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Human microbiota and allergy

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Abstract

Human microbiota plays an important role in the development of the immune system and food tolerance. The microbiome is a complex ecosystem, in constant regulation, influenced by the diet and environmental stimulus. Although bacterial communities are present in various body sites [airways, gut, mouth and skin], the gastrointestinal is the largest and most studied host-microbiome interface.

The microbiota is fundamental for maintaining homeostasis at the intestinal barrier and gut dysbiosis can contribute to inflammatory diseases.

Allergy is one of the most common inflammatory disorders, characterized by a hypersensitivity to a harmless substance, and influenced by genetic and environmental factors, including the microbiota.

Here, we aim to review evidences on microbiome´s influence on allergic disorders and microbiota-derived treatments.

Introduction and Discussion

Human microbiota and health

The human microbiota is composed of Eeucarya, Bacteria, Archaease and Viruses, these microorganisms play a fundamental role in the metabolism and immunity of humans. Alterations in the microbiome are linked to the development of many diseases such as inflammatory bowel disease, obesity and cancer [1].

The human contact with microorganisms begins in the first minutes of life, with the microbiota colonization in the newborn [2], being influenced by contact with microorganisms present at the moment of birth [3], due to the placenta being considerate microbiome-free [4].

The birth condition, vaginal or caesarean [elective or emergency], presents an implication in the development of the microbiota and extensively studied for the influence in the development of allergy and obesity [5-8]

The host´s microbiota is later influenced by sanitary conditions, food, drugs and environmental factors [9]. Therefore, the individual microbiome presents unique characteristics [10,11] and differs in composition according to the site in the human body, such as mouth, skin, gastrointestinal tract, respiratory tract and genitals. This is due to many factors such as: local pH, temperature and nutrients [12].

The human gastrointestinal [GI] is the largest interface between the host, environmental factors, antigens and microorganisms in the human body. There are approximately 10^{13}-10^{14} microorganisms in the GI, with greater genomic content that in the human genome [13].

Microbes and humans have a persistent and symbiotic relationship. Commensal microbes are fundamental for human health, regulating many physiological functions, degradation of substances, production of short-chain fat acids [14] and prevention of allergic sensitization [15]. As a result of this symbiotic process, the host and microorganism are sometimes referred to as “superorganism”.

The microbiome´s environment is in constant regulation, being modulated by external microorganisms and other non-bacterial compounds, for example food in the intestinal microbiota and cosmetical products in the skin. Abrupt change and microbial imbalance [dysbiosis] and/or opportunistic microbes can result in inflammatory stimuli and diseases [16].

The influence of the microbiota in the maturation and development of the immune system is well described [17,18], shaping vaccine´s efficacy, tolerance to food [19] and allergy [20].

Allergy

Allergy is a term first used by Clemens von Pirquet to designate a hypersensitivity to substances [21]. Nowadays, around 1 billion people worldwide are allergic, with an increasing prevalence [22]. The most common allergic manifestations are allergic rhinitis, atopic dermatitis, food allergy and allergic asthma [23].

Allergy is an inflammatory syndrome characterized by a Type 2 immunity with T helper [Th] cells and innate lymphoid cells [ILC] that produces high levels of interleukin [IL]-4, IL-5 and IL-13 denominated as Th2 and ILC2. This process also influences the class switch of B cells into IgE-producing B cells [24,25].

The IgE allergen-specific bind to FC receptors in innate immune cells, mainly basophils and mast cells, which upon a second contact with the allergen releases histamine and lipid mediators promoting the immediate allergic reaction and inflammation. It is crucial to highlight that this process can be lethal in an anaphylactic shock [26,27].

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In this second contact with the allergen, Th2 specific cells also migrate to the inflammatory site, promoting inflammation and recruitment of other cells, such as eosinophils [28].

The genetic predisposition to the development of allergy syndromes is well established such as atopy, characterized by the predisposition to high IgE production[29,30]. Dysfunction in genes associated with mucosal barriers, Th2-immunity or immunoregulation can also impact the development of allergy [31-33].

The environmental contribution to allergy development is well established, for example the exposure to many allergens or pollutants [34]. Recently many studies had connected the microbiome in the development and treatment of allergic diseases [35,36].

Microbiota and allergy

In 1989, the hygiene hypothesis was first proposed as a way to explain the growing incidence of allergies, where the Th1/Th17 immune response in bacterial infection could regulate the Th2 allergic immune response [37]. Later, different hypothesis as the counter-regulatory and "old-friends" were proposed [38,39], in summary the immune stimulation via innate immune receptors would regulate the differentiation of Th1/Th2/Th17 and T regulatory cells [Treg] and regulate not only allergy but other immune diseases [40,41].

This theory's based on observation and correlation in human´s studies [42-44] were tested in experimental model, where innate immune stimulation with bacterial compounds can in fact curb allergy sensitization [27,45,46], leading to the possibility of using bacterial compounds to regulate established allergic diseases [47-49].

The allergy-microbiota relation is not only retained to local microbiota and local allergy [example intestinal microbiota and food allergy], but also the relation between host microbiota and the development of allergy, for example in the lung-gut axis [50].

It is established that individuals with a low intestinal microbiota diversity or reduced in specific microorganisms are more susceptible to the development of allergic rhinitis [51] and food allergy [52]. In fact, Stefka, *et al.* shown that Clostridia-containing microbiota is crucial for the impairment of allergic sensitization [15].

The literature is conflicted about the early or later introduction of food and the development of allergies [53-56], although there are evidence that the introduction to common allergenic foods such peanut, egg or cow's milk at early age [between 3-6 mounts old] in addition to breastfeeding could help to prevent food-specific allergy [57-60]. And usage of antibiotics can lead susceptibility to allergy [53].

The literature is conflicted about the early or later introduction of food and the development of allergies [54–57], although there is evidence that the introduction to common allergenic foods such peanut, egg or cow's milk at early age [between 3-6 mounts old] in addition to breastfeeding could help to prevent food-specific allergy [58-61].

These observations are in opposition to the usage of formulas as a substitute for maternal's milk, which has been associated with the induction of milk´s allergy [62]. This is possible due to maternal´s breastfeeding ability to modulate the offspring's immune system and regulate allergen sensitization [63].

Diet is a major determinant of the GI microbiota [64]. High protein and fat consumption lead to a *Bacteroides* enterotype and a more carbohydrate-centered diet induces a *Prevotella* enterotype. Although short-term changes in dietary intake can impact the composition of the microbiota the magnitude is modest and not sufficient to change the enterotype [65].

High-fat diets (HFD) are a popular choice for weight loss [66] with similar results that a low-fat diet as long as energy restriction is similar [67]. HFD can result in changes in the microbiota and circulating inflammatory markers [68], and reduction in excretion of short-chain fatty acids [SCFA], which could suggest an increase in the risk of GI disorders [69]. This is greater explored by Kim, *et al.* which shows that high-fat diets are associated with an increase in allergic rhinitis [70].

Dietary changes can play an important role in the prevention and regulation of allergy [71,72]. This immunomodulation can be obtained by dietary intervention trough anti-inflammatory compounds [73,74] or via modulation of the microbiome [75,76].

High fiber diets can impact the microbiota in the GI protecting the development of food allergy [77] and allergic lung inflammation [78]. The abrogation of the Th2 allergic profile occurs through the production of microbiota-derived SCFAs, especially butyrate and propionate, that induces an anti-inflammatory profile via Treg cells [79]. High fiber consumption can also impact hematopoiesis and abrogate allergic lung inflammation, indicating an intestinal–bone marrow–lung axis that impairs allergic development but can also influence other immunological responses [78].

The oral consumption of butyrate can also directly attenuated lung inflammation and mucus production in OVA-challenged mice [79] and regulate the activation of ILC2 [80], via Gpr109a receptor [81]. Interestingly, SCFA not only promotes a regulation of type 2 immunity, but also induces Th1 and Th17 cell to release IL-10 [82], an anti-inflammatory cytokine [83], that can regulate the development of colitis, inflammatory bowel disease, [84], rheumatoid arthritis, psoriasis, and chronic hepatitis C [85].

The early development of allergies in the offspring can also be curbed by high fiber feeding during pregnancy, not only that but Thorburn, *et al.* suggest a possible epigenetic modification as a possible mechanism for this inhibition [86]. Microbiota´s metabolites can also promote allergic sensitization, as 12,13-diHOME produced by intestinal microorganisms can impair the activity of T regulatory cells and prejudice food tolerance [87].

Probiotics are another mechanism for allergy treatment, as the consumption of *Lactobacillus rhamnosus* strain GG and *Bifidobacterium lactis* Bb12 [88, 89]. This phenomenon can be partially explained by the increase in IgA [90] and increased capacity to secrete IFN- γ [91] or IL-10 [92].

As GI microbiome dysbiosis has been linked to the development of different diseases, fecal microbiota transplantation [FMT] is an emerging therapy for the regulation of GI microbiota [93]. FMT consists of the transfer of microorganisms from the stool of a healthy donor into the gastrointestinal tract of a recipient with a disease related to an unhealthy GI microbiome [94,95].

The FMT can be performed by the infusion in the colon or delivery through the upper GI tract and is currently being proposed for the treatment of ulcerative colitis [96] and inflammatory bowel disease [97,98]. Furthermore, the fecal transplant has been used for the treatment of neuroinflammation in an animal model of Parkinson's disease [99]. Although, the process offers risks related to the transfer of multi-resistant bacteria [100].

Microbiota transplant from allergic children or health children was able to transfer allergic sensitization do mice [101], therefore indicating a possible treatment for allergy trough FMT.

Conclusion

The microbiota-host interactions present a crucial role in the regulation of immune responses. Further researches are needed to confirm the safety and efficacy in the treatment of diseases via directly or indirectly manipulation of the microbiota.

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