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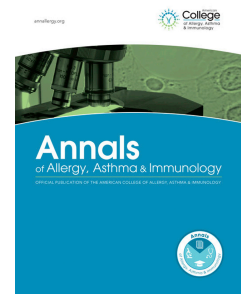
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Origins of allergic disease: Maternal and early childhood factors

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Abbreviations: AD = atopic dermatitis, FA = food allergy, AR = allergic rhinitis, FLG = filaggrin, Treg = regulatory T-cells, PM 2.5 = fine particulate matter, NO₂ = nitrogen dioxide, O₃ = ozone, TRAP = Traffic-related air pollution

Word Count: 943

Figures: 1

1 Introduction

2
3 The incidence of allergic diseases has increased over the last two decades.¹ The study of the
4 origins of allergy is an important topic, both to understand the mechanisms of allergy
5 development and to produce interventions to treat or prevent allergic diseases. The term atopic
6 march is used to describe the progression of allergic disease development, beginning with atopic
7 dermatitis (AD) and progressing to food allergy (FA), asthma, and allergic rhinitis (AR). While it
8 is necessary to focus on early childhood factors, the prenatal environment must also be
9 considered. In particular, factors contributing to epithelial barrier disruption in the skin, lungs,
10 and gut play a role in the type 2 inflammation associated with allergic diseases. Pollution, other
11 environmental irritants, food chemicals, and allergens are areas of focus driving allergy
12 development *in utero* into early childhood.

14 Epithelial dysfunction in the skin, lungs, and gut

15
16 The epithelial barrier serves an important role in multiple organs, and it is a major component of
17 the innate immune system.^{1, 2} The skin barrier is the body's largest organ and the first line of
18 defense for infectious organisms, while the respiratory and gastrointestinal epithelial linings also
19 block foreign microbe entry. When these barriers are disrupted, allergens and microbes are
20 allowed entry from the external environment. The body's response to foreign penetration
21 involves producing cytokines that propagate the type 2 inflammatory response. Thymic stromal
22 lymphopoietin (TSLP) and IL-33 are cytokines produced by skin, lung, and gut epithelium. They
23 play a key role in the development of type 2 inflammation.¹ The 15 lipoxygenase and ferroptosis

pathway in epithelial cells, along with dectin-1, play a role in asthma persistence. In the gastrointestinal tract, the decreased diversity of the gut microbiome leads to disrupted regulation.¹ *Staphylococcus aureus* colonization on the skin contributes to AD and FA.

There are known causes of epithelial dysfunction described above. These include genetic factors implicated in the development of various atopic conditions. Perhaps the most widely studied is the filaggrin gene (*FLG*) in the skin, as the *FLG* loss-of-function mutation is a prominent genetic factor predisposing to AD.¹⁻³ When examining children with AD and FA compared to the AD without FA group and the non-atopic group, the children with AD and FA have a pronounced decrease in *FLG* breakdown products and greater disruption of the stratum corneum.³ This is present even in the normal appearing, non-lesional skin, suggesting that their entire skin surface is vulnerable to allergen penetration and thereby placing the individual at risk for allergen sensitization. There are also genome-wide studies that have identified many asthma susceptibility genes.¹

Perinatal risk factors

Prenatal maternal exposures and early childhood exposures are implicated in atopy development.^{1,2,4} It is known that prenatal factors, such as maternal smoking, impact the *in utero* environment and programming of the immune system,⁵ so maternal factors may play a role in magnifying the allergic phenotype in the fetus. Outdoor and indoor pollutants or exposures should be considered when examining risk factors for atopy. In atopic diseases, regulatory T-cells (Tregs) have a critical role in immune expression. FOXP3 is a transcription factor essential

for Treg development and function, and it is present in CD4 + T-cells. Hinz et al demonstrated lower cord blood Treg numbers in infants who were exposed to air pollutants through maternal smoking or environmental smoke exposure and developed AD by one year of life. This suggests that maternal exposures can cause epigenetic changes and immune dysregulation in the fetus.⁵

Traffic-related air pollution (TRAP) exposure is a well-known factor in childhood asthma development.⁴ Fine particulate matter (PM_{2.5}) are small inhalable particles that are increased especially in the winter months when pollution buildup is at a maximum. PM_{2.5} exposure is linked to DNA methylation changes in FOXP3 of CD4 + T-cells in asthma.¹ Ozone (O₃) is most prevalent in the summer months, and both O₃ and nitrogen dioxide (NO₂) cause oxidative stress in the lungs and skin.^{4,5} A birth cohort with 17 years of follow-up demonstrated that exposures to O₃ and NO₂ conferred a higher risk of asthma and AD in these children.⁴ Finally, the increased use of soaps, detergents, and microplastics has led to more allergic diseases through the disruption of skin and mucosal epithelium.¹ These findings demonstrate that epigenetic changes are beginning *in utero* and should be considered in atopy prevention.

Regarding early life events, viral and bacterial respiratory pathogens are contributing factors for asthma progression.¹ Lung injury and subsequent remodeling can occur with both pathogen and allergen exposures, thus increasing the risk for further lung injury. When examining the microbiome, the influence of the industrialized lifestyle causes alterations of the microbiome with declining diversity of the microbiota.¹ There are many contributing factors to the origins of allergy. These include increased cesarean section births, increased formula feeding, refined diets,

and increased antibiotic use. Vitamin D has also been studied as it plays a role in skin development, innate immunity, and tolerance.¹

Conclusion

With the increase in allergic disease prevalence, it is important to examine prenatal and postnatal factors contributing to atopy development (Figure 1). Multiple organ systems are involved in allergy development. Understanding the epithelial dysfunction leading to type 2 inflammation in the skin, lungs, and gut is critical. Continued study of genetics will further elucidate causes of allergies. It will be important to perform prospective birth cohort studies to follow the pregnant mother and her offspring's early childhood, with close observation of environmental exposures, including TRAP, detergents and soaps, diet, and medication exposures. When proposing interventions for allergy prevention, the emphasis should begin with the maternal skin barrier and limiting adverse exposures,² and maintaining intact epithelial barriers of the skin, lungs, and gut in early childhood.

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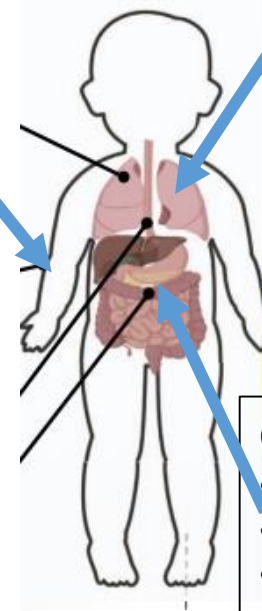
Maternal exposures:

- Outdoor and indoor pollutants
- Cigarette smoke
- Soaps and detergents
- Microplastics
- Increased antibiotic use

SKIN EPITHELIAL DYSFUNCTION -> AD & Atopic March:

- Outdoor & indoor pollutants
- Smoke exposure
- *S. Aureus* colonization
- Food allergen and aeroallergen skin penetration
- Vitamin D deficiency
- Decreased microbial diversity
- Genetic influence (ie. Filaggrin mutation)

Cesarean section delivery



LUNG EPITHELIAL DYSFUNCTION -> Asthma:

- Outdoor pollutants
- Smoke exposure
- Viral and bacterial respiratory pathogens
- Aeroallergen penetration
- Decreased microbial diversity
- Genetic influence (ie. 15 lipoxygenase and ferroptosis pathway, dectin-1)

GUT EPITHELIAL DYSFUNCTION -> FA:

- Formula feeding
- Increased antibiotic use
- Food allergen and aeroallergen penetration
- Processed foods
- Decreased microbial diversity
- Epithelial Gene influence

Figure Legend

Figure 1. Potential perinatal factors contributing to the development of atopy.

Left: The prenatal maternal-fetal environment can cause fetal epigenetic changes and immune dysregulation with various maternal exposures. *Right:* Birth delivery route and post-natal infant exposures are contributing to epithelial dysfunction in the skin, lung, and gut. Please note that the listed factors collectively affect multiple organ systems, as factors listed under one category can modulate the immune system leading to systemic and local Type 2 immune responses.