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Microbiota and Food Allergy

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Abstract

Emerging evidence suggests that the increasing prevalence of food allergies is associated with compositional and functional changes in our gut microbiota. Microbiota-host interactions play a key role in regulating the immune system. Development of a healthy gut microbiota and immune system occurs early in life and is largely shaped by exposure to maternal microbes through vaginal/natural delivery and breast milk, whereas use of antibiotics can disrupt gut homeostasis and significantly raise the risk of allergic diseases. Thus, changes in the quantity or diversity of gut microbes affect oral toleranace through interations of microbial molecules with pattern recognition receptors on immune cells and confer susceptibility to food allergies. On the other hand, short chain fatty acids which are fermentation end products of insoluble fibers by intestinal micoorganisms have been shown to confer protective effects on food allergy. As a preventive and therapeutic treatment for food allergies, probiotics have gained widespread attention in recent years. Reintroducing certain commensal microbes, such as Clostridia, both in animal models and clinical trials led to the prevention or resolution of allergic symptoms. This review highlights recent progress in our understanding of the gut microbiota's role in food allergy. However, mechanistic details underlying the anti-allergic effects of probiotics and the interaction between the gut microbiota and the immune system remain circumstantial and are not fully understood. Future studies should address possible factors and underlying mechanisms for microbiota-host interactions and gut immunity, as well as the efficacy, safety, and appropriate use of probiotics in establishing a standard treatment regimen for food allergies.

Keywords Hygiene hypothesis · Microbe-host interactions · Intestinal microbiota · Food antigens · Tolerance · Probiotics · Short-chain fatty acids

Abbreviations

Ags	antigens
BB	*Bifidobacterium infantis*
BLG	anti-β-lactoglobulin
CMA	cow's milk allergy
CMP	cow milk protein
DCs	dendritic cells
E/B	enterobacteriaceae and bacterioidaceae ratio
EHCF	extensively hydrolyzed casein formula
FAO	Food and Agriculture Organization
GALTs	gut-associated lymphoid tissues
GPRs	G protein-couple receptors
ILT	immunoglobulin-like transcript
IP	intraperitoneally

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LcS	*Lactobacillus casei* strain shirota (LcS)
OVA-	ovalbumin-specific t cell receptor
TCR-Tg	transgenic mice
LAB	lactic acid bacteria
LGG	*Lactobacillus* GG
LPS	lipopolysaccharides
MLNs	mesenteric lymph nodes
OM	outer membrane
PRRs	pattern-recognition receptors
PUFAs	polyunsaturated fatty acids
RA	retinoic acid
SCFAs	short-chain fatty acids
sIgA	secretory IgA
TLRs	toll-like receptors
Tregs	regulatory T cells
WHO	World Health Organization

Introduction

The microbial world interacts with the human body constantly. We are in daily contact with an infinite number and countless varieties of microbes in our environment. Some bacteria may pass through our bodies without causing any harm, while others can cause undesirable health hazards. Proper sanitization and hygiene are believed to be the first line of defense against infectious microbes. In addition, vaccines developed in the past have prevented numerous deadly epidemics [1, 2]. However, just as important as sanitization and vaccines is the gut microbiome in our own bodies in combating pathogens.

The pivotal role of gut microbiota in host immunity has become clear with the advancement of scientific knowledge in recent years. Disruption of the original microbiota composition (dysbiosis) is associated with development of food allergy [3]. Lifestyle changes, including relocating from rural to urban settings, transitioning from a predominantly high-fiber diet to a high-fat and protein diet, and opting for cesarean section birth and bottle feeding, influence the composition of our microbiota and consequently its effect on the immune system. Advances in molecular techniques, such as next generation sequencing of bacterial 16S rRNA genes for phylogenetic and taxonomic assessment of bacterial community, increase analytic efficacy and provide important information on the roles of certain bacteria in food tolerance. Short-chain fatty acids (SCFAs), the end products of dietary fiber fermentation by the intestinal microbiota, have been shown to exert multiple protective effects against food allergy. Through different mechanisms, these fatty acids are involved in epigenetic regulation of the immune system. The aforementioned evidence provides a foundation for developing innovative strategies in preventing and treating food allergy. Furthermore, probiotics have drawn great interest recently due to their potential for modulating the immune environment and the gut microbiota. Here, we will discuss factors which render our immune system more vulnerable to food allergy with regard to changes in the composition and function of the gut microbiota. Furthermore, we will present our perspectives on microbiome applications in developing prevention and treatment strategies for food allergy.

Hygiene Hypothesis

The increase in allergic diseases in the last 100 years has become an increasing health burden worldwide. Genetic predisposition alone is unlikely to explain the rise in prevalence of allergic diseases in such a short time span. In 1989, a concept known as the "hygiene hypothesis" was introduced when researchers theorized that the rise in allergic diseases resulted from inadequate microbial exposure due to improved sanitization practices after noting lower incidences of infection in early childhood of allergy patients. Although evidence still supports that microbe–host interactions drives immune regulation, emerging data suggests that the interaction with both microbes inhabiting the external environment as well as the human microbiota itself plays essential roles in modulating that process [4, 5]. Thus, the scope of the hygiene hypothesis has recently been broadened to include the role of commensal microbes in the regulation of both allergic and inflammatory diseases [6–10]. Disuption of the gut microbiome along with lower rates of parasitic infections due to better hygiene practices have resulted in a decrease in RORγt+ Treg cells of IL-10-producing regulatory B cells and a Th2-biased immune response when reacting to innocuous antigens such as pollens or food [4, 5, 11]. One recent article offered another possible explanation for the oppositional relationship between the hygiene hypothesis and food allergy. They found that the "blocking antibody" IgG induced by schistosoma, a parasitic flatworm, can cross-react with allergens such as Ara h 1 and block the allergic hypersensitivity reactions [12]. TGF-β, another molecule secreted by the parasite, can induce Foxp3+ Treg cells. Together, they can potentially counteract IgE and block the FcεRI on mast cells in allergic reactivity [13].

Besides exposure to parasites exterior to the body, as many as 100 trillion microbes colonize barrier sites within our body, with the majority being in the intestine. The composition of the microbiome is dynamic and strongly influenced by external factors, such as diet/lifestyle, antibiotic use, mode of birth, formula feeding, vaccinations, and pathogen exposure. Exposure to commensal microbes begins as early as gestation and continues throughout life. This process is necessary to educate the immune system on how to respond to the vast number of stimuli encountered. A disruption in any part of this process will result in a malfunctioned immune system that responds not only to harmful infectious microbes but also to innocuous targets, such as pollen or food proteins. A perfect

example is the germ-free mice whose Treg activation is depleted and is subsequently found to possess a strong disposition toward developing food allergy [14]. Clearly, disruption in the diversity and/or the function of the microbiota, referred to as dysbiosis, may play an important role in the development of food allergy [15]. As an extension to the original hygiene hypothesis, the "microbiome hypothesis" was proposed which emphasizes the importance of the gut microbiota in modulating host immunity in early life [16].

Factors Affecting Gut Microbiota

The microbial composition derived from biopsies, luminal contents, and feces can be analyzed using clone library analysis of the 16S rRNA gene. Gene clone libraries have shown that the intestinal microbiota of mice and humans consists of hundreds of different phylogenetic species that can be classified into four major microbial phyla: Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes. These groups make up 98% of the intestinal microbiota [17, 18]. Taxonomic composition of the microbiota changes with age as well: newborn gut microbiota is initially dominated by Proteobacteria (e.g., *Escherichia*, *Shigella*), followed by Actinobacteria (e.g., *Bifidobacterium*), before maturing into the adult-like microbiota dominated by Firmicutes and Bacteroidetes [19, 20]. This maturation is reflected in the ratio between Enterobacteriaceae (Proteobacteria and Actinobacteria) and Bacterioidaceae (Firmicutes and Bacteroidetes), or the E/B ratio, which declines with age as the relative proportions of Enterobacteriaceae decrease and Bacteroidaceae increase.

Pregnancy, Modes of Birth, and Breastfeeding

Exposure to microbes may occur as early as pregnancy, with gut microbe composition changing throughout development. Previously, it was believed that the placenta and meconium were sterile environments. However, recent studies demonstrate the existence of specific microbial groups at these sites [21]. Through natural birth, newborns are exposed to maternal vaginal microbiota. Later, the infant gut microbiota undergoes dynamic changes resulting in an adult-like microbiota at about 3 years of age, which corresponds to the time at which infants start a diet similar to other adults in the family and when major components of acquired immunity are developed [22]. Recent studies on the temporal association between intestinal microbiota colonization and distribution and food sensitization in early life suggest that the microbiome may play a role in the development of food allergy [23, 24].

Infants born by cesarean section develop a different colonization pattern of gut microbiota, as they are not exposed to maternal vaginal microbes. Data from 16S rRNA gene analysis reveal that lower levels of *Bacteroides*, a lower diversity within the Bacteroidetes phylum, and a higher level of diversity in the Firmicutes phylum, (*Bacilli* and *Clostridium g4*), exist in cesarean section-delivered infants [25]. Interestingly, lower diversity within the Bacteroidetes phylum, as well as lower overall microbial diversity in early infancy, has also been observed to precede the development of allergic manifestations in several clinical studies [26–28]. Azad et al. found that low gut microbe diversity and an elevated E/B ratio in infancy are associated with subsequent food sensitization [4]. This supports findings for the E/B ratio present in the gut microbiota of infants allergic to cow's milk at the time of diagnosis (abundance of Ruminococcaceae and Lachnospiraceae), when compared to age-matched, healthy 4-months-old controls (dominated by Bifidobacteriaceae, Enterobactericeae, and Enterococceae) [29]. Thus, early life gut dysbiosis likely contributes to the development of allergic diseases, including food allergy.

In addition to a lower abundance, diversity, and colonization of the Bacteroidetes phylum, Jakobsson et al. also found significantly lower levels of Th1-associated chemokines, CXCL10 and CXCL 11, in the serum of infants born through cesarean section [30]. The imbalance in Th1 and Th2 chemokine levels during infancy or childhood is highly associated with allergic symptoms and sensitization development [31]. The correlation between elevated E/B ratios and the development of allergic diseases appear to be consistent among various studies, but the mechanism remains unclear. Nonetheless, this correlation supports the argument relating cesarean sections to development of allergic diseases.

Colostrum and breast milk also play important roles in the development of gut microbiota during infancy. Formerly, breast milk was thought to be sterile. However, Jiménez et al. found that microbes can be transferred via breast milk in an elegant mice experiment. They orally inoculated pregnant mice with genetically labeled *Enterococcus*, isolated from the breast milk of a healthy human, and found the labeled bacteria later in the internal meconium of the pups delivered by cesarean section [32]. Thus, commensal bacteria are thought to exist even in the fetal gut, which is later sourced from breast milk after delivery.

In a 12-month longitudinal study, it was shown that the breastfed infants received 27.7% of their intestinal bacteria from breast milk and 10.4% from areolar skin during the first month of life [20]. The contribution of Proteobacteria (Moraxellaceae, Enterobacteriaceae, and Pseudomonadaceae) from breast milk and Firmicutes (Staphylococcaceae and Streptococcaceae) from areolar skin was highest during the first month and decreased as the infant aged. Bacterial diversity and composition change in proportion with daily breast milk intake in a dose-dependent manner, even after the introduction of solid foods [33]. Therefore, breastfeeding can transfer microbes to the infant while influencing the composition of a child's gut microbiota, as

breast milk is a source of nutrients for commensal microbes, such as *Bifidobacterium*, *Lactobacillus*, *Staphylococcus*, *and Enterococcus* [34]. It was reported that specific microbes are directed from the mother's gut to the mammary glands, along with specific immunological factors designed to introduce these microbes to the infant [35]. A recent work demonstrated that breastfed infant rhesus monkeys exhibit less fluctuations in their gut microbiota composition than bottle-fed infant, and therefore, a more robust development of T helper 17 cells at 1 year of age [36]. It is clear then from these studies that the stability of the infant gut microbiota is closely related to breastfeeding.

Secretory IgA (sIgA) in breast milk not only protects against pathogens but also promotes the development of microbiota in newborns [37]. In this model, mice without exposure to sIgA in breast milk exhibited compromised epithelial barrier function, which resulted in greater colonization of Firmicutes and an increased expression of intestinal epithelial cell genes associated with intestinal inflammation in humans. On the other hand, mice given maternal sIgA maintained intestinal homeostasis and underwent amelioration of intestinal damage caused by sodium dextran sulfate.

The development and evolution of the microbiota are influenced by many factors starting as early as pregnancy, and they are highly dynamic [38]. The microbiota may, under certain conditions, play a direct role in tolerance inhibition, leading to food allergen sensitization and dysbiosis. At other times however, it can facilitate the re-establishment of tolerance. More studies are necessary to understand the mechanisms behind the complex and dynamic interactions between the gut microbiota and our immune cells during this critical developmental stage. In doing so, preventive measures and appropriate education against the development of food allergies may be provided to pregnant women and new mothers.

Antibiotic Use

Antibiotics have served as powerful tools against infectious diseases for humans and livestock ever since their discovery in the early twentieth century. Consequently, their prominent usage has been shown to negatively affect microbe communities in the host's gut. The effects of antibiotics on indigenous gut microbes have long been a subject of intensive research. Antibiotics can alter the makeup of the indigenous microbial population, thereby reducing their diversity as well as affecting their genetic characteristics and function [39, 40]. Their effects on the gut flora often linger long after therapy has been completed. Exposure to antibiotics comes not only from pharmaceuticals but from agricultural products as well, where antibiotics are extensively used in livestock and persist in trace quantities in various food items.

Exposure to antibiotics during pregnancy can increase the risk of allergic disorders in children [41]. In particular, macrolides adversely affects microbiota diversity and function in young children, and those who receive this class of antimicrobials in early life have an increased risk for asthma in later childhood [42, 43]. Unfortunately, intrapartum antibiotic use is increasing due to rising cesarean section delivery rates [44]. As a result, infants born to mothers receiving intrapartum antibiotics for Group B streptococcus prophylaxis, pre-labor rupture of membranes, or cesarean section exhibited significant alterations in the composition and quantity of their gut microbiota. They possessed low levels of *Bacteroides* and high levels of *Enterococcus* and *Clostridium* at 3 months following maternal antibiotic use [45]. This observation supports findings from dysbiosis studies previously discussed. Follow-up studies on these infants to monitor for potential development of allergies should be strongly considered.

Most infants receive multiple courses of antibiotics during the first 2 years of life in developed countries, but there may be significant immunological consequences to such treatments as well. Studies using murine models support the theory that orally administered broad-spectrum antibiotics in early-life are associated with aberrant immune responses to respiratory and dietary antigens. Data emerging from human studies likewise link the use of antimicrobial agents to the increase in prevalence of food allergy. The neonatal period is a particularly critical time of exposure to antibiotics. Stefka et al. reported that neonatal antibiotic treatment reduced microbial diversity and bacterial load in both fecal and ileal samples and enhanced food allergen sensitization [14]. Love et al. also demonstrated that children receiving five or more antibiotic prescriptions in the first year of life were significantly more likely to be diagnosed with food allergy. The strongest correlation was noted among recipients of cephalosporin and sulfonamide antibiotics [46]. Additionally, the effect of frequent antibiotic use on food allergies varies with age. Penicillin and cephalosporins were associated with food allergy in children under 2 years of age, whereas macrolides were associated with food allergy diagnosed later in childhood [47]. Indeed, antibiotics can disrupt the balance of microbes and the regulation of the immune system in the gut, and the effects can persist for extended periods. Nevertheless, their effects can be modified by the environment we naturally encounter. One study examining the relationship between antibiotics and the development of allergy and the protective effects of exposure to a rural environment early in life found that Argentinean children living in urban areas suffered atopic diseases, such as wheezing and allergic rhino-conjunctivitis, when treated with antibiotics during the first year of life, but not with those living in rural areas [48]. Therefore, other confounding factors may be involved in restoring the balance in indigenous microbiota. Future investigations should examine how natural environments, lifestyles, or diets affect the gut microbiota and what kind of protection against dietary allergens these factors can provide.

Oral Tolerance and Gut Microbiota

The gastrointestinal tract contains the largest interface between the body and the external environment. It is exposed to microbes as early as the fetal stage, and as many as 100 trillion microorganisms reside in the large intestine by adulthood. Along with food, the gut is under constant bombardment by various other antigens (Ags). Therefore, it is essential that the body distinguishes between indigenous versus foreign Ags. Among the latter, some are innocuous while others pose harm to the body. The state in which the immune system is nonresponsive in the gut-associated lymphoid tissues (GALT) to innocuous Ags, such as food proteins that may never be or rarely ingested, is referred to as oral tolerance [49].

Normally, ingested food Ags are degraded by gastric acid and luminal digestive enzymes. A variety of cells, including CD103+ intestinal dendritic cells (DCs), phagocytic cells, and microfold cells that reside beneath GALT, express CX3C-chemokine receptors which allow for the endocytosis of Ags and their subsequent transfer to the lamina propria and ultimately, mesenteric lymph nodes (MLN), where they present these Ags to T cells (Fig. 1) [50]. Food Ags that escape proteolysis in the gut can be taken up by intestinal epithelial cells, which express MHC II and therefore act as nonprofessional Ag presenting cells for T cells in the gut. Within the proximal MLN, large amounts of TGF-β and retinoic acid (RA) produced by stromal cells and CD103+ dendritic cells induce naïve T cells to differentiate into Ag-specific Foxp3+ Tregs or IL-10-secreting type 1 regulatory cells [51]. RA has also been shown to induce upregulation of CCR9 and integrin-α4β7 receptors on these newly differentiated Tregs to recruit them back to the gut for suppression of unwanted immune responses. Any missing component in this process may cause unwanted or intolerant responses.

Emerging data underlie the importance of the gut microbiota's functional role in the development of host immunity [31, 52–55]. For example, germ-free mice failed to develop normal mucosal and secondary lymphoid tissues, supporting epidemiological observations that posit a protective role for the microbiota. These animals were predisposed to severe allergies due to an exaggerated systemic Th2 response and became more susceptible to oral Ag–induced anaphylaxis than mice colonized with a diverse microbiota [56–58]. The molecular interactions between microbial molecules in the immune regulation of food allergy responses was elegantly addressed in recent studies focused on pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs). Upon activation of PRRs, antimicrobial peptides and mucus are produced to eliminate infectious agents and to maintain intestinal barrier function. In support of this

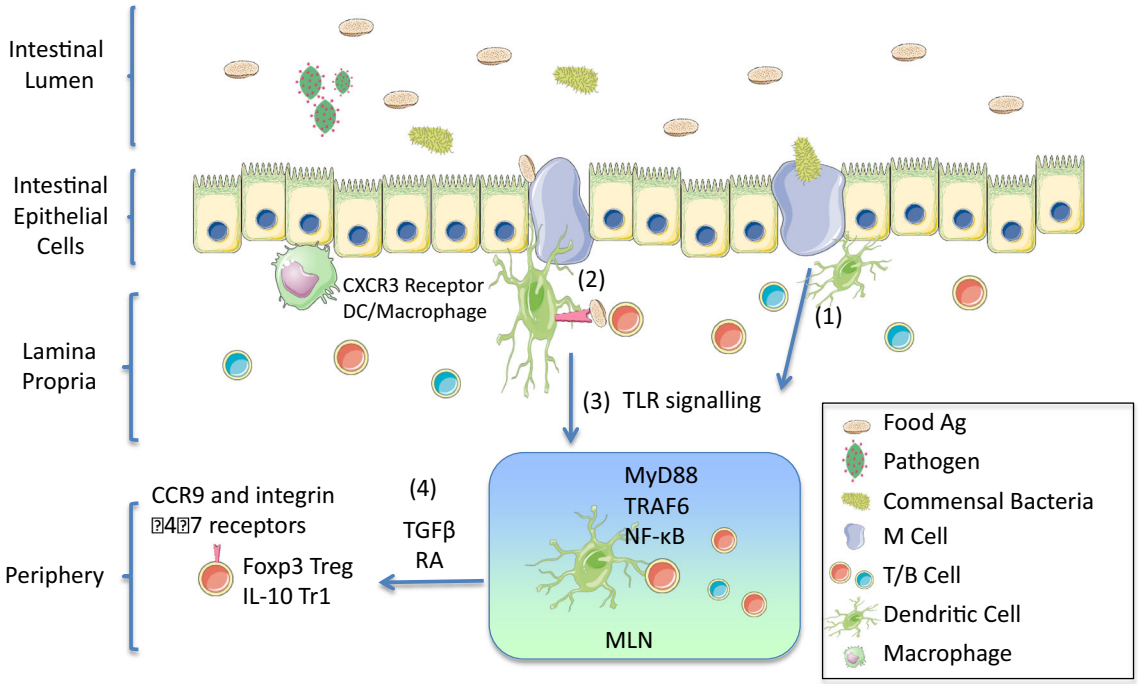

Fig. 1 Immune responses after Ag processing in the intestine: 1) In GALT, microbes transported by Microfold (M) cells are captured by immature DCs in the lamina propria. Ultimately, these DCs will migrate to and mature in the draining MLN where they present Ag to naive T cells. 2) By extending dendrites directly into the lumen, DCs beneath the epithelial layer capture and present Ags to naive T cells in the proximal MLN. 3) The degree of activation and migratory properties of DCs depend on the nature of the signals associated with the Ag. 4) After food Ag is presented, TGF-β and retinoic acid (RA) are produced by stromal cells and CD103+ DCs and subsequently induce naïve T cells to differentiate into Foxp3+ Tregs or IL-10 Tr1 cells. The production of different cytokines will control tolerance, inflammation, lymphocyte differentiation, and homing to effector sites

finding, administration of lipopolysaccharide (LPS) to germ-free mice restored oral tolerance [59]. Through TLR signaling, activation of latent TGF-β from intestinal 103+ DCs promotes Treg differentiation that helps to prevent allergic sensitization to food [5, 60, 61]. Without MyD88, an adaptor molecule for downstream TLR signaling, mice would develop more severe intestinal inflammation in response to sodium dextran sulfate epithelial damage, suggesting an important role for microbial sensing in modulating inflammatory responses [62]. Mice lacking MyD88 in B cells also produced elevated levels of IgE.

Finally, TRAF6 is another important adaptor molecule for TLR signaling that acts downstream of MyD88 to activate transcription factors, such as NF-κB, to induce cytokine production (Fig. 1) [63]. Mice with a specific TRAF6 deletion in CD11c + DCs have reduced numbers of Tregs and develop spontaneous Th2 associated inflammation, as well as IL-13, IL-5, and IL4, in their small intestines [64]. Intriguingly, when these mice were treated with full-spectrum antibiotics, which mimic a germ-free condition, the pathogenic phenotypes were ameliorated with increased colonic Tregs [6, 64, 65]. Therefore, aberrant immune homeostasis relating to TRAF6-deficient gut DCs is triggered only when commensal microbiota are present, which seemingly contradicts recent findings that show commensal microbes enhance gut Treg cell numbers [5, 66]. However, this discrepancy may be because these studies investigated Tregs mainly in the colon and not in the small intestine, which serves as the primary site of encounter for food Ags. The explanation for this tissue-specific and commensal microbe-dependent response may be the result of a breakdown in tolerance to food antigens. However, further investigation is required to delineate the mechanisms behind how a variety of TLR ligands on microbes interact with and signal via DCs in gut tolerance.

In addition to microbial ligands that can be sensed by PPRs, short-chain fatty acids (SCFAs), which are end-products that result from fermentation of insoluble dietary fibers by gut microbes, have been demonstrated to restore homeostasis of the intestinal immune system by binding with G protein-couple receptors (GPRs). Through GPRs, the microbiota can directly regulate the expression of epithelial alarmins in the intestine [6]. A dysbiosis in microbiome may elicit epithelial alarmins and prime the immune system toward allergic sensitization to food [67]. Administration of IL-25 can alter the expression of antimicrobial peptides and thus change the composition of the microbiota. When IL-25 is over expressed, it shifts the environment in the intestine from a tolerogenic state to an allergic one in response to food Ag [68].

As seen in developing countries where there is decreased dietary fiber and increased protein and fat intake, the composition of the gut microbial community as well as its metabolic end products are changing accordingly. In one study, subjects that consumed a high protein and high fat diet for 5 days had an elevated quantity of bile-tolerant microbes, such as *Bacteroides*, but a reduced quantity of *Firmicutes*, which helps to ferment dietary insoluble carbohydrates [69]. Indeed, butyrate can be converted from Acetyl-CoA by several Firmicutes [70]. The consequence of this dysbiosis may reduce levels of SCFAs and incur a phenomenon associated with one or more allergic phenotypes. There is a body of literature that supports a predisposition for an allergic diathesis secondary to low levels of SCFAs and that by increasing SCFA levels, the disease state can be ameliorated [71, 72].

Other mechanisms by which SCFAs protect against allergic diseases include direct inhibition of histone deacetylases (HDACs) to directly regulate gene expression or by acting on innate lymphoid cells (ILCs) to strengthen the protection of mucosal and barrier sites. In the first instance, previous studies show that SCFAs are inhibitors of histone deacetylases and suppress NF-κb activity. By comparing mice colonized with chloroform-resistant bacteria that were fed with either a high or low fiber diet, Furusawa et al. found that SFCAs in the gut was positively associated with the number of Foxp3 and Tregs in the colon [66]. Treatment with SCFAs in both rodent and human studies showed reduced global HDAC activity as well as increased global histone acetylation, which are both correlated with a decreased production of the inflammatory cytokines, IL-6, IL-8, and TNF-α, enhanced tolerogenic activity in MLN DCs, an increased percentages of intestinal Tregs, and higher levels of IgA production in the lumen of the intestine [73–75].

As mentioned earlier, SCFAs can also deter allergic diseases by interacting with ILCs as part of the intestine's innate immunity. For example, when they act on group 3 ILCs (ILC3), IL-22 is produced and induces a barrier-protective response by producing antimicrobial peptide (AMP) via Paneth cells and mucus via goblet cells in intestines with healthy microbiota [76]. This response protects the lamina propria against food Ags and allergic sensitization. However, as shown in a previous study by Stefka et al., this function is compromised in germ-free mice or mice treated with antibiotics, as both groups exhibited increased sensitization to peanut [32]. Nevertheless, reintroducing Clostridia, a class of Firmicutes residing in close proximity to the intestinal epithelium, into gnotobiotic mice repaired the barrier's protective function through IL-22 production by both RAR (retinoic acid receptor)–related orphan receptor gamma t (ROR-γt) + ILCs and Tregs in the intestinal lamina propria. Reduced levels of peanut-specific and total IgE were found in gnotobiotic mice compared to germ-free controls. Bunyavanich et al. also found that gut microbiota enriched with Clostridia and other Firmicutes in milk-allergic children between 3 to 6 months old was associated with resolution of allergic symptoms by age 8 [11]. The anti-allergic effects of Clostridia and Firmicutes may be attributed to the Treg responses regulated by SFCAs.

Table 1 Anti-allergic effects of various probiotic strains

Probiotic strain	Type of study	Anti-allergic effects
B. longum	Randomized, double-blind, placebo-controlled clinical trial [81]	Relieved eye symptoms in patients with pollen allergy, increased IFN-γ and decreased IgE
B. breve	In vitro using human monocytes [79]	Induced DC maturation and prolonged survival through TLR-2 with increased IL-10 production
L. plantarum	In vitro using RBL-2H3 cells [80]	Suppressed differentiation of Th2 cells and expression of Th2-associated cytokines, promoted differentiation of Th1 cells
	In vivo with mice [82]	Increased IL-12 level to suppress Ag-specific IgE
L. casei (Shirota)	In vivo using OVA-TCR-Tg mice [83]	Increased IL-12 level, decreased OVA-specific IgE and IgG1 levels
L. fermentum	In vivo using mice immunized with OVA [84]	Suppressed inflammatory cell infiltration in airways, OVA-specific IgE and mRNA expression of IL-4, IL-5, IL-13, and TGF-β
L. rhamnosus (LGG)	In vivo mice treated with LGG + EHCF [85]	Reduced acute allergic skin reaction, anaphylactic symptom scores, body temperature; increased levels of IL-4, IL-5, IL-10, IL-13, and IFN-γ
	In vivo mice treated with LGG [86]	Lowered hypersensitivity scores and CMP-specific IgG1; increased IFN-γ and CMP-specific IgG2a levels

Probiotics and Food Allergy

Modulation of Immune System by Probiotics

With increasing evidence suggesting dysbiosis as a leading cause of food allergy, potential preventive and therapeutic effects of probiotics on allergic symptoms have attracted the attention of both the general public and scientific community [77]. As defined by the Food and Agriculture Organization (FAO) and World Health Organization (WHO), probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit to host [78]." Probiotics are mostly composed of bacteria, but they can also contain yeasts, such as *Saccharomyces boulardii*. The most common probiotic bacteria fall into two groups, namely *Lactobacillus* and *Bifidobacterium*. There is a vast variety of species and strains. For instance, *Bifidobacterium longum*, *Bifidobacterium breve*, and *Lactobacilli plantarum* were found to possess anti-allergic potential in both animal models and clinical trials [79–81]. The anti-allergic effects of various probiotic strains demonstrated in in vivo and in vitro studies are summarized in Table 1. Various reports reveal that probiotics modulate the immune system by attaching to intestinal endothelial cells, producing antimicrobial metabolites, competing with pathogenic microorganisms for nutrients, strengthening the epithelial barrier, acidifying the gut environment to prevent pathogenic bacterial growth, and modifying immune responses [87]. Through these actions, probiotics can partially restore the bacterial cell number or epithelial layer in intestinal microbiota after dysbiosis and are therefore regarded as beneficial microorganisms [88].

Beneficial Effects of Probiotics

A number of mechanisms have been proposed to explain the beneficial effects of probiotics (Fig. 2), although their details are not fully understood. Servin reviewed the antagonistic actions of two common probiotic bacteria, *Lactobacilli* and *Bifidobacteria*. Their strains displayed different adhesive properties [89]. Some possessed proteins, glycoproteins or carbohydrates on their surfaces to aid in their attachment [90], while others were found to be able to adhere onto the intestinal epithelial cells and mucosa through passive forces, electrostatic interactions, hydrophobic steric forces, and lipoteichotic acids in several in vitro studies [89, 91]. Xu et al. studied the adhesion abilities, hydrophobicity, auto-aggregation, and coaggregation of *Bifidobacterium longum* B6, *Lactobacillus acidophilus* ADH, *Lactobacillus paracasei*, *Lactobacillus rhamnosus GG*, *Lactobacillus brevis*, *Lactobacillus casei*, *Leuconostoc mesenteroides*, and *Pediococcus acidilactici* using a Caco-2 cell line. They discovered a high correlation between the in vitro adhesion of the selected probiotics to Caco-2 cells and elimination of foodborne pathogens by competitive inhibition [92]. One outcome is that these probiotics can block pathogenic bacteria from binding onto the gut mucosa or epithelial cells so that pathogens are eradicated from the human body [89]. In effect, probiotics in the gut out-compete pathogenic bacteria due to stronger adhesion to the mucosa and epithelial cells in the intestine. Apart from attaching to epithelial cells in the gut, administration of probiotics can enhance barrier function [93]. As the epithelial barrier often faces new incoming microorganisms, its enhancement by probiotics can prevent pathogen invasion [94].

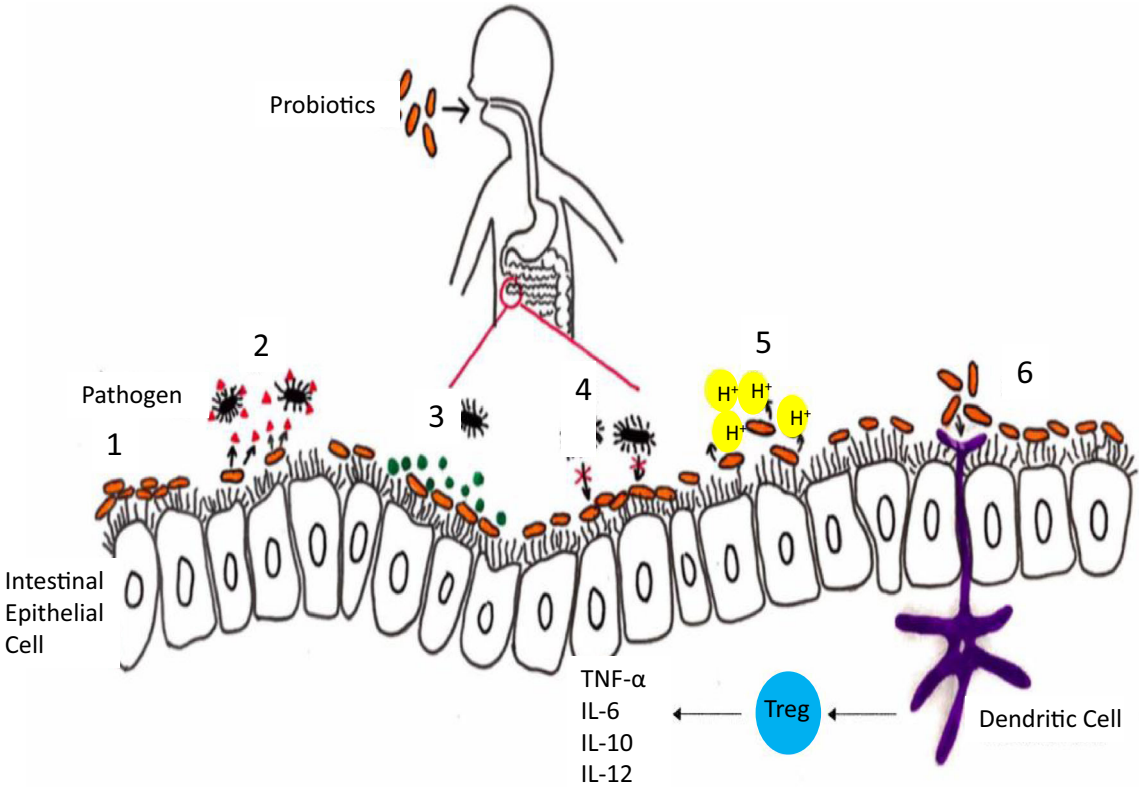

Fig. 2 A schematic diagram showing the potential mechanisms of probiotics in gut microbiota. 1: attachment to epithelial cells, 2: production of antimicrobial metabolites, 3: competition with pathogens for nutrients, 4: reinforcement of the epithelial barrier, 5: Acidification of the gut environment, 6: modulation of immune responses

In addition, probiotics can secrete antimicrobial substances against pathogens. Lactic acid bacteria (LAB) typically secrete organic acids, diacetyl, hydrogen peroxides, antibiotics, and bacteriocins [95]. Bacteriocins consist of colonizing peptides, killing peptides, or signaling peptides which help to introduce bacteriocin-producing bacteria into an established niche, prevent pathogen invasions directly, or signal certain bacteria to colonize the microbiota [96]. In most cases, bacteriocins destroy target cells by forming pores or inhibiting cell wall synthesis. Organic acids, such as lactic acids, produced by LAB in the intestine destroy pathogens by acidifying the environment so that pathogenic bacterial growth is hindered [97]. The outer membrane (OM) integrity of the bacteria is maintained by the lipopolysaccharides (LPS) layer above it [98]. Any chemical that can either release LPS from the OM or anchor to the membrane can increase membrane permeability [98]. Lactic acid disrupts the OM of gram-negative bacteria by increasing its permeability and lowering the intracellular pH [98]. Alakomi et al. demonstrated that lactic acid also reduced the viability of bacteria since LPS was released from the OM, rendering the bacteria more vulnerable to detergents or lysozymes [98]. Pathogens eventually die due to structural damage caused by antimicrobial substances.

Another mechanism for the antimicrobial effects of probiotics is immunomodulation [99]. Despite numerous results showing that strain-specific probiotics can modulate the immune system, how exactly probiotics induce immunocompetent cells is not well understood. As reviewed by Servin, different *Lactobacilli* and *Bifidobacteria* strains were reported to be capable of stimulating immune cells to secrete cytokines (e.g., TNF-α, IL-6, IL-10, IL-12) and shifting the Th2-type response back to a Th1-type response [89]. Enhanced proliferation of CD4+, CD25+ as well as NK cells also implies higher phagocytic activity in the immune system [89]. The details of these pathways are however not clearly understood since the results summarized in Servin's review are only measurements of various cytokine levels without an explanation of the phenomena.

Probiotics in Allergy Studies

Probiotics are an essential tool in restoring microbial balance in the gut microbiota and maintaining its homeostatic condition. Many review articles have summarized experimental models directed at investigating the mechanisms of select probiotic strains in alleviating allergic symptoms [100]. In allergy studies, probiotics are considered effective if they can shift the skewed Th2 profile back to a balanced Th1/Th2 profile. Among various probiotic strains, *Lactobacillus* GG (LGG) has been shown to improve gut microbial balance and allergic

symptoms across many animal and human studies. In particular, the anti-allergic effect of LGG on cow's milk allergy (CMA) has been extensively studied. Extensively hydrolyzed casein formula (EHCF) is commonly used to prevent CMA in infants. It has been reported that supplementing EHCF with LGG is more effective compared to EHCF alone in reducing CMA [101–103]. Aitoro et al. reported lower acute allergic skin responses, anaphylactic symptom scores and body temperatures, and elevated levels of in IL-4, IL-5, IL-10, IL-13, IFN-γ, and anti-β-lactoglobulin (BLG) IgE in EHCF-treated mice groups [85]. However, these results were much more pronounced in groups treated with EHCF+LGG, suggesting the importance of LGG in modulating the immune system [85]. Similar results were found in another study by Thang et al., who used 3-week-old newly weaned Balb/c mice with adjuvant-free LGG sensitization to simulate CMA in infants [86]. In LGG-treated mice, Th2 responses were suppressed, resulting in remarkably lower hypersensitivity scores and CMP-specific IgG1 levels, and Th1 responses were promoted, resulting in increased levels of IFN and CMP-specific IgG2a [86]. The in vivo responses were also the same as expected. An increase in serum IL-4 with significantly higher cow's milk protein (CMP)-specific IgG1 levels was observed in sensitized mice but not in the control group [86]. Moreover, LGG-treated mice had higher IFN-γ levels than sensitized mice [86]. These results are persuasive since whole CMP allergens were used, which more accurately simulate real life situations in humans, rather than single purified CMPs. However, the anti-allergic effects were only successful in mice sensitized intraperitoneally (IP) and not orally [86]. Since oral gavage is a commonly used delivery route to study food allergy, these findings should be reexamined by other research groups in the future.

Other *Lactobacillus* strains were similarly effective in modulating immune responses. *Lactobacillus casei* strain Shirota (LcS) was administered intraperitoneally to ovalbumin-specific T cell receptor transgenic (OVA-TCR-Tg) mice, which increased IL-12 levels, decreased IgE and IgG1 levels, and restored the Th1/Th2 balance [83]. The same immunological responses were also induced by *Lactobacillus plantarum*. *Lactobacillus plantarum* L-137 stimulated IL-12 production which led to lower serum IgE and IgG levels [82]. Based on the consistent results of administrating *Lactobacillus* strains across different studies, they are considered one of the most effective probiotics for alleviating food allergy [85]. Their beneficial effects have been demonstrated not only in mice but also in humans. For instance, incidence of allergic symptoms decreased in children with CMA after taking EHCF containing LGG [104].

Current studies have largely examined the immunobiological effects of specific probiotics strains administration. Data on the compositional change of microbiota by probiotics is limited. Yang et al. [105] analyzed the effects of probiotic administration on gut microbiota composition between animals treated with and without *Bifidobacterium infantis* (BB) in an ovalbumin (OVA)-sensitized murine model. 16S rRNA sequencing of fecal samples revealed a higher abundance of *Coprococcus* and *Rikenella* at the genus level in fecal samples along with reduced OVA specific-IgE and IgG1 levels, splenic Th2 cytokines levels, and occurrence of diarrhea in mice that received BB compared with controls. In addition, Canani et al. recently compared the composition of the gut microbiota of CMA infants to that of healthy infants [106]. Fecal samples were collected from healthy infants and CMA infants before and after taking EHCF with or without LGG supplementation. After EHCF+LGG intake, a remarkable increase in bacterial diversity was observed [106]. Cox et al. also studied changes in the gut microbiome after supplementing LGG in infants' diet and found that high doses of LGG led to changes in gut microbiota [107]. With these promising observations demonstrating the effects LGG produces in reducing the occurrence of allergic symptoms in CMA patients [104, 108], future studies should examine the efficacy, dosage, and the best initial exposure period for LGG in CMA patients. Furthermore, while the benefits of LGG are reported consistently across many studies, the underlying mechanisms of LGG or other probiotic strains in immunomodulation remain unsolved. The recruitment of participants in clinical studies was also limited to a population with similar environmental exposures and ethnicity [106]. Since the establishment of the intestinal microbiota is determined by both environmental and genetic factors [19, 20], it is important to examine whether probiotics have the same effect across populations under different environmental and genetic regimes.

Finally, multiple *Lactobacillus* strains may be used in combination to reduce allergic symptoms. Nawaz et al. compared the effects of three newly characterized probiotic strains, *Lactobacillus fermentum* NWS29, *Lactobacillus casei* NWP08, and *Lactobacillus rhamnosus* NWP13 together in a single study using real-time PCR under the same experimental conditions. The probiotic strains together with LGG were given to mice orally and then sensitized with ovalbumin. NWS29 and NWP13 demonstrated immunosuppressive effects by downregulating mRNA expression for IL-4, IL-5, IL-13, and TGF-β [84]. Instead of analyzing the effects of a single probiotic strain in one research project, more investigations studying multiple strains together under the same experimental conditions should be conducted to accurately compare the effectiveness of each probiotic strain. This type of study is also advantageous in that the combinatorial effects of probiotic strains can be analyzed to produce a multi-strain probiotic formula that maximizes the treatment efficacy of immunotherapy.

Mechanisms of Probiotic Actions Remains an Enigma

Although a significant number of studies demonstrate the usefulness of probiotics for treating food allergy, few studies explain how probiotics work on the human immune system. They tend to report only on the changes in principal immune mediators without discussing about causative mechanisms. In addition, most studies do not consider the appropriate administration dosage of different probiotic strains. For example, Thang et al. compared the anti-allergic effects between groups of mice with 5-week and 4-week LGG administrations. They noted that there was no significant improvement in anti-allergic effects in mice after supplementing LGG more than four times without providing an explanation [86]. Similar studies in the future should justify the rationale behind the most appropriate dosage of individual probiotic strains among different experimental groups. In addition, few studies address the efficacy of using probiotic in treating food allergy [109, 110]. The immunomodulatory effects elicited by probiotics are strain-specific, but only a limited number of probiotic strains have been tested [111]. Predicting the efficacy of probiotic strains that have not been studied based on data from other strains may lead to unsafe usage [112, 113]. It has been discovered that probiotics may possess variable characteristics within the same species and interact with the gut environment through different mechanisms [114], so proper selection of a probiotic strain in therapy is crucial [88, 115]. However, regulations regarding the selection of safe probiotics for use in the clinical setting are currently still ambiguous [116]. They have become a popular strategy today to treat not only gastrointestinal diseases, but also atopic dermatitis, urogenital infections, and renal diseases [117] and are widely reported to alleviate allergies in both mice and humans. Nevertheless, Marteau described four undesirable outcomes from probiotic use: (1) systemic infections, (2) deleterious metabolic activities, (3) excessive immune stimulation in susceptible individuals, and (4) antibiotic resistance gene transfer [118]. Liong reported that probiotic translocation rarely occurs in humans. Even if it does occur, harmful manifestations are rarely observed, although serious infections have occurred in immunocompromised patients [119, 120]. Regardless, the risks of using probiotics should not be neglected and need to be investigated thoroughly in animal models before clinical trials. Listing of probiotics confirmed safe by international food safety associations should be made available as soon as possible as well.

Other Anti-Allergic Substances

In addition to probiotics, polyunsaturated fatty acids (PUFAs), antioxidants and vitamin D exhibit anti-allergic effects [121]. PUFAs are highly associated with inflammatory processes; for example ω-6 PUFAs are pro-inflammatory, but ω-3 PUFAs are anti-inflammatory with the ability to influence cytokine production [122]. Vitamins C and E are examples of antioxidants. Besides reducing oxidative stress, antioxidants make dendritic cells resistant to functional and phenotypic changes after stimulation by pro-inflammatory cytokines [123]. This implies the usefulness of antioxidants in inducing tolerance. Vitamin D intake during pregnancy is associated with the expression of immunoglobulin-like transcript (ILT)3 and ILT4 genes in cord blood [124]. While the elevation of mRNA levels of these two genes theoretically promotes immune tolerance, further research is necessary to confirm the immunomodulatory effects of vitamin D [115]. Since many *Lactobacillus* strains were shown to improve allergic symptoms with immunosuppressive effects, further investigations on the treatment of food allergy should focus on the synergistic or additive effects of these anti-allergic substances and probiotics. On the other hand, the use of recombinant probiotics to deliver therapeutic proteins has also been

Table 2 Immunotherapy in food allergies with recombinant probiotics

Probiotic strain	Food allergy and allergen involved	Experimental model	Results	References
Lactococcus lactis	Peanut allergy: Ara h 2 protein in cytoplasmic form (LL1), secreted form (LL2), anchored form (LL3)	C3H/HeL mice	Re-establishment the balance of Th1/Th2 profile; ↑Th1 cytokines at systematic level; ↑ SIgA and Treg at local level	Ren et al. [125]
Lactococcus lactis	Cow's milk allergy: bovine β-lactoglobulin (BLG)	BALB/c mice	Induction of BLG-specific Th1response; ↓ specific IgE responses; ↑ specific IgG2a and IFN-γ	Adel-Patient et al. [126]
Lactobacillus casei	Cow's milk allergy: bovine β-lactoglobulin (BLG)	C3H/HeN mice	↑ IFN-γ; ↓ IL-5 secretion; Absence of BLG-specific IgG1, IgG2a, IgA in fecal samples	Hazebrouck et al. [127]
Lactococcus lactis	Ovalbumin (OVA)	BALB/c mice	↓ Local and systemic OVA-specific T cell response; ↑ IFN-γ and ↓ IFN-γ production in splenocytes reactivated in vitro	Huibregtse et al. [128]
Lactococcus lactis	Cow's milk allergy: bovine β-lactoglobulin (BLG)	BALB/c mice	↓ IgG1 production in serum and bronchoalveolar lavage fluid; ↓ IL-4 and ↑ IFN-γ by BLG-reactivated splenocytes	Cortes-Perez et al. [129]

explored (Table 2). CMA models are now available to deliver protein and DNA by recombinant LAB [130]. Researchers should consider both the correct strain for constructing recombinant LAB for immunotherapy and the route of delivery [129, 130]. Pouwels et al. discovered that *Lactobacillus* is a potential carrier for oral immunization, while Anzengruber et al. recently showed that His-SlpB-AH3a42 fusion protein derived from *Lactobacillus buchneri* surface layer and peanut allergen Ara h 2 could induce Ara h 2-specific IgG antibodies in rabbits and inhibit Ara h 2-specific IgE binding [131, 132]. This indicates that probiotics can be cloned with immunosuppressive genes to treat food allergy through the fusion protein produced by recombinant probiotic bacteria.

Conclusion

As living standards improve in developing countries, emphasis on proper hygiene has deterred transmission of infectious diseases. Unfortunately, a consequence of this practice is the continual rise in allergy prevalence [8, 133]. While hand washing is still considered a good habit to protect us from infectious pathogens, an old Asian proverb supports the special roles that the symbiotic microbiome plays in our gut: "No sickness when eating things that accidentally drop to the floor." Indeed, increasing interactions with animals, nature, and people in general, allows increased exposure to a variety of microbes, thereby, maintaining a healthy gut microbiota and a balanced immune status. Even as new drugs or therapeutics are created to alleviate allergic symptoms or prevent food allergy, one should consider if simply taking commensal microbes that live in the gut, such as probiotics, can serve as an effective treatment or lower the risk for children who develop food allergy due to the absence of a protective immune system [134]. A strong association has been observed between alteration of the microbiota during early life and the prevention of allergic sensitization [101–103]. However, it is not yet clear whether maintaing this "healthy" gut microbiota is enough to induce tolerance to food. Current studies do not provide sufficient data on the most appropriate strains with their respective efficacy and correct dosage. Differences in experimental conditions, bacterial strains, and methodologies used in individual studies also make the results difficult to compare. Nevertheless, many reports show alleviation of allergic symptoms in animal or clinical models after administration of probiotic bacteria. These studies at least provide some promising evidence of how microbiome-modulating therapies can be beneficial, especially later in life. In conjuction with current standard Ag-specific immunotherapy practices, specific tolerance may be induced and the effects long-lasting. More investigations will have to be focused on the safety, efficacy, and dosage of various probiotic bacterial strains in the future. Whatever the treatment may be, by incorporating multiple disciplines in tandem with a highly collaborative and "bench-to-bedside" approach will allow scientists to decipher the immunological mechanisms on how microbiota is regulated in the gut and subsequently, further enhance the prevention, diagnosis, and therapies of food allergy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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