



Editorial overview: Collusion between genes and environment in the pathogenesis of allergic disease

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Current Opinion in Immunology 2019, 60:iii–v

For a complete overview see the [Issue](#)

<https://doi.org/10.1016/j.coi.2019.09.002>

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The prevalence of allergic diseases has risen dramatically throughout the world in recent years, creating a major public health burden. This issue of *Current Opinion in Immunology* focuses on recent discoveries regarding the effects of genetic and interacting environmental factors on the pathogenesis and treatment of allergic diseases. With increasing access to genetic, epigenetic, and gene expression tools which can be correlated with specific exposures and to discrete outcomes, mechanistic work in models and clinical allergic diseases can better explain the ties between genetic variation, environmental exposures and clinical outcomes. These reviews tackle key elements of the pathways elucidated, providing novel basic, translational and clinically relevant findings related to allergic disease.

The increase in allergic diseases over the last few decades is highly correlated with changes in lifestyle and greater exposure to chemicals in our food, air, and personal care products. As discussed in this issue, these lifestyle changes, avoidances and exposures likely culminate in dramatic shifts in the microbiome that interrupt the immunoregulatory mechanisms that normally promote tolerance to allergens. [Chatila and Victor](#) review the role of dysbiosis in the pathogenesis of food allergy, where loss of members of the Clostridial order have been linked to the development and delayed resolution of food allergy. Dysbiosis may play a direct role in the pathogenesis of food allergy, as stool from mice genetically predisposed to food allergy due to a gain-of-function mutation in the gene encoding the alpha subunit of the IL-4 receptor (IL4raF709 mice) was sufficient to transmit a greater susceptibility for food allergy to germ free mice. On the other hand, healthy infants may harbor commensals, including members of the Clostridiales and Bacteroidales orders, that are protective against food allergy, even in a host genetically predisposed to the disease. The mechanisms by which microbes confer protection against food allergy are still under investigation, but may include MyD88-dependent induction of RORγt+ T regulatory cells (Tregs). Efforts are underway to identify and harness protective microbes as a strategy to prevent and perhaps treat food allergy.

Dietary factors have a dramatic effect on the composition and function of the microbiome, and [Perdijk and Marsland](#) describe the role of these changes in determining susceptibility to atopic phenotypes. The influence of nutrition may begin in pregnancy where consumption of raw cow's milk and supplementation with vitamin D or omega-3s reduce an infant's risk of developing asthma. Early in life, breastmilk may cultivate a tolerogenic microbiome through its high levels of human milk oligosaccharides. The fiber and fat content of the diet also modulates the microbiome with implications on tolerogenic immune pathways. Over the coming years, improvements in

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microbial analyses, metabolomics, and *trans*-kingdom interactions will further inform nutritional interventions for allergic disease.

Multiple studies have revealed that exposure to farms and a farming environment (livestock, hay, unpasteurized milk) early in life reduces the risk of allergic disease. As discussed by [Deckers, Lambrecht, and Hammad](#), this protection has been attributed to microbes and their metabolites that are present in farm dust, including endotoxin and beta-glucans, as well as non-microbial and/or plant-derived metabolites. These environmental exposures are thought to impact colonization of the skin, lung and intestines, but the subsequent immunologic consequences may be influenced by the dosing and timing of exposure.

Although intended to protect against harmful microorganisms, the increasing use of antimicrobial products in our everyday lives may be contributing to dysbiosis and the development of allergic disease as reviewed by [Anderson, Weatherly, and Shane](#). Growing evidence has identified a positive association between exposure to antimicrobial agents, either occupationally or through the use of personal care products, and the incidence of multiple forms of allergic disease. These chemicals are common in cleaners and disinfectants used in industrial and clinical settings, but are also encountered by the general population in antibacterial hand sanitizers, soaps, cosmetics and even food additives and preservatives. Exposure to these chemicals has been linked to the development of both type I IgE-mediated reactions as well as type IV delayed type hypersensitivity reactions. The mechanisms responsible remain to be fully elucidated, but changes in the microbiome may contribute.

Several early life risk factors, many of which promote dysbiosis, have also been shown to increase the risk of eosinophilic esophagitis (EoE), an allergic condition characterized by an excessive accumulation of eosinophils in the esophagus that leads to esophageal dysfunction. As detailed in the review by [Lyles and Rothenberg](#), the risk of EoE is influenced by a number of environmental exposures, including antibiotic use, method of delivery, infectious history, and geographic variables. Likewise, variants in genes involved in epithelial barrier function and Th2 immunity are also associated with a higher risk of EoE. Efforts are underway to better understand how the interaction between these environmental and genetic risk factors contribute to the pathogenesis of EoE, which may have broader relevance to the allergic diathesis.

Air pollution emitted from vehicles and industrial sources is a growing cause of morbidity and mortality around the globe and is specifically associated with a higher risk of asthma in both children and adults. [Johansson, Merisha, Brandt, and Hershey](#) examine the evidence from candidate gene studies, including the family of glutathione S-transferases (GST) genes, as well as genome wide association studies for how indoor and outdoor air pollution interact with host genetics to promote allergic respiratory disease. Interestingly, many single nucleotide polymorphisms (SNPs) associated with asthma are located in non-coding regions of genes that are subject to DNA methylation, suggesting that epigenetic changes may underly the connection between air pollution, genetic susceptibility, and asthma. These studies point to improvements in air quality as a modifiable risk factor for asthma and perhaps other allergic diseases.

Single gene disorders that strongly predispose to allergy provide an extraordinary opportunity to understand the mechanistic pathways that lead to these complex phenotypes. [Sacco and Milner](#) discuss how environmental

factors, including diet, infections, and psychological stress, may contribute to the variable expression of allergic disease in primary atopic disorders. Potential mechanisms include the ability of dietary nutrients to affect T cell metabolism and function, infections to influence the severity of inflammation at barrier sites, and stress to modulate mast cell activation and other effector functions. A greater understanding of gene-environment interactions in this context will open the door to new interventional strategies for allergic disease in the general population.

Among the pathways identified to contribute to the pathogenesis of allergic disease is that mediated by the multi-functional cytokine transforming growth factor beta (TGF β). As described in the review by [Weissler and Frischmeyer-Guerrero](#), mutations in the gene encoding the receptor for TGF β , as well as more common variants in genes in the TGF β signaling pathway, are associated with a higher risk for allergic disease and in some cases variable response to treatment. TGF β promotes tolerance to innocuous antigens by supporting Treg development, B cell

class-switching to IgA, and inhibition of mast cell activation. However, TGF β can also have pro-inflammatory activities by promoting the differentiation of Th9 cells and mast cells as well as tissue fibrosis and remodeling in the setting of allergic inflammation. Identification of the environmental factors that fine-tune the balance of TGF β signaling will inform future efforts to direct the TGF β pathway in a tolerogenic direction.

The relatively rapid rise in prevalence of allergic disease indicates that genetic factors alone are not responsible; nonetheless, allergic diseases tend to run in families, suggesting a genetic contribution. As discussed in these reviews, a better understanding of how environmental factors intersect with host genetics to lead to allergic disease will reveal new opportunities to prevent and treat these common diseases.

Funding

This research was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, N.I.H.