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Preventive effects of *Bifidobacterium lactis* Probio-M8 on ovalbumin-induced food allergy in mice

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ABSTRACT

Food allergy is a significant public health concern globally. Certain probiotics have been found to enhance food allergy by regulating immune-microbe interactions in animal models and patients. However, the effects of *Bifidobacterium lactis* Probio-M8 on food allergy have not been thoroughly investigated. The present study examined the anti-allergic properties of Probio-M8, particularly in relation to immune response and gut microbiota composition. Results demonstrate that oral administration of Probio-M8 effectively mitigated the allergy symptoms triggered by ovalbumin (OVA) by ameliorating the morphological damage in the jejunum, reducing OVA-specific IgE and histamine levels in the serum, and suppressing Th2 cytokines (interleukin (IL) 4 and IL-13) while increasing Th1 cytokines (interferon (IFN) γ) and regulatory T (Treg) cytokines (IL-10 and transforming growth factor (TGF) β1) in the culture supernatants of splenic cells. Furthermore, Probio-M8 effectively altered the diversity and composition of gut microbiota, particularly the relative abundances of *Akkermansia_muciniphila* in OVA-induced mice. Compared to the OVA group, the Probio-M8 group showed a decrease in the relative abundance of *Akkermansia_muciniphila*. In conclusion, Probio-M8 demonstrates the potential to alleviate food allergy by regulating the Th1/Th2 response and modulating gut microbiota, thereby offering a novel therapeutic strategy for patients with food allergy.

1. Introduction

Food allergies are triggered by specific immune mechanisms that arise from exposure to normally innocuous dietary antigens[1]. The increasing incidence of food allergies has become a significant public health issue, with an estimated 5%–10% of individuals in developed countries suffering from food allergies that can impair quality of life[2]. Food allergy can cause skin, gastrointestinal and respiratory symptoms, ranging in severity from mild to life-threatening, even to death[3]. Currently, many treatments are available for food allergies, but most have limitations. For instance, the primary treatment of food allergy is avoidance of foods containing a specific allergen, which may reduce diet quality and diversity[4]. Oral immunotherapy (OIT) is also commonly used, but it typically fails to induce long-term tolerance[5]. Thus, it is necessary to develop novel anti-food allergy therapies.

Food allergy is a complex disease with multiple risk factors, and growing evidence suggests that the composition of the intestinal microbiota plays a causal role in food allergy pathogenesis and is likely interconnected[6-8]. Significant differences in gut microbiota have been captured between healthy individuals and patients with food allergy[9]. For example, the fecal microbiome signatures of children with food allergy differ from those of genetically similar

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non-allergic siblings[10-11]. Although the development of food allergy is related to gut microbiota composition, the exact mechanism is not clear. Some studies have reported that gut microbiota may influence the development of allergic diseases include, but are not limited to: 1) Effects on immune response regulation (such as promoting Foxp3$^+$Treg cell induction and maintaining the Th1/Th2 cell balance); 2) Enhancement or disruption of epithelial barrier integrity; 3) Alteration of its derived metabolites (such as short-chain fatty acids, tryptophan, and secondary bile acids), thereby affecting antigen presentation, allergen penetration, and tolerance induction[12-14]. Taken together, there is a strong relationship between gut microbiota and food allergy. Therefore, the gut microbiome is a logical target for novel strategies to prevent and treat food allergies.

Breast milk is the primary source of nutrition for infants, which contains many essential nutrients and microbial flora that can be transmitted to infants endogenously or by breastfeeding and plays an important role in the maturation and development of the immune system[15]. *Bifidobacterium lactis* Probio-M8, a probiotic strain isolated from healthy human colostrum, has been reported to exhibit positive effects on various health conditions, such as alleviate asthma[16], Alzheimer's disease[17], acute respiratory tract infections[18], alcoholic liver disease[19], coronary artery disease[20], type 2 diabetes[21], postmenopausal osteoporosis[22] and Parkinson's disease[23], and improve growth performance[24]. In addition, from those studies, we found that *B. lactis* Probio-M8 is a well-known probiotic strain exhibiting positive host that could improve immunity, and modulates gut microbiota and its derived metabolites. Many studies have indicated that probiotics can intervene the abundance, diversity, and metabolic activity and function of gut microbiota in food allergy. However, the effects and mechanism of *B. lactis* Probio-M8 on food allergy have not yet to be investigated previously.

In this study, we established an ovalbumin (OVA)-induced allergic model to investigate the impact of *B. lactis* Probio-M8 on experimental food allergy in mice. We analyzed whether *B. lactis* Probio-M8 could relieve allergy symptoms and examined the effect on T cell immune response and gut microbiota. The results of this study seek to provide a new basis for the application of *B. lactis* Probio-M8 in the prevention and treatment of food allergy.

2. Materials and methods

2.1 Probiotic

B. lactis Probio-M8 was provided by the Key Laboratory of Dairy Biotechnology and Engineering, Ministry of Education, Inner Mongolia Agricultural University, China. *B. lactis* Probio-M8 isolated from healthy human colostrum of Han and Mongolian ethnicity in Inner Mongolia.

2.2 Animal

Four weeks-old mice (BABL/c, specific pathogen-free (SPF)) were purchased from the Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China).

Mice were fed with a regular basal diet and tap water ad libitum and kept in a regulated environment (temperature, (25 ± 2) °C; relative humidity, (60 ± 5)%; 12-h light/dark cycle). The Institutional Animal Ethics Committee of Southeast University approved the experimental protocol.

2.3 Induction of food allergy and probiotic administration

All mice were randomly divided into four groups: the negative control (NC), the OVA, the live *B. lactis* Probio-M8 (M8), and the heat-killed *B. lactis* Probio-M8 (HKM8). The experimental period is shown in Fig. 1. The mice of OVA, M8, and HKM8 groups were sensitized by intraperitoneal injection with 50 μg OVA (Sigma-Aldrich, Germany) plus 1 mg of alum (Sigma-Aldrich, Germany) dissolved in 200 μL sterile normal saline on days 0 and 14. All the mice were orally challenged with 50 mg OVA in 200 μL sterile normal saline on days 28, 30, 32, 34, 36, 38, and 40. The NC group received 200 μL sterile normal saline at each sensitization and challenge point. Before the mice were administrated with probiotics, the freeze-dried powder samples (2×10^{11} CFU/g formula) were dissolved in sterile saline water. The heat-inactivated Probio-M8 was obtained by heat treatment at 90 °C for 15 min. During OVA sensitization and challenge point, mice in the M8 and HKM8 groups received M8 and HKM8 orally (2×10^9 CFU/0.2 mL per mouse daily), respectively. The NC and OVA groups were given equal volumes of sterile saline water. The mice were killed on the first day after the final challenge.

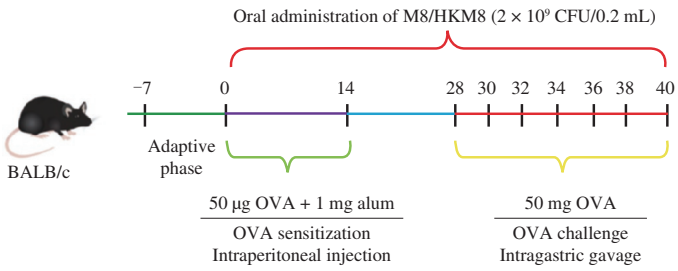

Fig. 1 Experimental schedule for the induction of OVA-mediated food allergy in mice.

2.4 Enzyme linked immunosorbent assay (ELISA) determination

The OVA-specific IgE (OVA-sIgE) and histamine contents in serum were detected using assay kits (MEIMIAN, China) according to the manufacturer's instructions. For cytokine analysis, splenocytes were cultured for 72 hours at a concentration of 2×10^6 cells/mL at 37 °C, 5% CO_2 with 100 mg/mL OVA. Cytokine concentrations in culture supernatants were measured by ELISA kits for interleukin (IL) 4, IL-13, IL-10, transforming growth factor (TGF) β1, and interferon (IFN) γ (CUSABIO, China), according to the manufacturer's instructions.

2.5 Histological analysis

The jejunum tissues of mice were fixed overnight in 4% paraformaldehyde and were subsequently embedded in paraffin. Then, tissues were cut into 5 mm sections and stained with hematoxylin and eosin (H&E) staining to measure the severity of inflammation. The sections were observed using a light microscope at 400 × magnification.

2.6 16S rDNA gene sequencing

The fecal samples of mice were collected and stored at –80 °C. Bacterial DNA was extracted from the fecal samples using the Power Soil® DNA Isolation Kit according to the manufacturer's instructions. After extraction, the 16S full-length primer was designed based on the conservative region 27F-1492R for the target area's polymerase chain reaction (PCR) amplification. Subsequently, the quality control of the resulting sequencing library was performed, and high-quality circular consensus sequencing (CCS) sequences were subjected to processing, including barcode recognition. The generated optimization CCS sequences were then clustered at 97% similarity (USEARCH, version 10.0), and species classification was based on the operational taxonomic unit (OTU) sequence composition. The platforms 16S: Silva database and RDP Classifier platforms were employed for species annotation, taxonomy analysis, and the assessment of gut microbiota diversity.

2.7 Statistical analysis

All data are described as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS 19.0 (SPSS Inc, Chicago, IL), with statistical significance set to $\alpha = 0.05$. One-way ANOVA with the least significant difference (LSD) was used to analyze significant differences.

3. Results

3.1 Probio-M8 alleviates allergic responses in OVA-induced food allergy mice

In this study, an OVA-induced mouse model was established to investigate the effects of live Probio-M8 and heat-killed Probio-M8 on food allergies. Compared to the NC group, mice treated with OVA demonstrated a significant increase in serum OVA-sIgE and histamine levels ($P < 0.001$). M8 treatment, but not HKM8, significantly decreased serum OVA-sIgE and histamine production induced by OVA-sensitization (Figs. 2A and B). Fig. 2C shows typical images of HE-stained jejunum tissue. The mucosal layer, mucosa, submucosa, and muscular layer in the NC group were normal. In contrast, OVA-induced severe histopathological jejunal damage is reflected in destroyed jejunal mucosa, crypt loss, and shorter villus height. However, M8 treatment preserved the integrity of jejunum tissue. Together, these findings imply that live Probio-M8 suppressed the development of illness in mice with an OVA-induced food allergy.

3.2 Probio-M8 suppresses Th2-type responses

Th2 immune response contributes to immune tolerance failure and causes food allergic reactions. Therefore, regulating the T cell immune response may alleviate allergic diseases. In this study, to characterize the systemic T cell responses induced by M8, splenic cells were isolated from the mice of different groups and cultured *in vitro*. After OVA stimulation, the culture supernatants were collected. Compared to the NC group, the OVA group showed increased production of Th1 (IFN-γ), Th2 (IL-4/13), and regulatory T (Treg) (TGF-β1) cytokines, with decreased production of Treg (IL-10) type cytokines, indicating the triggering of inflammation and immune balancing. M8 and HKM8 treatments reduced the concentrations of IL-4 and IL-13 compared to the OVA group ($P < 0.001$) (Figs. 3A and B). Furthermore, oral administration of M8, but not HKM8, significantly increased the release of IL-10, TGF-β1, and IFN-γ (Figs. 3C–E). These results demonstrated that M8 and HKM8 induced Treg-mediated oral tolerance and skewed the immune system towards inflammatory Th1 polarization and away from allergenic Th2 polarization to relieve allergic responses.

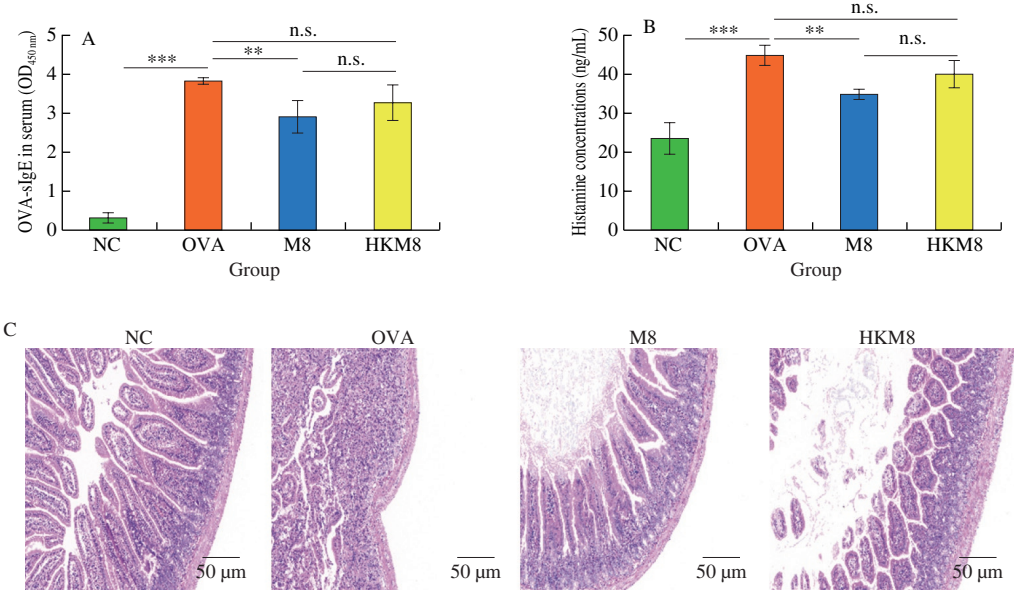

Fig. 2 Effect of *B. lactis* Probio-M8 on the levels of serum OVA-sIgE and histamine, and tissue morphology of jejunum. (A) OVA-sIgE and (B) histamine levels in serum; (C) The pathological sections of the jejunum (HE stained, 20 ×). The results are the mean ± SEM ($n = 3$). $^{**}P < 0.01$, $^{***}P < 0.001$, n.s., not significant.

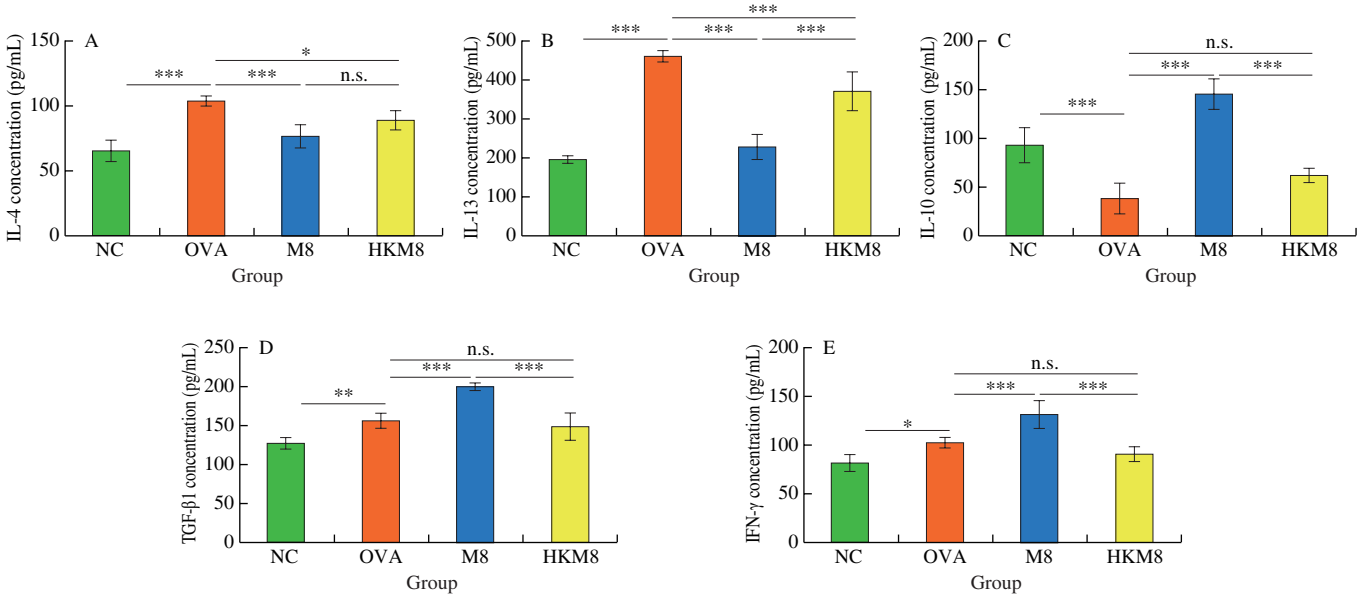

Fig. 3 Effect of *B. lactis* Probio-M8 on cytokine secretions. (A) IL-4, (B) IL-13, (C) IL-10, (D) TGF-β1, and (E) IFN-γ levels in the culture supernatants of splenic cells. The results are presented as the mean ± SEM ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, n.s., not significant.

3.3 *Effect of Probio-M8 supplementation on gut microbiota*

In recent years, numerous studies have demonstrated that gut microbiota dysbiosis are frequently associated with food allergies. Therefore, we postulated that variations in intestinal microbiota among the NC, OVA, and M8 groups were the underlying cause of disparities in clinical features and immunological responses. In this study, the ACE, Chao1, Shannon, and Simpson indexes representing α-diversity for all groups are shown in Figs. 4A–D. The OVA and M8 groups showed almost the same diversity as the NC group in ACE and Chao1 indexes ($P > 0.05$). Shannon and Simpson's indexes indicated a lower α-diversity in the OVA mice's feces than in the NC mice. In contrast, the Shannon index of the M8 group increased significantly more than the OVA group ($P < 0.05$). But M8 had no significant effects on the relative abundances of the Simpson index decreased by OVA. β-Diversity, represented by principal coordinates analysis (PCoA) on the OTU level, is displayed in Fig. 4E. PCoA showed that the microbial community structure significantly differed in the OVA and M8 groups compared with the NC group (Fig. 4E). However, it's worth noting that the NC group is much closer to the M8 group than the OVA group. These findings suggest that OVA treatment induced changes in the gut microbiota, which were alleviated by M8 administration.

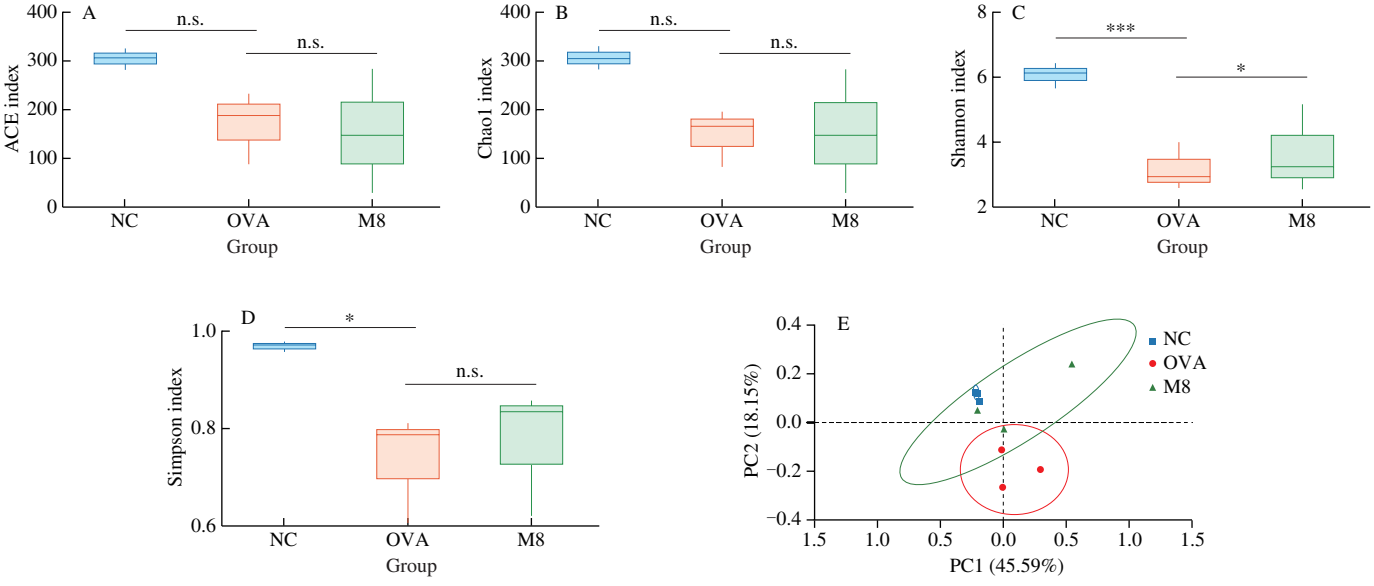

Fig. 4 Effects of SCP *B. lactis* Probio-M8 on the gut microbiota. (A) α-Diversity evaluated from the (A) ACE, (B) Chao1, (C) Shannon, and (D) Simpson indexes; (E) Principal component analysis (PCA) (Unweighted UniFrac); The relative abundance of the top 10 (F) phyla and (G) species. The results are the mean ± SEM ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$, n.s., not significant.

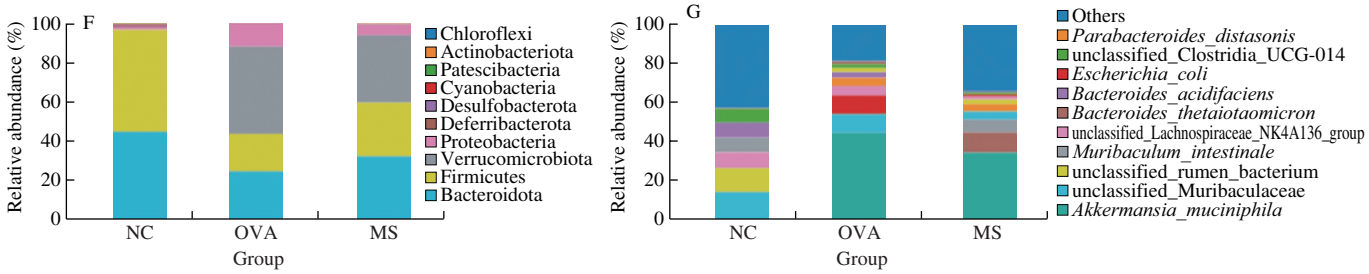

Fig. 4 (*Continued*)

The relative abundance of feces microbiota at the phylum level is presented in Fig. 4F. The most commonly represented phylum was Firmicutes (44.9%), followed by Bacteroidetes (51.6%) in the NC group. In contrast, Verrucomicrobiota (44.3%), Bacteroidetes (25.0%), and Firmicutes (18.9%) were the most commonly represented phylum in the OVA group. Notably, M8 administration could reverse the reduction of the relative abundance of Bacteroidetes (32.5%) and Firmicutes (27.1%) induced by OVA, while decreasing the relative abundances of Verrucomicrobiota (34.3%) compared to the OVA group.

The alterations in the predominant microbiota at the species level are depicted in Fig. 4G. Administration of OVA resulted in a significant increase in the relative abundance of *Akkermansia_muciniphila*, *Bacteroides thetaiotaomicron*, and *Escherichia coli*, while a decrease in the abundance of unclassified_rumen_bacterium was observed when compared to the NC group. However, M8 could reverse these changes to some extent. Particularly noteworthy was the over 600-fold increase in abundance of the mucin-degrading *Akkermansia_muciniphila* induced by OVA, which was reduced by over 169-fold by M8 treatment. The results indicated that M8 could also regulate gut microbiota structure in mice with food allergy.

3.4 The gut microbiota taxa in the feces associated with immune factors

The correlations between the most commonly represented genus and seven immunological variables were analyzed by Spearman's correlation analysis (Fig. 5). The results displayed that the concentration of *Akkermansia_muciniphila* exhibited a positive correlation with OVA-sIgE, histamine, IL-4, and IL-13, implying *Akkermansia_muciniphila* may elevate allergic symptoms and promote Th2-mediated allergic responses. In contrast, *Muribaculum_intestinale* was negatively correlated with histamine, demonstrating that *Muribaculum_intestinale* may alleviate allergic symptoms. Lachnospiraceae_NK4A136_group showed a negative correlation with IFN-γ. Furthermore, unclassified_rumen_bacterium was negatively correlated with histamine, TGF-β1, and IFN-γ. Unclassified_Clostridia_UCG_014 was negatively correlated with TGF-β1 and IFN-γ.

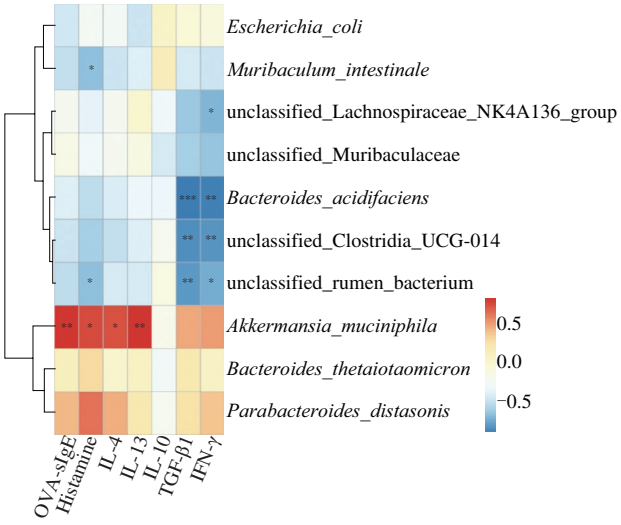

Fig. 5 The Spearman correlation heat map of the relationship between the immunological variable and gut microbiota taxa. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.01$.

4. Discussion

Many studies have reported that gut microbiota plays an important role in food allergy pathogenesis. Moreover, there has been increasing research on the potential of probiotics to ameliorate food allergy by modulating the composition and function of the microbiota[25-27]. A previous study found that patients with food allergy history consuming Probio-M8 showed a higher increase in the concentration of IL-10 and IFN-γ and had a lower concentration of IL-4 as compared to the placebo group[18], indicating that Probio-M8 possesses anti-allergic potential. In the present study, the alleviating effects of Probio-M8 on the OVA-induced allergic model were investigated, and the impact of immune response and gut microbial were explored (Fig. 6).

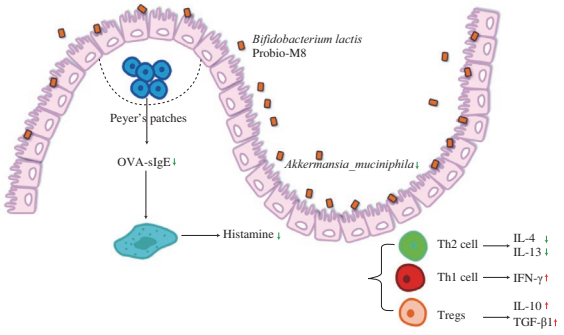

Fig. 6 M8 may alleviate OVA-induced food allergy by balancing the Th1/Th2 ratio and regulating the gut microbiota.

A typical symptom of a food allergy is the production of specific IgE antibodies at high levels[28]. Thus, suppressing the elevation of the allergens-specific is crucial for alleviating the food allergy response. In the study, the level of OVA-sIgE in the OVA group was significantly higher than that in the NC group, indicating the efficacy of our established allergic mice model. In addition, M8, but not HKM8, could decrease the level of OVA-sIgE caused by OVA. Histamine also is a critical mediator that causes allergic symptoms in food allergy. It is well known that histamine released from mast cells plays a vital role in the induction of allergic symptoms in food allergy[29]. The supplement of M8 significantly decreased the histamine level in serum. However, no significant difference was seen in the concentration of histamine between the OVA and HKM8 groups. The results suggested that live Probio-M8 has anti-allergic effects.

Food allergy is generally considered a disease mediated by impaired Th1/Th2 immune response balance[30]. In most cases, Th2-type response skewing leads to high allergens-specific IgE antibodies[31]. Many studies have shown that probiotic supplementation can enhance the Th1/Th2 response balance in a mouse model of food allergy, resulting in a reduction in allergic reactions[32-33]. Consistent with these findings, our study demonstrated that oral administration of M8 attenuated the release of Th2 cytokines (IL-4 and IL-13) from splenocytes and elevated the production of IFN-γ (a Th1 cytokine) as well as IL-10 and TGF-β1 (Treg cells). The result suggested the anti-allergic functions of M8 by suppressing Th2-type response and expanding Treg cells.

The interaction between probiotics and intestinal microbiota is vital for immune system maturation and tolerance acquisition. In this study, there was a significant increment in the abundance of the Verrucomicrobiota at phylum by OVA-induced. Additionally, *Akkermansia_muciniphila*, which belongs to Verrucomicrobiota, was significantly upregulated in the OVA group. In contrast, the abundance of *Akkermansia* was lower in patients with food allergy than in healthy individuals[34]. *Akkermansia_muciniphila*, a Gram-negative, non-motile anaerobic bacterium specialized in the degradation of mucin[35]. *Akkermansia_muciniphila* is considered to be a next-generation beneficial microbe[36], due to its association with intestinal health and improved metabolic status in obesity, type 2 diabetes, and inflammatory bowel disease subjects[37]. However, excessive *Akkermansia_muciniphila* may leading to intestinal leakage and subsequent allergic reactions. Indeed, a previous study showed the abundance of the mucin-degrading *Akkermansia_muciniphila* was 8-fold increased by heme, which facilitates the heme-induced hyperproliferation by opening the mucus barrier and might eventually lead to colorectal cancer[38]. M8 administration decreased the abundance of *Akkermansia_muciniphila*, maintaining the mucus barrier preventing OVA-induced allergy.

In the study, the correlation between the immunological factor and gut microbiota was further explored. The results revealed a positive correlation between *Akkermansia_muciniphila* and OVA-sIgE, histamine, and Th2 cytokine (IL-4 and IL-13). The findings highlight the extent to which gut flora mediates the link between the immune system and food allergy.

5. Conclusion

In conclusion, the results showed that food allergy symptoms could be alleviated by affecting epithelial barrier integrity, immunoregulation and gut microbiota by Probio-M8. The supplementation of Probio-M8 might be an effective strategy to against food allergy.

Declaration of competing interest

The authors declare there is no conflict of interest.

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Data availability

The 16S rRNA sequencing data have been deposited in the NCBI Sequence Read Archive (SRA) repository under BioProject accession number PRJNA932865.

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