

Human microbiome and allergy

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Email: vafanos@tin.it**Editor:** Elena Chiappini**Abstract**

Human microbiome contributes to critical functions that impact health and disease. It influences the development of the immune system, and the pathogenesis of immunological disorders included allergy. While it is easy to understand how airway microbiome, influencing local inflammation and immune activity, could contribute to shaping asthma phenotype, it is not so obvious to understand the influence by the gut microbiome, but there is growing evidence about it. The increase of allergic disorders in western countries led to investigate the role environment is playing and how it may change our microbiome and immune system, with the hope of finding new preventive approaches for allergy.

KEYWORDS

allergy, human microbiome

The microbiome is the sum of microbes (microbiota) and their genome in a specific environment. We can consider the human body as a complex ecosystem and its microbiome as an integral component of human physiology.

Bacteria are the most studied organisms, thanks to new technologies based on the sequencing 16s rRNA gene. 500-1000 distinct bacterial phylotypes¹ are estimated to cohabit in a healthy human body, mostly in the gut; fungi and viruses are also present in this community, but their functional contribution is still largely undefined.

Studies in the last years have underlined the critical role of the gut microbiota in shaping the immune system. It is involved in the development of the organs of immunity, and it seems to determinate the tendencies of host immune response² modulating type 2 immunity, maintaining a regulatory tone of the mucosal immune system, regulating basophil hematopoiesis, and promoting intestinal barrier function.³

Short-chain fatty acids, the main product of the digestive action of the gut microbiota, are viewed as a critical factor in promoting immunological tolerance, influencing the metabolism and determining epigenetic changes in DNA.²

They reduce pro-inflammatory cytokines, including IL-1 β , IL-6, and IL-17, inducing anti-inflammatory mediators, including IL-10.

Moreover, they increase IgA production and the percentages of T regulatory cells, essential in oral tolerance.²

Investigations on microbiome could help to understand the pathogenesis of many immunological disorders included allergic disorders.

Allergy is a hypersensitivity reaction toward harmless antigens, initiated by immunologic mechanism and reproducible on subsequent exposure. It is mediated by adaptative immunity, mostly based on T helper 2 cells response and IgE antibody isotype. Allergic disorders are often interconnected and include eczema, allergic asthma, rhino-conjunctivitis, and food allergy, with a huge clinical heterogeneity of symptoms, in different districts. The pathogenetic basis is an alteration of the immunological tolerance, due to genetic predisposition and influenced by environmental factors yet to be clarified.

There is emerging evidence that early gut microbiota establishment, during critical periods of immunological development, has the potential to influence the risk of allergic disease.⁴

This critical temporal window of microbiota colonization is represented by the first 2/3 years of life when the gut microbiota is still unstable.² However, it is very likely that appropriate microbial stimulation, both pre- and postnatally, is required to avoid the pathological process that leads to allergy.^{4,5}

Indeed, contrary to the “sterile womb” paradigm, recent studies suggest that maternal microbial transfer to the offspring may begin during pregnancy, providing a pioneer microbiome that dictates the types of organisms that co-colonize the niche.^{4,6}

The dramatic rise of allergic diseases of the last decades, in western countries, led Strachan to formulate the “hygiene hypothesis” in 1989. It suggested that the decrease in infections in infancy could explain the allergy epidemic. This hypothesis was later revised by the “gut microbial deprivation hypothesis,”⁴ proposing that the reduced diversity of early microbial exposure underlies the allergy epidemic.

Most of the last studies concluded that microbiome biodiversity is protective.⁷

Moreover, Fujimura et al noted that bacteria-impooverished residences, that conferred a higher risk of allergic disease development, held a more extensive range of fungal species.¹

Searching for risk factors for allergy epidemic in western countries, most studies agreed that the cesarean section, maternal antibiotic intake, diet, urbanization, and synthetic chemicals might have played a critical role.

A population-based birth cohort study revealed that children born by cesarean section had a threefold higher chance of developing food allergy.²

Infants born vaginally are exposed to both maternal fecal and vaginal microbiota. In contrast, infants born by cesarean section are exposed to maternal skin and environmental microbes, and are more likely to have a lower abundance of *Bacteroides* and a higher abundance of *Firmicutes*, with a microbiome enriched by *staphylococcus* and *streptococcus*.¹

Bacteroidetes and *Firmicutes* are currently the major taxa associated with food allergy across multiple studies in children.²

Moreover, maternal antimicrobial administration acutely depletes gut microbiome diversity and may influence the pioneer species transmitted to the offspring.^{4,6}

Epidemiological studies indicate that maternal farm environment exposure during pregnancy protects against allergic sensitization.⁴

Formula feeding has been shown to deplete commensal *Bifidobacteria* populations in the infant gut.¹ Instead, breast milk contains oligosaccharides that stimulate the growth of *B bifidum* and genus *Lactobacillus*, forming an acidic environment enriched by short-chain fatty acids.²

Diet plays an essential role in the establishment of the gut microbiota; therefore, the “western diet” with its high fat but low fiber content is proposed to be one of the reasons for the allergy epidemic.²

Higher ambient levels of air pollutants have been associated with the increased risk of allergies.² Although the mechanism remains unknown, studies suggested that inhaled air pollutants were able to directly or indirectly modify gut permeability, inflammation, and gut microbiota composition.

Currently, the concept of “gut-lung axis” is used to describe the mutual interference existing between the two organs. Gut microbiome influences the immune activity locally and at remote mucosal

Key message

Human microbiome has a complex relationship with immune and metabolic networks. It plays a strong role in perinatal programming of environmentally influenced diseases such as allergic disorders.

sites such as the airway mucous membrane, so that it can affect the pathogenesis of allergic asthma.

By the way, airway microbiota, too, seems to shape the disease phenotype of asthma, influencing the type of inflammation pattern that underlies this heterogeneous disease.

Distinct microbiome features may be protective toward virus infections in early life, such as VRS and rhinovirus infections, associated with a significant increase of subsequent childhood asthmas in atopic children.¹ They may influence steroid responsiveness too,¹ maybe through their capacity of steroid degradation.

Alterations in the nasopharyngeal microbiome also have been associated with allergic asthma.

A review of 2020⁸ recollected interesting studies. For example, in an Australian infant cohort, they demonstrated that a nasal microbiota dominated by *Moraxella* spp., *Streptococcus* spp., or *Haemophilus* spp. were associated with a higher probability of having persistent wheeze by age five years in atopic children; In a Danish cohort, differences in nasal microbiota profiles, associated with asthma, were linked to differences in mucosal immune mediators; moreover, an earlier study noted an inverse relationship between type 2-airway inflammation and airway bacterial burden.⁸

To date, modification of gut microbiota through probiotics, prebiotics, or synbiotics is the main target attempting to prevent allergic diseases.

In 2014, WAO did not recommend the use of probiotics for reducing the risk of allergy in children, but they took into consideration the possibility of benefit in atopic dermatitis.

Since then, literature has grown, but most of the meta-analysis do not include enough articles, or they do not conduct a homogeneity test. The most recent one is Li et al,⁹ in 2019, that showed a significant reduction in eczema with both pre-natal and post-natal probiotics supplementation. Protective effects were only seen with microbial mixtures or with single-species interventions of *L rhamnosus* or *L paracasei*. Although this promising result, the utility of probiotics is still not well understood because efficacy is likely species-dependent, it may be host-dependent as well, and, most of all, the evidence on food sensitization and allergy is inconclusive.¹⁰

In conclusion, it is almost clear the role of the microbiome in allergy, but the essential mechanism for proper immunological stimulation, in humans, has not been clarified yet. We hope that a better knowledge of microbiome function and how the environment may influence its development could lead to novel approaches to attempt to prevent allergic diseases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Vassilios Fanos: Conceptualization (equal); Data curation (equal); Project administration (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-review & editing (equal).

Vittoria Montecchiani: Investigation (equal); Methodology (equal); Writing-original draft (equal).

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