REVIEW

Microbiome and Allergy: New Insights and Perspectives

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J Investig Allergol Clin Immunol 2022; Vol. 32(5): 327-344
doi: 10.18176/jiaci.0852

Abstract

The role of the microbiome in the molecular mechanisms underlying allergy has become highly relevant in recent years. Studies are increasingly suggesting that altered composition of the microbiota, or dysbiosis, may result in local and systemic alteration of the immune response to specific allergens. In this regard, a link has been established between lung microbiota and respiratory allergy, between skin microbiota and atopic dermatitis, and between gut microbiota and food allergy.

The composition of the human microbiota is dynamic and depends on host-associated factors such as diet, diseases, and lifestyle. Omics are the techniques of choice for the analysis and understanding of the microbiota. Microbiota analysis techniques have advanced considerably in recent decades, and the need for multiple approaches to explore and comprehend multifactorial diseases, including allergy, has increased. Thus, more and more studies are proposing mechanisms for intervention in the microbiota.

In this review, we present the latest advances with respect to the human microbiota in the literature, focusing on the intestinal, cutaneous, and respiratory microbiota. We discuss the relationship between the microbiome and the immune system, with emphasis on allergic diseases. Finally, we discuss the main technologies for the study of the microbiome and interventions targeting the microbiota for prevention of allergy.

Key words: Human microbiome. Gut microbiota. Food allergy. Cutaneous allergy. Respiratory allergy. Omics.

Resumen

El papel del microbioma en los mecanismos moleculares de las enfermedades alérgicas se ha vuelto muy relevante en los últimos años. Cada vez más estudios sugieren que una composición alterada de la microbiota, o disbiosis, puede resultar en una alteración local y sistémica de la respuesta inmune a alérgenos específicos. En este sentido, se ha establecido un vínculo entre la microbiota pulmonar y la alergia respiratoria, así como la microbiota cutánea y el desarrollo de dermatitis atópica, y la microbiota intestinal y la alergia alimentaria.

La composición de la microbiota humana es dinámica y depende de diversos factores asociados al huésped como la dieta, las enfermedades y el estilo de vida, entre otros. Para el análisis y comprensión de la microbiota, las ómicas son las técnicas de elección. En las últimas décadas, las técnicas de análisis de microbiota han tenido un gran avance y han aumentado la necesidad de múltiples enfoques para explorar y comprender las enfermedades multifactoriales, incluidas las enfermedades alérgicas. De esta manera, cada vez son más los estudios que proponen mecanismos de intervención sobre la microbiota de pacientes.

En esta revisión, presentamos los últimos avances encontrados en la literatura sobre la microbiota humana, centrándose en las microbiotas intestinal, cutánea y respiratoria. Discutimos la relación entre el microbioma y el sistema inmunológico, con especial énfasis en las enfermedades alérgicas. Finalmente, discutimos las principales tecnologías para el estudio del microbioma y los estudios de intervención dirigidos a la microbiota propuestos para la prevención de alergias.

Palabras clave: Microbioma humano. Microbiota intestinal. Alergia alimentaria. Alergia cutánea. Alergia respiratoria. Ómicas.

Definitions

- Microbiota: The set of microorganisms (mainly bacteria, but also fungi, archaea, viruses, and parasites) that reside in our body.
- Microbiome: The collection of genes that are expressed by these microorganisms and contribute to a specific biological niche or ecosystem.
- Omics: The branches of science that study the entire set of biomolecules (genes, transcripts, proteins, metabolites) in a biological sample (cell, tissue, organ, organism).

Human Microbiome/Microbiota

Many anatomical locations, such as the skin, mucous membranes, respiratory tract, uterus, vagina, and digestive tract, are home to complex microbial ecosystems adapted to the particularities of each niche [1].

The study of microbial ecosystems is a field of rapid scientific progress. However, it has been hampered by controversy over the large number of microorganisms that cohabit in the human body. Although former estimations placed the ratio of bacteria to human cells at 10:1, adjusted calculations have shown that this ratio is closer to 1:1 (3.8×10^{13} bacteria: 3×10^{13} human cells) in a reference person of 70 kg [2].

Microbial communities are resilient but dynamic. From birth, the symbiotic relationship between the microbiota and our cells evolves constantly, adapting to changes [3]. These communities are also characterized by an interaction between environmental microbiota and different human body sites that contributes to the composition of our microbiota. The diversity of the microbiome is individual-dependent. This could make the microbiome a powerful tool in personalized medicine, where health care decisions could be based on the diversity of the microbiome rather than the host genome [4].

Such individual variability and temporal particularities make it difficult to define what constitutes a "normal" or healthy microbiota; however, it is generally considered that the greater the diversity and balance between species, the healthier the microbiota [5,6]. Other parameters related to healthy microbiota include the ability to produce short-chain fatty acids (SCFAs) [7] and the maintenance of epithelial barrier integrity [8].

It is known that changes in the composition of the microbiome—dysbiosis—are linked to the pathogenesis of certain conditions (cardiovascular, gastrointestinal, metabolic, and neurodegenerative diseases and cancer) and can increase the risk of others, including allergic diseases such as asthma, allergic rhinitis, atopic dermatitis (AD), and food allergy (Figure 1) [9–18].

1.1 Human Gut Microbiota

The microbial ecosystem found in the digestive tract is the most complex, diverse, and numerous of the whole body, with most microbes found on the oral mucosa and in the gastrointestinal tract. The number of bacteria in the gastrointestinal tract, particularly in the section between the colon and the appendix, is around 109 to 1011 per gram of

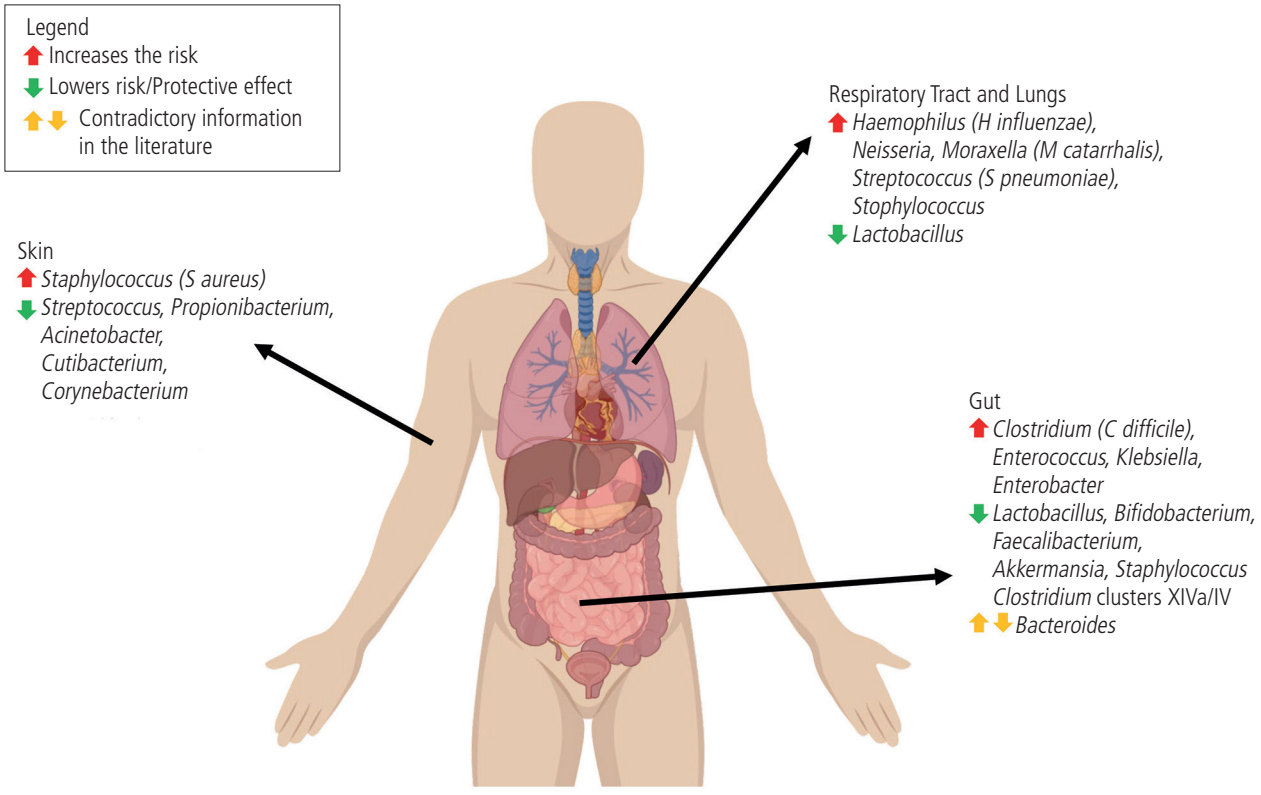


Figure 1. Changes in the microbiome related to the risk of asthma, allergic rhinitis, atopic dermatitis, and food allergy. The presence or increased abundance of certain bacterial genera and species have been linked to either an increased risk of developing allergic diseases (red arrow pointing upward) or a protective effect (green arrow pointing downward). For example, dysbiosis in the skin with increased colonization by *Staphylococcus aureus* has been linked to the onset of atopic dermatitis [146], while increased *Cutibacterium* and *Corynebacterium* is a consequence of treatment with dupilumab and correlates with an improvement in eczema [148]. In the airways, higher levels of *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* have been linked to wheezing in infants [78]. As for the gut, a higher proportion of *Clostridium difficile* than *Bifidobacterium* has been linked to higher rates of food allergy [123]. Similar examples are described throughout the text. Adapted from references [34,95,185].

luminal content, and the number of genera ranges between 1000 and 3000 [15-17]. One gram of human feces can host between 10 000 and 100 000 million bacteria. Feces is therefore representative of the microbiota composition of the colon segment. This, and the fact that samples can be collected noninvasively, makes it the biological sample of choice for the study of the gut microbiota [18-20].

It is estimated that there are thousands of bacterial species along the intestine, of which 60% cannot be cultured. High-throughput sequencing technologies, together with the development of bioinformatics and big data, have enabled the description of all the main microbial communities inhabiting the intestine and of their functional contributions to host health. Full metagenomics, for instance, helped to identify nonredundant microbial genes encoding up to 20 000 biological functions in the gut [21]. The most common microbiota phyla are Bacteroidetes (25%) and Firmicutes (60%). Proteobacteria, Verrucomicrobia, Fusobacteria, Cyanobacteria, Actinobacteria, and Spirochaetes are detected in smaller proportions. Given that it is critical to keep the proportions of bacteria in balance, the Firmicutes/Bacteroidetes ratio has been established as a parameter for evaluating the balance of the intestinal microbiota and its functionality [22].

Classically, the microbial colonization of the gastrointestinal tract was considered to begin immediately after birth; however, in recent years, it has been shown to begin in utero [23]. It is thought that 70% of the primary colonization of the gut microbiota is of maternal origin [24] and that the first 1000 days of life, when the body is faced for the first time with external factors, is critical for the development of the intestinal microbiota [3]. Moreover, the development of the gut microbiota in the first years of life correlates with the development and maturation of the intestine and the immune system [25]. After the first 2-3 years, when solid food is well established in the diet, the gut microbiota establishes itself for the rest of our life [26]. However, the composition of the gut microbiota changes throughout life, since it depends on host-associated confounding factors such as age, diet, use of antibiotics, smoking, lifestyle, and environmental conditions [12,27-36]. The main factors affecting gut microbiota are summarized in Figure 2.

Changes in intestinal bacterial communities can influence the onset of diseases in distant organs, such as the lungs or the skin [37-40], as shown in animal model experiments involving transfer of dysbiotic microbiota [41-43]. This crosstalk between gut microbiota and distant organs has been well studied, leading to the concept of the lung-gut axis and skin-gut axis, respectively. In these interactions, beneficial effects are observed through the presence of SCFAs such as propionate, butyrate, and acetate, which are end products of dietary fiber fermentation by commensal bacteria in the gut that can reach distant organs and exert a positive effect on the immune system. Acetate, for instance, which is produced by members of the Lachnospiraceae family in the gut, has been proven to prime the pulmonary innate immune system [44]. SCFAs may also play an important role in determining the prevalence of certain skin microbiota profiles, subsequently affecting cutaneous immune defense mechanisms [45,46]. With respect to the interaction between gut microbiota and distant regions of the body, it is worth mentioning the gut-brain axis, by which the central nervous system connects to the intestinal microbiota through the vagus nerve [47]. Bacterial metabolites can act as neurotransmitters. Thus, in addition to the classic diseases associated with alterations in the microbiota, the microbiota is also related to central nervous system conditions, ie, autism, anxiety, and depression [48-50].

Bile acids are also a relevant class of metabolites related to the gut microbiota. These are amphipathic steroid acids whose primary function is to facilitate the absorption of lipids and fat-soluble vitamins in the intestine, but which are increasingly recognized as key metabolic and hormonal mediators at distant locations [51]. The gut microbiota plays a fundamental role in the metabolism of these molecules by transforming primary bile acids into secondary bile acids, thus leading them to be considered mediators between the host and gut microbiota [52]. In addition, previously unknown microbial pathways giving rise to novel bile acid derivatives were recently discovered [53]. Bile acids are a hot topic in health and disease, and very recent publications have presented groundbreaking discoveries about the immunomodulatory effects of specific bile acids in T-cell differentiation [54,55] and about their role in intestinal inflammation in irritable bowel diseases [56,57]. Thus, these molecules hold promise as a possible mechanism and therapeutic option in allergy.

Animal models and studies focusing on specific preventive and therapeutic interventions, such as administration of probiotics, prebiotics, and synbiotics, support the role of the bacterial gut microbiota in modulating enteric and distant organ infections.

1.2 Human Cutaneous Microbiota

The skin is the largest human organ, with a surface area of approximately 2 m^2. It contains many microhabitats conditioned by anatomical variations and physical factors, such as temperature, lipid content, and humidity [58-60]. The microbiota composition in skinfolds and hair follicles, as well as in the eccrine, apocrine, and sebaceous glands, differs in terms of diversity, but also in density, being higher at sebum-rich and wet skin sites [59,61,62].

The 2 main types of skin microbiota are resident microbiota, which is always on the skin, and transient microbiota, which can be acquired after exposure to other surfaces. Transient microbiota is much more abundant in the epidermis (outermost keratinized epithelial barrier) than resident microbiota in the dermis, which is stable and universal in human hosts [63]. New molecular massive sequencing techniques have made it possible to discover a cutaneous microbiota with an average bacterial density of ~1×10^7 bacteria per cm^2, consisting of 1000 different species [61,64], with the genera *Corynebacterium*, *Propionibacterium*, and *Staphylococcus* being predominant [59]. Colonization of the skin by microbiota begins at birth and is dependent on mode of delivery. Vaginally delivered newborns are mainly colonized by the mother's vaginal microbiota, whereas neonates born

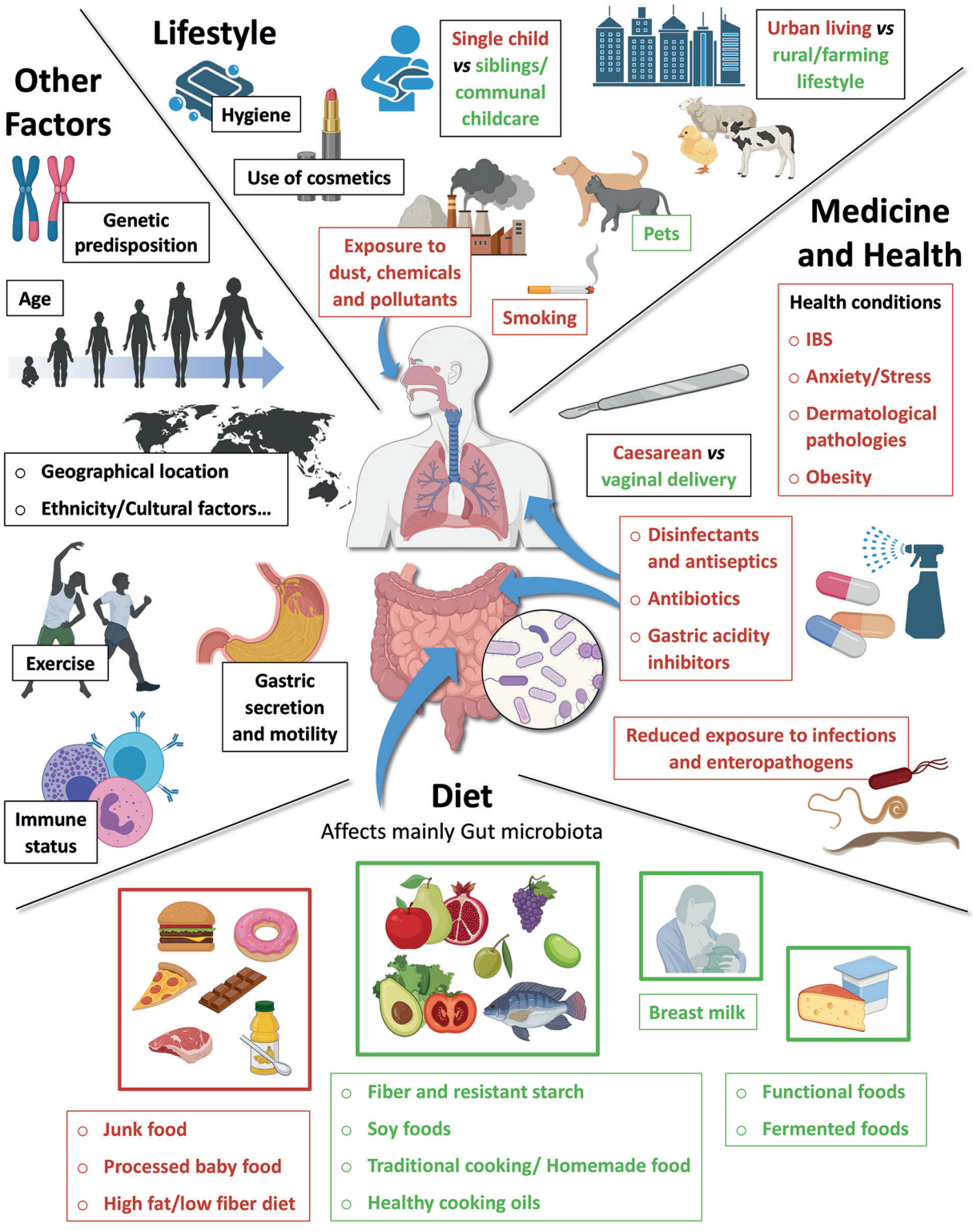


Figure 2. Factors that affect the different microbiotas in the body. Many factors have been shown to alter microbial populations in the different areas of the body. In this figure, we present the main factors, classified into 4 main groups: Diet (encompassing all those related to food intake), Medicine and Health (including crucial factors such as mode of delivery, health conditions, and use of antibiotics), Lifestyle (including exposure to dust and chemicals, pollution, smoking, and exposure to animals such as pets or livestock), and Other Factors (including complex variables such as genetics, age, and ethnicity). Those factors that have been linked to allergy are shown in red (if linked to increased risk) or in green (if linked to a protective effect). Factors shown in black are known to affect the microbiota but have not been clearly linked to allergic conditions. IBS indicates irritable bowel syndrome. Adapted from references [12,32-36].

by cesarean delivery acquire microbiota present in the skin of the mother, but also in that of health professionals [65,66]. During puberty, when the main hormonal changes occur, the microbiota shifts notably, with Corynebacterium and Propionibacterium becoming the most abundant species, to the detriment of Firmicutes (including *Staphylococcus* and *Streptococcus* species) [67].

The crosstalk between skin microbiota and the host is not fully understood. Bacterial dysbiosis on the skin is associated with the appearance of chronic inflammatory disorders such as psoriasis and AD [68-71]. The increase in *Staphylococcus* and decrease in other species such as *Streptococcus* or *Propionibacterium* is related to the development of AD [72]. *Acinetobacter*, a commensal skin bacterium, seems to exert a protective effect against allergic sensitization and inflammation, playing a relevant role in the T_H1-T_H2 balance and anti-inflammatory responses to environmental allergens [73]. In addition, some studies prove an association between the emergence of allergic skin diseases and dysbiosis of the intestinal microbiota, pointing to a gut-skin axis [74].

1.3 Human Respiratory Microbiota

Until recently, the consensus was that a healthy lung was a sterile organ in terms of microbiota. However, the latest studies have shown that the lung also harbors a functional and relatively stable microbiota [75,76]. The microbial density of the respiratory tract is lower (103 to 105 bacteria per gram of tissue) than that of the lower gastrointestinal tract and the skin [17,61,77]. Around 750 different species have been described in the respiratory tract; these belong to the phyla Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and Fusobacteria [78-80], most of which come from the outside. Colonization of the respiratory tract begins at birth and is dependent on mode of delivery. The main changes occur during the first year of life. Colonization is initially by *Staphylococcus* and *Corynebacterium*, followed by *Moraxella* and *Alloiococcus* [78,81].

The density of the microbiota differs along the respiratory tract, ie, it is higher and more diverse in the upper respiratory tract (nasopharynx: 106 bacteria per nasal swab) than in the lower part (lung: 102 bacteria per bronchoalveolar lavage specimen) [81-83]. Comparison of the lung microbiome in health and disease points to significant differences in terms of composition, with the microbiome being less diverse when respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and respiratory viral infections appear [84-86].

The prospective study carried out by Teo et al [87] in the first year of life of 234 children identified the role of the nasopharyngeal microbiome as a cause of infection of the lower airways and a prognostic factor in future development of asthma. In 2007, Bisgaard et al [88] demonstrated that the presence of Staphylococcus pneumoniae, *Moraxella catarrhalis*, or *Haemophilus influenzae* in the nasopharynx at 1 month of age was linked to an increased risk for subsequent diagnosis of recurrent wheeze and asthma at 5 years of age.

2. Interaction Between Microbiota and the Immune Mechanisms of the Allergic Response

The balance between the immune system and the resident microbiota is critical for the maintenance of health. The dysbiosis caused by population disturbances and imbalances in the microbiota have been associated with several inflammatory diseases such as obesity [89,90], Crohn disease and ulcerative colitis [91,92], type I and type II diabetes [93,94], and allergic diseases [95-97]. In addition, it has been shown that certain factors influence the composition of the microbiota and produce adequate stimulation of the developing immune system, resulting in immune tolerance [30,98,99].

Interactions with the microbiota under homeostatic conditions stimulate transforming growth factor β, retinoic acid, and thymic stromal lymphopoietin (TSLP), which promote tolerogenic antigen-presenting cells (APCs) and, in combination with IL-10, the production of regulatory T cells (Tregs) [100]. In addition, growth of Tregs and their accumulation in tissue are influenced by microbiota-derived metabolites such as secondary bile acids and SCFAs. Among the immune mechanisms of action, butyrate, the main source of energy for colonocytes, and other SCFAs, such as acetate and propionate, act through different pathways [101]. For instance, butyrate modulates immune system functions through binding to specific G protein–coupled receptors expressed on intestinal epithelial cells and on gut immune cells such as Tregs and dendritic cells. These receptors mediate the role of butyrate in production of IL-18 in the colonic epithelium; butyrate is responsible for improving tolerance of commensal bacteria and maintaining gut homeostasis. Butyrate can also act through epigenetic mechanisms, inducing histone deacetylation in dendritic cells and thus stimulating the differentiation of Tregs [102-104].

Allergic diseases arise when the immune system reacts to a normally harmless substance (allergen), generating a specific humoral and cellular immune response and the onset of symptoms that can spread throughout the organism [105]. The mechanism of action and the main cells and molecules involved in each of the immune processes of the hypersensitivity responses and in immune tolerance are detailed below and shown in Figure 3.

2.1. T_H2-Mediated Hypersensitivity

While a wide variety of immunological mechanisms are involved in the pathogenesis of allergy, most allergic responses are considered immediate hypersensitivity reactions, characterized by IgE production [106-108].

IgE-mediated allergic reactions are characterized by 3 main phases. First, during the sensitization phase, the allergen is captured by APCs that phagocytize it and present it to T_H0 lymphocytes, which express IL-4 and differentiate into T_H2 lymphocytes. In the presence of IL-4, IL-9, and IL-13, these interact with B lymphocytes that produce specific IgE against the allergen. The IgE binds to mast cells and basophils through their high-affinity receptors for IgE. Upon a second exposure, in the acute allergic reaction phase (effector phase),

the allergen directly targets the specific IgE antibodies that had been previously generated. Allergen-antibody binding leads to the release of histamine and other mediators, which induce an inflammatory state. This is the moment when allergic symptoms (eg, itching, sneezing, difficulty breathing) begin to manifest.

In food allergy, mast cells are involved not only in the effector phase, but also in sensitization. They generate cytokines (including IL-4 and IL-9 in response to the alarmin IL-33) that promote T_H2 responses and IgE production while suppressing Treg responses. Mast cells can also stimulate growth of type 2 innate lymphoid cells (ILC2) by producing IL-33 and IL-4, thus increasing the risks of IgE-mediated anaphylaxis [109-111].

Tuft cells, which are found throughout the mucosal epithelium, also play a role in the T_H2 response. Alarmins (IL-25, IL-33, and TSLP) released by tuft cells stimulate the development of ILC2 and the production of IL-4, IL-5, and IL-13, which induce B-cell class switch to IgE and activation of basophils and eosinophils [100,112,113].

Finally, the late allergic reaction phase occurs 4 to 6 hours later owing to the effect of the initially released chemotactic mediators, whose mission is to attract eosinophils to the site of inflammation. Here, the eosinophil granules release cytotoxic substances that generate longer-term local damage and inflammation, thus perpetuating the symptoms [96,105,114].

2.2. T_H1-Mediated Hypersensitivity

In T_H1-mediated hypersensitivity, the antigen is captured by APCs as it enters through the epithelium, transported to the lymph nodes, and transformed into peptides that are expressed on the surface of the APC. Naive T lymphocytes interact with these peptides—recognizing them through their

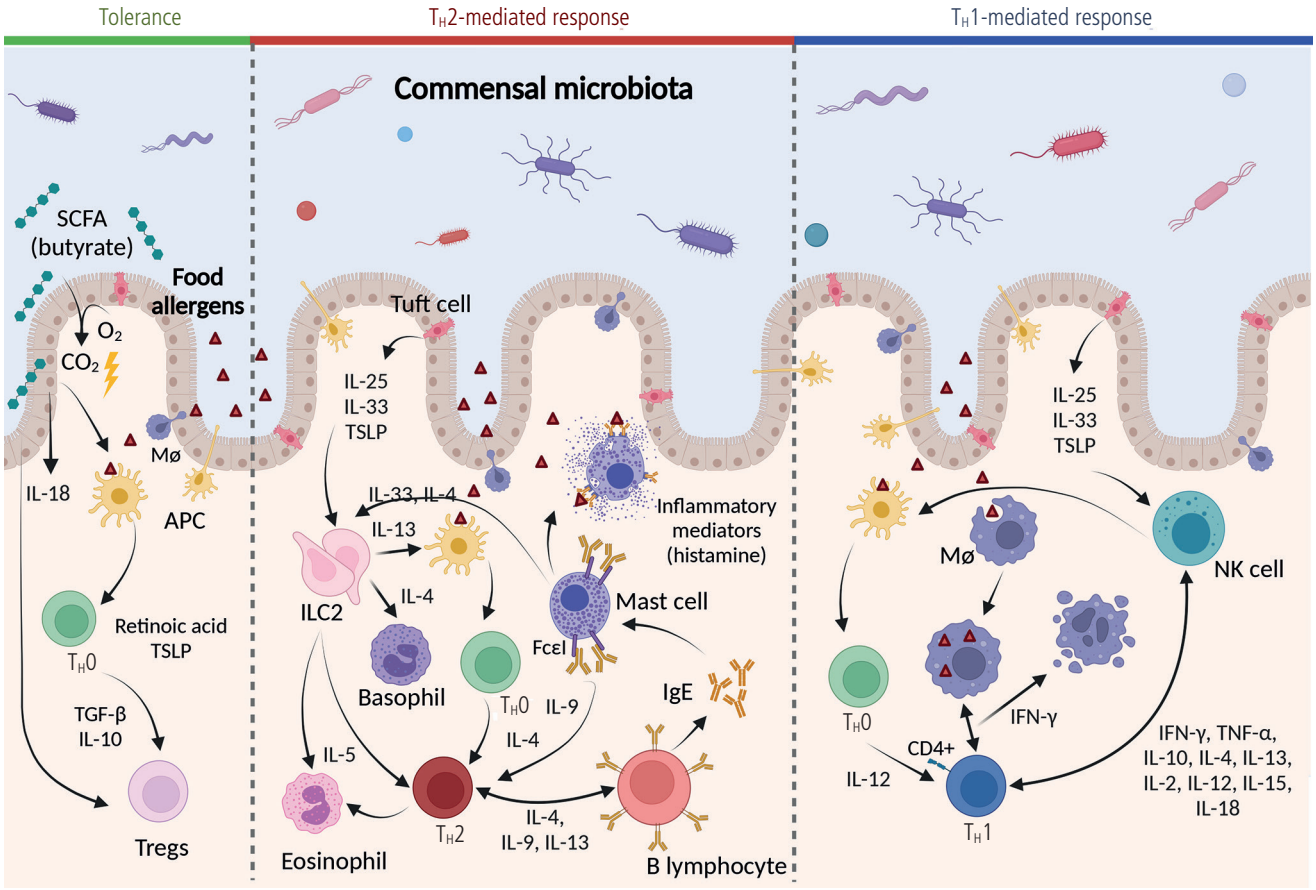


Figure 3. Detailed mechanism of tolerance and immune responses (T_H2 and T_H1 cell–mediated hypersensitivities) in the organism. Example adapted to the intestinal microbiota. Interactions with the microbiota under homeostatic conditions stimulate transforming growth factor β (TGF-β), retinoic acid, and thymic stromal lymphopoietin (TSLP), which promote tolerogenic antigen-presenting cells (APCs) and, in combination with IL-10, the production of regulatory T cells (Tregs) [100]. The immune system can generate 2 immune responses: T_H2 and T_H1 cell–mediated hypersensitivities [105]. In T_H2 responses (IgE-mediated), T_H0 lymphocytes, which express IL-4, differentiate into T_H2 lymphocytes. In the presence of IL-4, IL-9, and IL-13, these interact with B lymphocytes, which produce specific IgE against that allergen. IgE bind to mast cells and basophils through their high-affinity receptors for IgE [96,105,114]. On the other hand, in T_H1 cell–mediated hypersensitivity, T_H0 lymphocytes differentiate into effector and memory T lymphocytes (T_H1) in the presence of IL-12. Effector T lymphocytes migrate to the inflamed sites and encounter the antigen for which they are specific. The subpopulation of antigen-specific effector $CD4^+$ T lymphocytes secretes cytokines that enable macrophages to eliminate the phagocytosed microorganisms [105]. Herein, the mechanism of action and the main cells and molecules involved in each of the immune responses are presented. SCFA indicates short-chain fatty acid; Mø, macrophage; APC, antigen-presenting cell; Treg, regulatory T cell; Fcεl, high-affinity receptor for IgE; TSLP, thymic stromal lymphopoietin; NK, natural killer.

T-cell receptor—before proliferating and differentiating into effector and memory T lymphocytes (T_H1) in the presence of IL-12. Effector T lymphocytes migrate to the site of inflammation, encountering the antigen for which they are specific. The subpopulation of antigen-specific effector $CD4^+$ T_H1 lymphocytes secretes cytokines such as IFN-γ, which enable macrophages to eliminate the phagocytosed microorganisms [115].

Natural killer (NK) cells play an important role in this type of immunity, as they are functionally characterized by their cytotoxicity. Key effector functions of NK cells comprise cytokine secretion and cytolytic granule–mediated cell apoptosis. The secretion of IFN-γ and TNF-α by NK cells promotes APC and phagocyte function, including enhanced phagocytosis, production of antimicrobial peptides, and oxidative burst. NK cells are activated via cytokines such as IL-2, IL-12, IL-15, IL-18, and IFN-γ [116].

The microbiota also promotes the release of the cytokines IL-25, IL-33, and TSLP by epithelial cells, which can stimulate innate lymphoid cell responses, such as that of NK cells. In turn, these contribute to the induction and control of commensal-specific T cells [117].

3. Microbiome and Food Allergy

Food allergy generates reactions that affect various organs and systems: the skin (itching, redness, hives); the digestive system (nausea, vomiting, diarrhea); the respiratory system (sneezing, nasal mucus, respiratory distress, chest tightness); and the cardiovascular system (cardiac arrhythmias, drop in blood pressure); and the nervous system (dizziness) [114]. If the reactions are very serious, they can prove fatal. Any food can trigger an allergic reaction. Some, on the other hand, do so more regularly, and this is largely dependent on the eating patterns in each location and the age of the patient. Thus, in Spain, the foods that most commonly cause allergy in children are milk, eggs, and fish. However, in adults, allergy to fruits and vegetables, nuts, and shellfish is more common [114,118,119].

Food allergy is a specific immune response that occurs when the individual is exposed to a certain food. This immune reaction may be due to an IgE-mediated mechanism or a non–IgE-mediated mechanism. IgE-mediated food allergy is much more common than non–IgE-mediated food allergy, symptoms are easily recognizable, and underlying mechanisms are better established. Although the relationship between food allergy and gastrointestinal dysfunction has been known for several years, the exact mechanisms involved have yet to be clearly defined [120].

The prevalence of food allergy is increasing worldwide, but the cause of this increase is uncertain [121]. Factors such as alterations in the microbiota, pollution, lack of contact with microorganisms, and a lower amount of unprocessed natural products in the diet have played a key role in the development of allergic diseases in recent decades [122]. For this reason, the study and understanding of the different allergic phenotypes is essential if we are to develop accurate therapeutic approaches and personalized treatments.

3.1. Role of the Gut Microbiota in Health

The symbiotic relationship between humans and microbes is the evolutionary result of biological interaction. Resident microorganisms defend the host from diseases, maintaining their ecological niches and using the plant fibers we ingest to obtain energy and produce the metabolites used by our cells. For instance, the presence of certain strains from the genera *Lactobacillus* and *Bifidobacterium* in the gut provide nutritional benefits, inhibit pathogens, and modulate the immune system [95,123]. In our intestinal microbiota, these microorganisms increase the absorption of minerals and vitamins, improve lactose intolerance, exert antidiabetic effects, lower cholesterol levels, increase resistance to infections of the gastrointestinal tract [124,125], and exert local and systemic anti-inflammatory effects, thus improving the development of the immune system [126]. Most of the studies carried out to understand how the gut microbiota regulates food allergy have been performed in preclinical models. Feehley et al [127] colonized germ-free mice with feces from healthy infants and infants with cow's milk allergy, showing that healthy microbiota had a protective effect.

3.2. Role of the Intestinal Microbiota in Allergic Reactions

The development of the intestinal microbiota during the first years of life is related to the development and maturation of the immune system [97,128-130]. The major source of stimulation of the immune system is the mucosal surfaces, which come into contact with the external environment. In addition, several studies have shown that the emergence of tolerogenic responses to antigens is mediated by the presence of specific bacteria in our gastrointestinal tract [131-133]. In this way, imbalances in microbial communities have been linked to inadequate modulation of the immune system and the development of diseases affecting parts of the body other than the digestive tract. Approximately 70%-80% of immune cells are found in the small intestine and mainly in the large intestine [134]. The gut microbiota seems to play an essential role in modulating allergic responses to food antigens.

The gut microbiota stimulates and modulates the immune system through dendritic cell–mediated regulation. Microbes promote differentiation of Tregs by activating dendritic cells on the mucosal surface of the gut through Toll-like receptor recognition [95]. These activated cells produce interleukins, which, in turn, activate T_H0 lymphocytes to mature into the corresponding T-lymphocyte subtype (T_H1, T_H2, T_H17, Tregs) [95]. In healthy individuals, all T_H lymphocyte subpopulations are present in a dynamic balance with Treg lymphocytes. However, alterations in the gut microbiota and decreased levels of Tregs have been found in people with rhinitis, atopic eczema, asthma, and allergy to peanuts, eggs, or cow's milk [12,135,136]. One study showed that children who have spontaneously overcome food allergy have higher numbers of antigen-responsive Tregs and $CD4^+$ T cells expressing IL-10 than children with active food allergy and nonallergic controls. This finding supports the function of Tregs in the establishment of food tolerance in humans [137].

The amount of Treg lymphocytes in the mucosa seems to be linked to the presence of specific genera of bacteria in the intestinal microbiota [138]; therefore, this could be one of the mechanisms by which the gut microbiota influences the development of food allergy. Which bacterial groups or species are involved in the presence of Tregs in the intestinal mucosa remains unknown, although it seems that the genera *Lactobacillus*, *Bifidobacterium*, and *Clostridium* stimulate their presence and appear to reduce the symptoms of food allergy [111,139]. Abdel-Gadir et al [140] analyzed the fecal microbiota of 56 infants with food allergy and 98 controls at different times, finding that the composition of dysbiotic fecal microbiota in the infants with food allergy evolved over time. The same study used mouse models with fecal transplants from food allergy patients and found that therapy with dysbiosis-affected *Clostridium* species suppressed allergy in mice, as did a separate consortium of immunomodulatory Bacteroidetes [140]. In addition, a recent study found that early inoculation with *Clostridium* class IV and XIV species resulted in decreased IgE levels in adulthood. Conversely, 3-week-old infants with a higher proportion of *Clostridium difficile* than *Bifidobacterium* more frequently had positive skin test results to food and aeroallergens [123]. Furthermore, SCFAs produced by the microbiota, such as butyrate, also increase the proportion of Treg lymphocytes and are able to accelerate tolerance to cow's milk [139].

The lack of microbiota-mediated signaling should also be taken into account, as it has been associated with deficiencies in Treg lymphocytes and consequent expression of effector cells [141].

Despite advances in this field, it is still unknown whether the imbalance of the gut microbiota triggers the disease or, on the contrary, whether the disease itself alters bacterial populations and their functionality.

4. Microbiome and Cutaneous Allergy

AD is an inflammatory skin disease with multiple and interconnected associated genetic and environmental factors. For many years, it has been known that AD in early life is strongly associated with allergy, initiating the so-called allergic march. This finding led to the so-called dual allergen route hypothesis, where exposure to low doses of foods on the skin led to sensitization and high doses by the gastric route promoted tolerance [142]. Besides intrinsic factors (eg, atopic parents and skin barrier protein filaggrin mutations), microbiome-related features, such as decreased SCFAs in the gut of children, are strongly associated with an increased risk of AD [143,144]. Moreover, microbiome formation in the gut and the skin occur in parallel [145].

AD has a characteristic microbiome signature with dysbiosis towards enhanced colonization of *Staphylococcus aureus* and reduced microbial diversity [146]. The different factors that contribute to this dysbiosis are currently the subject of active research [147] and a potential target for new intervention strategies. With the advent of new monoclonal antibody–based therapies for the treatment of AD, the effect of the blockade of inflammatory pathways in the skin microbiome can be assessed. In this context, it has been demonstrated that after 12 weeks of treatment with dupilumab, which simultaneously blocks the IL-4 and IL-13 pathways, there is a significant increase in the diversity and abundance of *Cutibacterium* and *Corynebacterium* species. This increase correlated with an improvement in the Eczema Area and Severity Index [148]. Microbiome composition can also be targeted with other intervention strategies such as pre- and probiotics. More knowledge is necessary, and personalized medicine–based approaches and prevention strategies must be developed.

5. Microbiome and Respiratory Allergy

In recent years, the exploration of the respiratory microbiome as a potential diagnostic and intervention target has gained increasing attention [149]. While the correlation between inflammation, barrier remodeling, and chronic infection is perfectly known, the association between different bacterial colonization patterns and disease severity is becoming clearer. In an interesting recent work, Zhao et al [150] used a LASSO regression model to demonstrate that the nasal microbiome could predict recurrence of nasal polyps. This approach outperformed models based only on clinical features. A significant number of studies have been carried out on the effect of the microbiome on COPD. The complexity of health- and disease-associated microbiome makes it an attractive area for potential intervention [151].

In asthma, 2 populations related to a decrease in the risk of asthma in early life include the genera *Corynebacterium* and *Dolosigranulum*, as these increase the balance of the microbiome in the first months of life. Interestingly, the mode of delivery modifies the microbiome: cesarean delivery increases the risk of asthma by 20%, as it reduces the populations of *Corynebacterium* and *Dolosigranulum*. Breastfeeding also plays an important role, increasing the aforementioned bacterial populations, even up to 3 months of age [152].

Frequent use of medications such as antibiotics and corticosteroids affects the microbiome, and there is an increasing awareness of the need to limit their use, especially during pregnancy and early life, and to develop intervention strategies to mitigate their impact [153]. On other hand, helminth infections in early life appear to play a protective role, as they increase the diversity of the microbiome [154-158]. Furthermore, *Moraxella* species–dominated profiles in the nares and nasopharynx of children are associated with a protective role against upper respiratory tract infections, except for the species *Moraxella catarrhalis*, which together with *H influenzae* and *Streptococcus pneumoniae*, are linked to wheezing in infants [159]. In addition, *Streptococcus*, *Acinetobacter*, and *Corynebacterium* populations, as well as Prevotella, are more numerous in the lungs of healthy individuals than in those of asthma patients [160].

Many studies on asthma have focused on the perinatal period and adulthood. Interest in asthma in the elderly is growing because the population is aging. In a recent review, Saint-Criq et al [161] described changes in the microbiome

during aging and addressed their connection with immune senescence, malnutrition and the link between gut and lung, again paving the way for new prevention and intervention strategies, with a focus on nutritional treatments [161]. The interplay between gut and lung microbiomes and their influence on T-cell regulation, as well as the influence of genetic alterations, is a hot research topic [162]. Harb et al [163], for instance, argue that upregulation of the Notch4 receptor on lung tissue Tregs, which is dependent on the transcription factors IL-6 and STAT3, is a risk factor in that it enables allergens and pollutants to promote airway inflammation, identifying Notch4-mediated subversion of immune tolerance as a key mechanism underlying tissue inflammation in asthma [163].

In summary, the airway microbiome is highly dependent on exposure during the first hours after birth, as well as during the first 4-5 months of life. Therefore, this is the perfect time to act, since during this period, modifying the microbiome will reduce the predisposition to respiratory diseases such as asthma in adulthood. Overall, most studies point to the fact that illness is often linked to reducing diversity in the upper and lower respiratory microbiome, both in early life and in adulthood. As findings become clearer in the near future, novel intervention strategies on the microbiome will be critical for control of allergic respiratory diseases.

6. Main Technologies for the Study of the Microbiome

In recent years, human microbiome composition and biological function have become major topics, since both contribute to the metabolic health of the human host. While traditional culture-based methods can only identify specific bacteria commonly sought for diagnostic purposes, new sequencing techniques and omics sciences have recently been applied to gain a more complete picture of the microbiome (Figure 4) [164-166].

6.1 Genomics

Among these novel technologies, 16S ribosomal RNA (rRNA) gene sequencing and shotgun metagenomics for bacteria have been widely used [167]. The 16S rRNA gene is highly conserved and contains hypervariable regions that are widely divergent between different bacterial taxa [168]. Research on the 16S rRNA gene in a biological sample attempts to answer the question "Who's there?" [169]. Thus, this technology has become the most widely used method for investigating the composition of microbial ecosystems [164]. However, the biggest challenge for 16S rRNA gene sequencing lies in the identification of unique sequences that differentiate between individual taxa [167]. Its main characteristic is that it provides information on bacterial diversity, thus enabling detection of microbial dysbiosis. This technology has been widely applied to identify bacteria related to health and disease. Regarding its limitations, as stated above, only taxonomic information is obtained, and as such, the technique is not suitable for archaea and viruses, restricting the technique to bacteria [169].

Shotgun metagenomics is another DNA sequencing methodology that provides valuable information in the study of microbial communities, including archaea and viruses. It displays all the genes in a community by randomly sequencing the entire DNA extracted from a sample [169]. Shotgun metagenomics sequencing can be used to answer the question "What might happen here?" [169]. Compared to 16S rRNA gene sequencing, which only provides taxonomic information, shotgun metagenomics provides functional information on the microbial ecosystem [168]. This approach is perfect for sequencing all the genes in a system, uncovering microbial diversity, and finding new microbial genes. It has been used to reveal dysbiosis, as well as to find microbial genes, investigate their functional expression in various diseases, and assess their role in the interaction between host and microbiome [169]. This powerful approach is subject to limitations. It requires complex bioinformatics analysis and, compared with 16S rRNA gene sequencing, requires greater sequence coverage, has a higher cost, and takes longer. Furthermore, metagenomics requires a sufficiently large quantity of high-quality DNA from the biological sample, and the quality of the underlying functional annotations of metagenomic sequence fragments is crucial [169].

Metatranscriptomics is yet another emerging technology that complements those described above. This sequencing approach aims to define the activity of genes in a specific environment [169]. Metatranscriptomics specifically targets the RNA transcribed from the microbiome, thus enabling the expression functions of these organisms to be assessed [167]. This technology could answer the question "What seems to be happening in this environment?" As a methodological handicap, obtaining sufficient high-quality RNA from biological samples is not always easy owing to the presence of RNases in host-derived samples [165]. Although metatranscriptomics enables characterization of transcribed RNAs, it does not provide a true representation of protein functionality, as its expression depends on translation and posttranslational modifications [167]. Another limitation is the difficulty isolating the mRNA of interest from other types of RNA, which in many cases are more abundant. Furthermore, the low stability of mRNA hampers detection. Finally, reference databases are insufficient, as the technique is in its initial application stages [169]. The limitations affecting this approach mean that it is not widely used. However, it is a powerful complement to 16S rRNA gene sequencing and shotgun metagenomics.

6.2 Metabolomics

Metabolomics is defined as the study of the entire collection of metabolites (molecules involved in metabolism) present in a biological sample. In this context, metabolomics focuses on analyzing the metabolites that the microbiota produces and how these metabolites interact with both their own microbial environment and the host [167]. Metabolomics is based on high-throughput techniques such as mass spectrometry (usually coupled to a separation technique such as liquid chromatography [LC-MS]) and nuclear magnetic resonance spectroscopy, both of which enable structure elucidation. With this technique, the differences

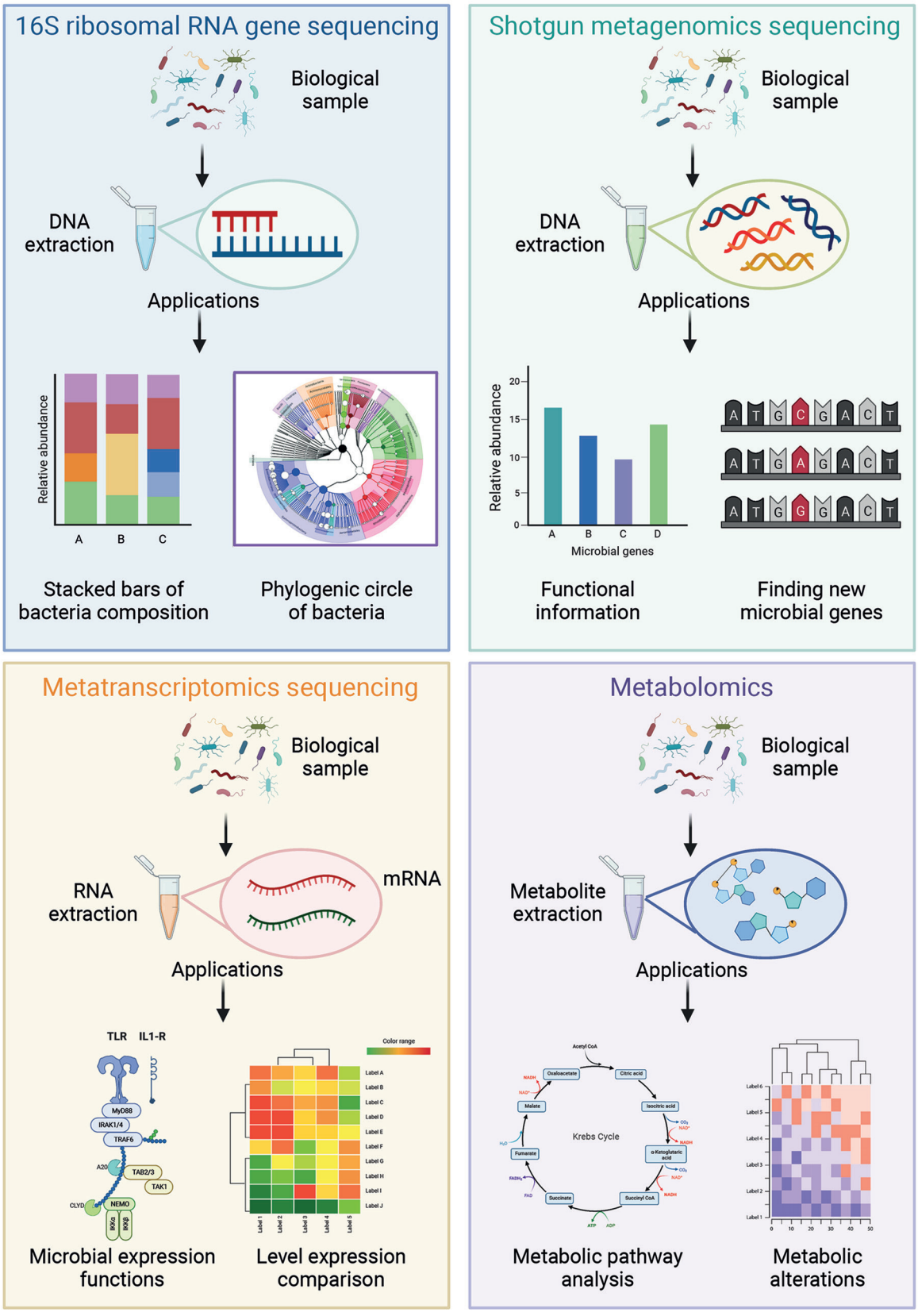
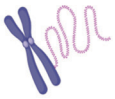
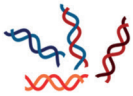
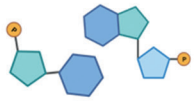


Figure 4. A framework of the main technologies applied for the study of the microbiome. For each technique, the figure shows the material extracted from the sample and the information that can be obtained after application.

Table. Comparison of the Different Technologies Used to Study the Microbiome

Technologies	Traditional culture-based methods	Genomics			Metabolomics
		16S ribosomal RNA gene sequencing	Shotgun metagenomics	Metatranscriptomics	
					
Sample	Biological sample	DNA from bacteria	Total DNA from a sample	Total RNA from a sample	Biological sample
Target	Microbiota	16S ribosomal RNA gene	DNA	mRNA	Metabolites
Applications	Diagnosis Specific bacteria	Bacterial diversity (taxonomic information)	Functional information on a microbial ecosystem	Expression functions of the microbial ecosystem	Metabolic alterations between host and microbiota
Limitations	Unable to detect uncultured microbiota	No information for archaea or virus	Complex bioinformatics analysis Expensive and time-consuming	Requires sufficiently large quantity and high-quality DNA	Difficulty to distinguish metabolites from host and microbiota

between 2 groups after data processing can be obtained using statistical analysis, thus enabling the detection of metabolic changes associated with a disease. This makes it possible to conduct joint analyses of the microbiome, metabolome, and host clinical information to identify potential associations of interest [97]. Metabolomics can be used to answer the question "What has happened?" This omic science has been applied to reveal and confirm new pathways and identify novel potential biomarkers for diagnosis and prognosis. However, like the above-mentioned techniques, it is subject to limitations. First, reference databases for metabolites belonging to specific microbial taxa are insufficient. Second, there is no single protocol for metabolite extraction, thus hampering comparison of results between studies [169]. Finally, the major challenge for metabolomics in human microbiome studies is the difficulty that arises when distinguishing between metabolites from the host or the microbiome and intra- or extracellular microbial metabolites that directly link the results to specific taxa [165].

In conclusion, no single technology can provide all the information on the human microbiome. The technologies defined in this section have strengths and weaknesses (Table). To date, combining several techniques when possible is always the best option for covering a broader view of a specific environment. However, there is still a long way to go before we understand the information exchanged between the host and the microbiome. Better integration of these technologies could lead to a more unified and synergistic view of the host–microbiome relationship.

7. Microbiota as a Therapeutic Target in Intervention Trials: Probiotics, Prebiotics, and Synbiotics

Within the intervention studies proposed for allergy prevention, the use of probiotics, prebiotics, and synbiotics can make the intestinal microbiota more balanced and healthier and modulate the immune response.

Defining the exact timing for administration of probiotics, prebiotics, and synbiotics is key to the efficacy of the intervention. However, this task is difficult because study designs vary widely. The best results have been obtained when the administration is either before birth (from the second to the last trimester of gestation) or in early childhood, coinciding with maturation of the infant's immune system (first months of life, preferentially through breastfeeding) [170].

7.1 Probiotics

Probiotics are defined as living microorganisms that, when administered in adequate amounts, confer a beneficial effect on host health.

Probiotics play an immunomodulatory role by helping to establish a diverse and healthy microbiota, but they also exert a protective effect by competing with pathogenic bacteria, maintaining barrier integrity, and preventing antigenic sensitization. The most common and widely studied probiotics are *Lactobacillus rhamnosus* and *Bifidobacteria* [170,171]. It has been postulated that perinatal use of probiotics modulates

the infant's immune system and promotes the transition from a T_H2 response (fetal response) to a T_H1 response (prevention of allergy) in the newborn [172]. However, the role of probiotics in allergy prevention remains unclear.

In the 2015 meta-analysis conducted by the World Health Organization [173] on the prevention of allergic diseases (eg, AD, food allergy, and persistent wheezing and/or asthma), most of the studies reviewed showed that probiotics were given during the last trimester of pregnancy, during breastfeeding, and/or directly to the newborn. Of the studies assessing the use of probiotics in the prevention of AD, a significant decrease in the relative risk of developing eczema was observed compared to the placebo group (0.72; 95%CI, 0.61-0.85). For food allergy and persistent wheezing/asthma, supplementation with probiotics did not reduce the relative risk of these conditions in children.

Probiotics in Pediatric Asthma Management (PROPAM), the most recent study on probiotics and asthma [174], points to 2 specific strains, *Ligilactobacillus salivarius* LS01 and *Bifidobacterium breve* B632, as auxiliary remedies for asthma treatment, since they reduced the frequency of asthma exacerbations by more than a third in 422 asthmatic children.

Sensitization to food allergens is a previous step in the development of food allergy, but not all sensitized individuals develop food allergy symptoms. In this sense, most studies suggest that probiotics have a modulatory role in development of food allergy, rather than in the prevention of food allergy per se [175].

7.2 Prebiotics

Dietary prebiotics are food ingredients selectively fermented by gut microbiota, whose degradation products, SCFAs, result in specific changes in the composition and/or activity of the gut microbiota. These changes stimulate the growth and/or activity of some microorganisms in the large intestine, usually *Lactobacillus* and *Bifidobacteria*, thus conferring health benefits on the individual [176-178]. The main prebiotics with beneficial effects on human health are mostly oligosaccharide carbohydrates, such as fructans (inulin, and fructo-oligosaccharides [FOS]), galacto-oligosaccharides (GOS), and lactulose. Noncarbohydrate oligosaccharides, such as flavanols, are also considered prebiotics because they can stimulate lactic acid bacteria [179].

Prebiotics promote the colonization of beneficial bacteria in the gut, indirectly playing the same immunomodulatory role as probiotics (see above). The degradation products of prebiotics are mainly SCFAs, which can enter the bloodstream and spread beneficial effects not only in the gastrointestinal tract, but also in distant organs [180].

Intervention trials with prebiotics mainly include those carried out with a combination of GOS and FOS. The results obtained when assessing their role in allergy prevention are controversial [181,182]. A meta-analysis evaluating the effect of various prebiotics, duration of administration, and follow-up time reported a 32% reduction in the relative risk of eczema and dermatitis, but not asthma [181].

7.3 Synbiotics

When probiotics and prebiotics are administered together, they are known as synbiotics, which provide a synergistic and beneficial effect, favoring more efficient implantation of certain bacteria in the intestine. Few studies have compared supplementation with synbiotics to probiotics and prebiotics.

Breast milk can be considered a natural synbiotic, as it contains bacteria from the mother's gut (probiotics) and human milk oligosaccharides (prebiotics); therefore, the beneficial effect of breastfeeding in allergy prevention could be associated with a synbiotic effect. In this sense, interventions with amino acid–based formula supplemented with *Bifidobacterium breve* M-16V and FOS in infants with suspected non–IgE-mediated food allergy has been shown to have a modulating effect on the gut microbiota, shifting it towards a healthier microbial profile characteristic of breastfeeding [183]. In the case of AD and asthma, a multicenter, double-blind, placebo-controlled study of 90 infants with AD found that asthma-related symptoms were significantly reduced when treated with an extensively hydrolyzed formula enriched with *Bifidobacterium breve* M-16V and a GOS/FOS mixture [184].

At present, the results of clinical studies on administration of probiotics, prebiotics, and synbiotics are preliminary, and findings require further confirmation before these options can be applied in clinical practice. The discrepancies observed between the results of intervention strategies are due mainly to the heterogeneity of the designs and the large number of factors affecting them (eg, genetic, epigenetic, immunological, metabolic, and environmental). Thus, multidisciplinary approaches will be necessary in the future to deepen our understanding of the effects of these supplements and their specific interaction with the host microbiome.

Conclusions

The microbiota colonizes the skin and the mucosal surfaces of the body and has a considerable impact on basic aspects of human physiology and health. This impact depends on several factors such as diet, use of antibiotics, and lifestyle. Early life alterations of the microbiota are associated with the development of specific diseases, including allergy.

The development of high-throughput technologies has been determinant in the study of human microbiota, with genomics and metabolomics being the most applied techniques.

The influence of microbiota in the development of allergy is a hot topic. Moreover, the microbiota has been considered an important target in allergy treatment and prevention. However, interindividual variability and heterogeneity in study designs make it difficult to reach consistent conclusions in this sense. Further, long-term clinical trials are needed to shed light on the role of microbiota in allergic diseases.

Acknowledgments

We would like to thank the Institute of Applied Molecular Medicine (IMMA, Universidad CEU San Pablo, CEU

Universities, Madrid) and the Centre of Metabolomics and Bioanalysis (CEMBIO). Images were created using BioRender.com.

Funding

This work was supported by ISCIII (PI19/00044), cofunded by FEDER "Investing in your future" for the thematic network and co-operative research centres ARADyAL RD16/0006/0015. It was also supported by Agencia Estatal de Investigación, Ministry of Science and Innovation in Spain (PCI2018-092930) cofunded by the European program ERA HDHL - Nutrition & the Epigenome, project Dietary Intervention in Food Allergy: Microbiome, Epigenetic and Metabolomic interactions DIFAMEM. TB-T is supported by an FPI-CEU predoctoral fellowship. DB acknowledges financial support from Instituto de Salud Carlos III (PI19/00044).

Conflicts of Interest

DB reports grants from ALK and Allero Therapeutics and personal fees from ALK and AIMMUNE. The remaining authors declare that they have no conflicts of interest.

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Manuscript received February 28, 2022; accepted for publication, August 4, 2022.

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