelial gut barrier and has immunomodulatory and anti-inflammatory properties. Higher SCFA levels may reduce inflammation at various body sites, including the airway mucosa. The authors also focused on factors that may alter the rate of the gut microbiome maturation progress. They found that maternal smoking during pregnancy, breastfeeding beyond the first six months of life, antibiotic consumption in the first year after birth or being born by cesarian section are factors that hinder the maturation progress and ultimately, linked to asthma development. On the other hand, growing up in a farm, exposure to animal sheds, unpasteurized farm milk and egg consumption or having at least two older siblings, speed up the maturation progress and decrease asthma risk (44). These data emphasize the need for prevention strategies in the first year of life, when the gut microbiome is highly plastic and amenable to modification.

Table 1 summarizes the external factors that interact with our genome and gut microbiome pre- and post-natally and possible intervention praxis.

CONCLUSIONS

There is a sustained crosstalk between the environment, the human genes, and the immune system, pre- and post-natally. External factors may alter gene expression through epigenetic mechanisms and shape the immune responses, transforming an individual's lung health in the long run (**Figure 1**). Of importance, growing up in a farm environment may act as an epigenetic factor and protect from childhood asthma and allergies. It seems that contact with animal sheds and consumption of farming products such as milk or eggs has an important protective role. Maternal smoking during pregnancy may also act as a significant noxious epigenetic factor. All available studies stress the importance of the first 1000 days of life, from conception (or even before) to two years as a critical window for interference to prevent asthma development. To finally succeed in, we need to better understand the mechanistic properties of the external-internal world interaction. This will enable health physicians to apply tailored therapeutic interventions on their patients.

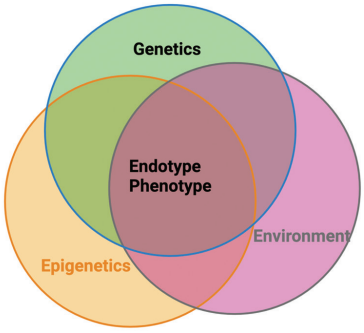

***Figure 1**. The interaction between genetics, epigenetics, and environmental factors in the formation of an individual's endotype/phenotype (created by BioRender).*

***Table 1**. Risk modification: environmental factors interacting with our genes and gut microbiome that could be manipulated to modify future asthma risk.*

Pregnancy	Early life and childhood
Optimize maternal nutrition	Optimize early life microbiome (opt for vaginal delivery, breastfeeding, grow in farm environment)
Advise against maternal obesity	Avoid injurious exposures (tobacco smoke, indoor and outdoor air pollution)
Advise against maternal smoking and other nicotine exposure	Avoid early sensitization to aeroallergens
Avoid maternal medication (*e.g.*, steroids that dysregulate maternal immune system)	Prevention of acute severe asthma attacks (to avoid epithelial damage)
Optimize fetal growth (prevent intrauterine growth retardation)	Meticulous use of asthma medications (to prevent epithelial damage and facilitate lung recuperation)
Advise against maternal alcohol consumption (leads to IUGR and deranges the immune lung defense)	Prevention of acute lower respiratory tract infections (that wound the lung)
Try to prevent premature birth	Immunizations (*e.g.*, pneumococcus, annual influenza, respiratory syncytial virus)

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

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Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

Data are available upon motivated request to the Corresponding Author.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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