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THE MICROBIOTA AND ALLERGIC (TYPE 2) DISEASE: A REVIEW

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Abstract: Allergic diseases, such as respiratory, cutaneous, and food allergy, have dramatically increased in prevalence over the last few decades. Increasing use of antibiotics has been linked with dysbiosis and enhanced prevalence of allergies and asthma. Despite the clear involvement of the microbiome in atopic disease, it remains to be determined whether microbial alterations are a cause or a consequence of the disease.
Human microbiota is defined as the multitude of microorganisms that live in or are associated with a variety of human tissues: the gut, respiratory tract, skin and genital tract. Recent advances in metagenomic sequencing and bioinformatics have enabled detailed characterization of these vital microbial communities and their role in different diseases. In particular, the relationship of microbiota with immune responses and immunological or allergic diseases is well known. The composition of gut, respiratory and skin microbiota can influence systemic inflammatory responses that mediate food allergy, rhinitis, asthma, immunodeficiency diseases, atopic dermatitis and chronic urticaria. This review discusses the role of microbiota in the major allergic Type 2 diseases evaluating the composition of the main commensal bacteria species and their relation with these pathologies.

Keywords: Microbioma, Type 2, Food allergy, Asthma, Probiotics, Dysbiosis.

INTRODUCTION

The genome of all microorganisms living in and on the surfaces of the human is defined as the microbiome and contains 150 times more genes than the 23,000 protein-coding genes of human origin[1]. The increase in the prevalence of allergic diseases over the last decades has been associated with lifestyle changes in industrialized countries. Nutritional factors and their interaction with the gut microbiota influence immunological processes, especially early in life, also greatly affect the intestinal microbiota – currently considered to be a "super organ", necessary for the proper functioning of the immune system and the development of immune tolerance[2].

Increasing use of antibiotics has been linked with dysbiosis and enhanced prevalence of allergies and asthma[3].

Host-microbiome interactions in early life play a central role in intestinal and pulmonary immune maturation and development; however, only few functional analyses of these interactions have been described.

Some studies indicate that short-chain fatty acids (SCFAs) that are the result of fermentation by gut bacteria from undigested complex carbohydrates, play an important role in the immune homeostasis through epigenetic modulation of local colonic FOXP3 + regulatory T cells and their effects on peripheral T cell function[4].

ROLE OF THE MICROBIOME IN THE DEVELOPMENT OF ALLERGIC DISEASES

Epidemiologic studies reveal that an association exists between environmental exposures, which alter the microbiota, and developing atopic dermatitis, food allergy, and/or asthma. In fact, samples from the skin, gastrointestinal tract, and respiratory tract reveal distinct microbiota compared with healthy controls, with dysbiosis often preceding the development of allergic disease.

Recent experimental and human investigations have strengthened the mechanistic substance to the hygiene hypothesis, providing evidence for the causal relationship between early life microbial perturbation in the gut, skin, and airways and the development of allergic diseases (Fig. 1).

Microbiota and Food Allergy

Food allergy (FA) is a common IgE-mediated disease resulting from a breakdown of immune tolerance to dietary antigens.

Environmental factors associated with FA, including a low-fiber/high-fat diet, cesarean delivery, drug therapies, lack of breastfeeding or lack of appropriate microbial exposure in early life (deriving from pets or contacts with older siblings) can drive to allergic disease[5-6]. These factors are able to modify the composition of the gut microbiome leading to dysbiosis and giving higher food allergy susceptibility.

In recent years, several studies revealed an important role played by gut microbiome in the development and clinical manifestation of food allergy (FA).

Significant differences in the composition of gut commensal microbiome are observed in 141 children with and without food allergy[7].

Using 16S rRNA gene sequencing, they found genera belonging to the Lachnospiraceae and Streptococcaceae families were enriched in children with egg allergy, while Leuconostocaceae were enriched in health controls.

Another study of 39 Italian children revealed that infants with cow's milk allergy have a diverse gut microbial community dominated by Lachnospiraceae and Ruminococcaceae compared with health controls[8].

Dysbiosis occurs early in life, preceding the onset of FA, and it is able to influence the clinical natural history of the disease. By studying a population of 226 infants with milk allergy and following them for 8 years, Bunyavanich et al[9] demonstrated that the microbiome found in the early childhood (3-6 months) influences the spontaneous resolution or less of FA. The investigators found that taxa from the Firmicutes phylum, including Clostridia, were enriched in the gut microbiome of infants aged 3-6 months with a faster resolution of milk allergy compared to infants with persistent FA. Moreover, the gut microbial richness at age 3 months was associated

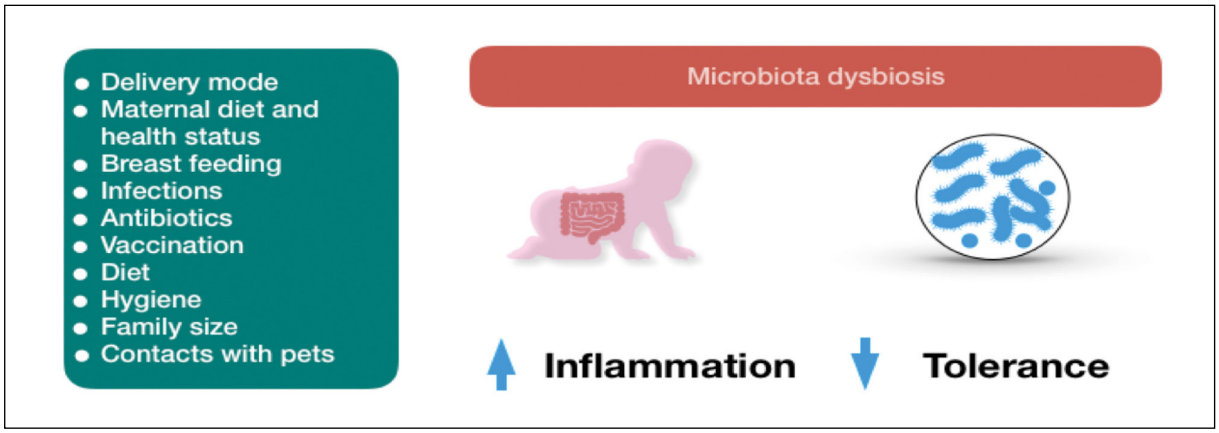

Figure 1. Environment induces quality and quantitative changes in microbiota composition leading to dysbiosis and lost of immunological tolerance.

with a reduced risk for food sensitization testing by skin prick test (SPT) by age 1 year[10]. These findings suggest the importance of commensal microbial exposures during early phases of immune system development in influencing the onset and the natural history of food allergy.

Evidence on the role of gut microbiome dysbiosis in FA were provided also from animal models. T-regs were found reduced in mice treated with antibiotics or devoid of a commensal microbiota with consequent iper-IgE production and an individual predisposition to food sensitization[11]. T cells production can be induced by the presence of Clostridia species contained in the microbioma. Stefka et al[12] have shown a clinical protective role of Clostridia strains against the peanut allergy development in mice models, suggesting a novel approach to prevent or treat FA based on modulating the composition of the intestinal microbiota.

THE ESOPHAGEAL MICROBIOME IN EOSINOPHILIC ESOPHAGITIS

An increase in the incidence and prevalence of eosinophilic esophagitis (EoE) in recent decades suggests that the environmental factors may have a primary role in onset of this disease. Some studies reported to date have hypothesized that microbial oral and esophageal alterations could predispose to development of EoE.

The protective role played by H. pylori infections has already been widely demonstrated[13], but less is known about the role of overall esophageal microbiome composition.

The study by Benitez et al[14] is one of the first to assess the esophageal microbiome in EoE. They aimed to evaluate differences in the oral and esophageal microbiome in children with and without EoE and to determine whether the microbiome would undergo changes after dietary therapeutic intervention.

They found a significantly difference comparing EoE esophageal microbiota to non-EoE controls, with enrichment of Proteobacteria (Neisseria and Corynebacterium) in the EoE cohort, and predominance of the Firmicutes in non-EoE control subjects. Targeted dietary intervention did not lead to significant changes in esophageal microbiota, although, in some cases, reintroduction of allergenic foods led to enrichment in Granulicatella and Campylobacter genera in the esophagus. Harris et al[15] analyzed specimens from 70 children and adults, including 11 with untreated active EoE, 26 with EoE in remission, 8 controls with gastroesophageal reflux disease, and 25 normal controls. They found that Streptococcus was increased in normal controls compared with patients suffering from gastroesophageal reflux, and that Haemophilus was increased in active EoE compared with healthy controls. Additionally, the bacterial load was increased in EoE subjects compared with normal controls regardless of the treatment or disease activity and the level of esophageal eosinophilia did not influence the microbiome measures. Another recent study[16] observed a marked decrease in Firmicutes and Clostridia and an increase in Bacteroidetes in adult patients with EoE compared to the healthy controls. These studies provide novel information about association between specific microbial populations and EoE which could reveal important pathophysiological aspects in the development of EoE. However, it remains to be clarified whether the microbial alterations directly contribute to cause the disease or they are an effect of the morphological changes and of the reduced esophageal motility caused by the EoE itself.

Further studies are needed to outline these aspects and to identify novel potential therapeutic targets for this disease.

MICROBIOTA AND AIRWAYS TYPE 2 DISEASE

A number of different animal studies support the concept for a role of the microbiome in development of airway diseases.

The involvement of upper respiratory microbiota in chronic inflammatory diseases of the upper airways has been of considerable interesting. Dysbiosis of the upper airway microbiota could induce chronic upper airway inflammation, such as allergic rhinitis (AR) and chronic rhinosinusitis (CRS). The commensal microbiota plays both regulatory and stimulatory roles during host immune development, and its dysbiosis provokes aberrant immune responses.

ALLERGIC RHINITIS (AR)

Allergic rhinitis (AR) is among the most common diseases globally and usually persists throughout life. His typical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also present; allergic rhinoconjunctivitis is strongly associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip, and cough.

Hyun et al[17] used 16S rRNA gene-based pyrosequencing to characterize and compared the inferior turbinate mucosa microbiota in healthy controls and AR patients and founded that microbial dysbiosis of the inferior turbinate in the latter is associated with high levels of total IgE but not with AR occurrence, the number of sensitized allergens, or house dust mite allergen-specific IgE.

In another recent study, Kim et al[18] described how Bifidobacterium longum IM55 and Lactobacillus plantarum IM76 from human faecal microbiota and kimchi, respectively, and examined their effects on ovalbumin (OVA)-induced AR and gut microbiota disturbance in mice; especially this probiotic supplementation reduced OVA-induced interleukin (IL)-4 and IL-5 levels in nasal tissues and bronchoalveolar lavage fluid (BALF) but increased OVA-suppressed IL-10 levels. Other studies showed that probiotics may be effective for allergic rhinitis[19].

Tonsils, consisting of lymphoid tissue, play an important role in local and systemic immune response to bacterial and viral pathogens and allergens. Tonsil microbiota is influenced by age and health status, but more substantial studies are still needed to confirm this ideal correlation[20].

CHRONIC RHINOSINUSITIS (CRS)

Symptoms of CRS include nasal obstruction, nasal secretions, postnasal drip, loss of smell, and headache or pain and/or pressure over the sinuses. In particular, in patients with CRS without nasal polyps (CRSsNP) is present pain, whereas patients with nasal polyps (CRSwNP) experience loss of smell.

In the study of Gan et al[21] the predominant bacteria were similar between the CRSwNP (chronic rhinosinusitis with nasal polyps and control groups, their relative abundance was different, with the abundance of Actinobacteria (predominantly Corynebacterium) significantly higher in the control group than in the CRSwNP group at both the phylum and genus levels. in recent analysis of Paramasivam et al[22] has been shown the dominance of Corynebacterium (mean relative abundance = 48.7%; prevalence = 88.49%) and Staphylococcus species (mean relative abundance = 29.25%; prevalence = 79.86%) in the sinonasal microbiota of healthy patients. Amongst patients suffering from CRSwNP, a statistically significant reduction in relative abundance of Corynebacterium (40.29% vs 50.43%; p = .02) was identified. In particular, Streptococcus, Moraxella and Haemophilus species are commonly respiratory tract organisms and constitute the most cultured pathogens in patients with acute bacterial tonsillitis, otitis media and acute sinusitis. The sinonasal tract connects these three distinct anatomical regions and while these organisms appear to be commensals, it is possible that the sinuses act as a reservoir for these organisms to subsequently initiate acute.

Important to consider are possible differences that may exist between various subgroups of CRS such as those with comorbid asthma, aspirin-associated respiratory disease, nasal polyposis. Of the selected articles, some failed to delineate these subgroups, others controlled for these subgroups, and a few specifically analyzed differences that may exist between these populations. In conclusion multiple authors failed to find a significant difference in bacterial composition between CRSwNP and CRSsNP.

BRONCHIAL ASTHMA (BA)

Gollwitzer et al[23] demonstrated that during the first 2 weeks after birth, the bacterial load in the lungs increased, and representation of the bacterial phyla shifts from a predominance of Gammaproteobacteria and Firmicutes towards Bacteroidetes. The changes in the microbiota were associated with decreased aeroallergen responsiveness and the emergence of a Helios-Treg cell subset that required interaction with programmed death ligand 1 (PD-L1) for

development. In various studies, for example Ni et al[24] showed that an exposure to antibiotics within the first year of life was significantly associated with asthma, but not with AR. Furthermore, there was a significant association between lifetime antibiotic exposure and asthma and AR. In Demirci study[25], Akkermansia muciniphila and Faecalibacterium prausnitzii may have induced anti-inflammatory cytokine IL-10 and prevented the secretion of pro-inflammatory cytokines like IL-12. These findings suggest that Akkermansia muciniphila and Faecalibacterium prausnitzii may suppress inflammation through its secreted metabolites.

In particular for severe asthma patients one important study did correlate corticosteroid use and corticosteroid sensitivity in asthma patients with the presence of specific microbes in the lower airways. At the RNA level, Neisseria species, Haemophilus species, Campylobacter species and Leptotrichia species were present in the lower airways of patients with corticosteroid-resistant asthma, but not in patients with corticosteroid-sensitive asthma[26]. Others have demonstrated that corticosteroid use, particularly the combination of inhaled and oral corticosteroids, is associated with an increased abundance of Proteobacteria and the genus Pseudomonas, and decreased abundance of Bacteroidetes, Fusobacteria, and Prevotella species.

MICROBIOTA AND ATOPIC DERMATITIS, CHRONIC URTICARIA, AND IMMUNODEFICIENCIES

Microbiota and primary immunodeficiency diseases (PIDDs)

The role of gut microbiota in the primary immunodeficiency diseases is shown in literature and its relationship with gastrointestinal host immunity is both symbiotic and dynamic. Alterations of gut microbiota seem to be associated with many gastrointestinal diseases characterizing different primary immunodeficiency diseases (PIDDs) and this can be explained by his important role in the immune regulation[4]. A recent review put in relation the IgA deficiency of many primary immunodeficiency diseases as selective IgA deficiency (sIgAD), common variable immunodeficiency (CVID), X linked agammaglobulinemia, hyper IgM syndromes, DiGeorge syndrome, WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) syndrome and ADA2 deficiency with gut microbiota dysbiosis and systemic inflammation. IgA was shown to have an important role in maintaining gut microbiota homeostasis with effects both on symbionts and pathobionts. The intestinal microbiota contributes to the maturation of the mucosal immune system, including the development of gut-associated lymphoid tissues and the secretion of IgA. At the same time, IgA is thought to modulate the intestinal microbiota through various different mechanisms, including immune exclusion, neutralization and modulation of bacterial gene expression[27].

Common Variable Immunodeficiency (CVID)

Many studies put in relation the role of gut microbiota and Common Variable Immunodeficiency (CVID): the most frequent symptomatic immune disorder characterized by reduced serum immunoglobulins and its association with a dangerous complication: CVID enteropathy[28]. Patients who suffer from this disease, usually have an increased susceptibility to bacterial infections, which mainly involve the mucus membranes, and are predominantly caused by *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Haemophilus influenzae*. Moreover, more than half of patients with CVID develop noninfectious complications such as malignancies, autoimmunity, lymphoproliferative and granulomatous disease, which often affect the gastrointestinal tract. As previously said, IgA has an important role in maintaining gut microbiota homeostasis and IgA deficiency, especially in CVID, is strongly correlated with increased morbidity for inflammation. Moreover, patients with severe IgA-deficiency had significantly reduced alpha diversity indices compared to patients retaining low or normal IgA levels. In CVID four bacterial taxa were more abundant than in healthy donors: Clostridia (Lachnospiraceae Dorea and Lachnospiraceae Roseburia genera), Bacilli and Gammaproteobacteria. At the same time, Firmicutes (Christensenellaceae family and Lachnospiraceae Blautia genus), Actinobacteria (e.g., Bifidobacteriaceae family), and Deltaproteobacteria (Desulfovibrionales genus) classes were found to be drastically decreased in CVID[29]. Microbial dysbiosis and trans-

location induced by the immune defect might explain immune dysregulation in different cell types. Several CD4 T cell abnormalities have been documented in CVID patients, including reduction of CD4 T cell count with inversion of CD4/CD8 ratio, high T cell activation, reduced proliferation capacity in response to bacteria antigens, and/or impaired production of cytokines. The combination of IgA deficiency and perturbed microbiota may also be responsible for regulatory T cell (Treg) dysfunction in CVID. Reduced Treg frequency and impaired suppressive capacity have been frequently documented in CVID patients, while the same presence of these cells mediate regulation of IgA diversification and selection and facilitate the diversification of bacterial species responsible for immune homeostasis[29].

In a recent study[30], it was showed a reduction of bacterial diversity in CVID patients with an increase of Streptococcaceae, Lactobacillaceae, and Enterobacteriaceae families and this finding was associated with a more severe CVID phenotype in these patients. Instead no significant differences in fungal alpha-diversity were found between these patients and controls.

In another study, Jørgensen et al[31] proposed a complex picture of CVID immunopathogenesis that involves an interplay of genes, environmental factors, and dysregulation of immune cells, where gut microbiota and GI inflammation can both be important contributors or endpoints to the systemic immune activation seen in CVID, and the epigenetic mechanism may be the undiscovered link between these contributors.

Selective IgA deficiency (SIgAD)

IgA deficiency is the most prevalent primary immunodeficiency and is characterized by low or absent serum IgA (< 7 mg/dL) with normal levels of IgG and IgM. Patients who suffered from this disease are primarily affected by infections of the respiratory system due to bacteria, e.g. Haemophilus influenzae and Streptococcus pneumonia. Moreover, these patients are associated with allergy, autoimmunity and disorders of the gastrointestinal tract (e.g., celiac disease or inflammatory bowel diseases)[29]. Fadlallah et al[32] showed that microbiota diversity did not differ significantly between patients and controls, but the relative bacteria compositions were different. In particular, Firmicutes, Bacteroidetes and Proteobacteria (exclusively Gammaproteobacteria, including E.coli) phyla were higher in the IgA-deficient subjects. In addition, *Streptococcus sanguinis*, *Veillonella parvula* and *Haemophilus parainfluenzae* and two species of Prevotella were also represented in these patients. The bacteria decreased belonged to the Firmicutes phylum (Lachnospiraceae family and Faecalibacterium genus) and also to the Bacteroides phylum. In summary IgA deficiency led to depletion of some typically beneficial symbionts and expansion of pathobionts. Moreover, selective IgA deficiency patients had altered Th17 profiles in circulating CD4+ T cells which were associated with increased serum sCD14, a marker of monocyte activation. In addition as just seen in CVID patients, CD4+ PD-1+ cells were increased in these patients, and this can reflect T cell exhaustion induced by persistent bacterial translocation[29].

Microbiota and atopic dermatitis (AD)

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory skin disorder characterized by intense itch, recurrent eczematous lesions and a fluctuating course. AD had an increasing incidence during the past few decades, especially in developed countries[33]. Recent studies have demonstrated that the skin microbiota, characterized by an overgrowth of Staphylococcus aureus, plays a critical role in the manifestation of this disease and it can modulate the development and progression of AD. Many studies have found alterations in the composition of the microbiome in patients with AD compared with that of healthy individuals, and microbiota differs between lesional skin and non-lesional skin[34]. The pathology of AD includes three critical factors: impaired skin barrier function, microbial dysbiosis, and cutaneous immune abnormality predisposed to T helper 2 (Th2) immunity, which may aggravate one another. The microbiota dysbiosis in AD is thought to be strongly related to the colonization of S. aureus on the skin, and the colonized skin lesions are closely correlated with the relative level of this bacterium[35,36]. The affected skin sites, especially inflamed areas, were predominantly colonized by more S.aureus and Staphylococcus and Corynebacterium

spp. increased dramatically in untreated patients during a flare. At the same time there is a reduction of Propionibacterium, Streptococcus, Acinetobacter, and Corynebacterium spp[35,37]. Studies showed that the severity of AD is usually associated with biofilms formed by S. aureus[38]. Recently, it has been proven that this bacterium plays a crucial role in occurrence and development of Th2 skewing and skin inflammation by multiple ways: through the induction of T cell independent B cell expansion, the release of cytokine and proinflammatory lipoproteins and the stimulation of mast cell degranulation with the release of many interleukins (ILs), such as IL-31 which is related with the pruritus of these patients[39,40]. The production of S. aureus superantigen facilitates the maturation of Th2 cells, and eventually leads to inflammatory response. Moreover, the skin colonization of S. aureus can produce different toxins and enzymes contributing to the inflammation and skin barrier dysfunction. They consequently cause bacteremia and sepsis through the invasion of human skin infection by S. aureus[41].

At the same time the gut microbiome might play an important role in the development of AD by regulating immune system maturation through cross-talk between the microbiome and the host, especially in early life[42]. In these patients Clostridia, *Clostridium difficile*, *Escherichia coli*, and *Staphylococcus aureus* are increased in the gut microbiome compared to healthy controls, while *Bifidobacteria*, Bacteroidetes, and Bacteroides are decreased and butyrate-producing bacteria, such as *Coprococcus eutactus*, are increased in infants with milder AD or healthy infants than in those with severe AD[43,44,45,46].

Microbiota and chronic urticaria (CU)

Chronic urticaria (CU) is defined as the continuous or intermittent presence of urticarial for a period exceeding 6 weeks and sometimes occurring with angioedema. Between 66 and 93% of these patients have chronic spontaneous urticaria (CSU) in which it is not possible to define a specific cause or pathogenesis. In a recent study Detong Wang et al showed that in the CSU patients we find a decrease of alpha diversity of the microbial population compared with a healthy control group. Particularly the Enterobacteriaceae were increased, while Bacteroides, Faecalibacterium, Bifidobacterium, and unidentified Ruminococcaceae were significantly reduced in these patients. In addition they found altered levels of docosahexaenoic acid, arachidonic acid, glutamate, and succinic acid, suggested changes in unsaturated fatty acids and the butanoate metabolism pathway. These alterations in gut microbes and metabolites may contribute to exacerbate inflammatory responses and to dysregulate the immune function with or without regulatory T cell dependence in the pathogenesis of CSU[47]. In another study Tao et al[48] showed that the bacterial diversity was reduced in CU patients compared with healthy individuals. Escherichia coli were significantly higher in CU, while Faecalibacterium prausnitzii, Prevotella copri, and Bacteroides spp. were significantly lower in these patients when compared with the healthy controls. Akram et al[49] do not showed a significant difference among the frequencies of detectable Lactobacillus, Bifidobacterium, or Bacteroides in stool samples of patients with chronic urticaria and healthy controls, even if it was detected a relative amounts of Lactobacillus and Bifidobacterium in fecal samples from controls compared to patients with CU. Edris Nabizadeh et al[50] found that the frequencies of Akkermansia muciniphila, Clostridium leptum, and Faecalibacterium prausnitzii in healthy controls' stool samples were significantly high than those of patients with CU while there was no difference between the frequency of the Enterobacteriaceae family in the patients with CU and the healthy controls. According to other studies Enterobacteriaceae family members are among proinflammatory members of gut microbiota and they could contribute to the development and the maintenance of chronic urticaria in these patients.

CONCLUSIONS

The perturbation of the development and maturation of the microbiome during the first few years of life can have a variety of harmful effects on immune health, contributing to determining the development of atopic diseases. In the Table 1 are resumed the main studies mentioned in this review regarding microbiota composition in the described allergological and immunological diseases.

TABLE 1. MAIN STUDIES REGARDING MICROBIOTA COMPOSITION IN ALLERGOLOGICAL AND IMMUNOLOGICAL DISEASES

Study-first authors [ref.], year	N°	Allergical or immunological disease	Bacterial genus
Fazlollahi M et al7, 2018	141	FA (eggs)	Lachnospiraceae ↑ Streptococcaceae ↑ Leuconostocaceae ↓
Stefka AT et al[11], 2014 Berni Canani R[8], 2016	MM 39	FA (peanut) FA (milk)	Clostridia ↓ Lachnospiraceae ↑ Ruminococcaceae ↑
Benitez et al[14], 2015	68	EoE	Proteobacteria (Neisseria and Corynebacterium) ↑ Firmicutes ↓
Harris et al[15], 2015	70	EoE	Haemophilus ↑
Kashyap PC et al[16], 2019	24	EoE	Bacteroidetes ↑ Firmicutes ↓ Clostridia ↓
Kim W.G et al[18], 2019	MM	AR	Bifidobacterium longum ↓ Lactobacillus plantarum ↓
Gan et al[21],2019	37	CRSwNP	Firmicutes ↑ Proteobacteria ↑ Actinobacteria (Corynebacterium) ↓ Bacteroidetes ↑
Paramasivan et al[22], 2020	172	CRSwNP	Actinobacteria (Corynebacterium) ↓ Staphylococcus spp ↓
Gollwitzer ES et al[23], 2014	MM	BA	Bacteroidetes ↓ Firmicutes ↑ Gammaproteobacteria ↑
Demirci M et al[25], 2019	92	BA	Akkermansia Muciniphila ↓ Faecalibacterium prausnitzii ↓
Goleva E et al[26], 2013	39	CRBA	Neisseria spp ↑ Haemophilus spp ↑ Campylobacter spp ↑ Leptotrichia spp ↑
Fiedorová K et al[30], 2019	27	CVID	Streptococcaceae ↑ Lactobacillaceae ↑ Enterobacteriaceae ↑
Jorgensen SF et al[29], 2016	44	CVID	Lachnospiraceae Dorea ↑ Lachnospiraceae Roseburia ↑ Bacilli ↑ Gammaproteobacteria ↑ Firmicutes (Christensenellaceae and Lachnospiraceae Blautia) ↓ Actinobacteria (Bifidobacteriaceae) ↓ Deltaproteobacteria ↓
Fadlallah J et al[32], 2018	21	SIgAD	Firmicutes ↑ Bacteroidetes ↑ Gammaproteobacteria ↑ Streptococcus sanguinis ↑ Veillonella parvula ↑ Haemophilus parainfluenzae ↑ Prevotella ↑ Firmicutes (Lachnospiraceae and Faecalibacterium) ↓ Bacteroides ↓
Kong HH et al[35], 2012	12	AD	Staphylococcus spp. (Staphylococcus aureus) ↑ Corynebacterium spp. ↑ Propionibacterium spp. ↓ Streptococcus spp. ↓ Corynebacterium spp. ↓

Continued

TABLE 1 (CONTINUED). MAIN STUDIES REGARDING MICROBIOTA COMPOSITION IN ALLERGOLOGICAL AND IMMUNOLOGICAL DISEASES

Study-first authors [ref.], year	N°	Allergical or immunological disease	Bacterial genus
Abrahamsson TR et al[43], 2012	20	AD	Bacteroidetes ↓
Penders J et al[44], 2006	26	AD	Escherichia coli ↑
Lee E et al[45] 2016	12	AD	Clostridia ↑ Bacilli ↑ Escherichia coli ↑
Nylund L et al[46] 2015	28	AD	Coprococcus eutactus ↓ (in severe AD)
Wang D et al[47], 2020	100	CU	Enterobacteriaceae ↑ Bacteroides ↓ Faecalibacterium ↓ Bifidobacterium ↓ Ruminococcaceae ↓
Lu T et al[48], 2019	10	CU	Escherichia coli ↑ Faecalibacterium prausnitzii ↓ Prevotella copri ↓ Bacteroides spp ↓
Nabizadeh E et al[50], 2017	20	CU	Akkermansia muciniphila ↓ Clostridium leptum ↓ Faecalibacterium prausnitzii ↓

FA = Food allergy; EoE = eosinophilic esophagitis; AR = Allergic rhinitis; CRSwNP = chronic rhinosinusitis with nasal polyposis; BA = Bronchial asthma; CRBA = corticosteroid-resistant bronchial asthma; CVID = Common Variable Immunodeficiency disease; SIgAD = Selective IgA deficiency; CU = Chronic urticaria ; AD = Atopic dermatitis; MM = Murine models; ↑ = increase of bacterial genus in affected patients/increase of disease risk; ↓ = increase of bacterial genus in heath controls/ protective role;

Despite the clear involvement of the microbiome in atopic disease, it remains to be determined whether microbial alterations are a cause or a consequence of the disease. Trends are observed most commonly in clinical trials studying allergic diseases; however, they cannot be fully supported, as the number of participants is generally limited. In addition, clinical studies on the intestinal microbiome can be confounded by the dominant diet of the country where the study was performed.

Lastly, the therapeutic avenues that either target the microbiota, the barrier surfaces or the host immune system to restore tolerance and homeostasis will be explored.

Conflict of interest

The authors declare that they have no conflict of interests.

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