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Gut microbial composition and metabolites influence serum IgA homeostasis

Xiaobo Zhang[a], **Han Xiao**[a], **Yan Wang**[a], **Zhifeng Pan**[b], **Guangshu Hao**[b,*]

[a] Cuiying Biomedical Research Center, The Second Hospital & Clinical Medicine School, Lanzhou University, Lanzhou, Gansu 730030 China

[b] Department of Pathology, Gansu Provincial Maternity and Chlid-Care Hospital, Lanzhou, Gansu 730050 China

[*]Corresponding author, e-mail: hgs199099@126.com

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ABSTRACT: Immunoglobulin A (IgA) is a key regulator of gut microbiota homeostasis, shaping both microbial community composition and metabolic output to maintain host-microbe symbiosis. However, the detailed mechanisms underlying how IgA modulates microbial diversity and coordinates the production of metabolites critical for immune and metabolic fitness remain poorly investigated. We combined clinical sampling, murine models, and multi-omics analyses to dissect these interactions. Specifically, fresh fecal samples were collected from adult volunteers and analyzed for gut microbiota diversity using 16S rDNA sequencing, while serum IgA concentrations were measured via ELISA. Subsequently, a high-IgA (HIgA) mouse model was established to validate the association between *Prevotella* and serum IgA level, which confirmed that metabolites derived from *Prevotella*, rather than viable bacteria or culture medium components, dominantly reduce serum IgA concentrations. Furthermore, metabolomics and proteomics analysis identified critical metabolites influencing IgA expression. Gut microbiota diversity was significantly reduced in the HIgA group, with a robust inverse correlation between *Prevotella* abundance and serum IgA levels. Metabolomic analysis further identified 596 differentially expressed microbial metabolites, with fatty alcohols, purines, and their derivatives emerging as key regulators of IgA levels. Additionally, pathways related to penicillin metabolism and cholinergic drugs, as well as the key neural signaling proteins UNC13B and CNTNAP1, were implicated in IgA modulation. These findings highlight the strong link between gut microbiota composition and serum IgA regulation, particularly the negative correlation with abundance of *Prevotella*, which suggests considerable potential for developing targeted immunotherapies based on microbiota-driven immune modulation.

KEYWORDS: gut microbiota, serum IgA, *Prevotella*, metabolomics, proteomics

INTRODUCTION

Immunoglobulin A (IgA) is the predominant antibody at the intestinal mucosal surface, where it plays a key role in protecting against pathogens and toxins. By binding to these harmful agents, IgA prevents their adhesion to intestinal tissues [1, 2]. Additionally, IgA helps trap microorganisms in mucus, facilitating their clearance through peristalsis. Recent studies have shown that IgA also plays a crucial role in regulating the gut microbiota, which consists of trillions of microbes residing in the intestine. Disruptions in IgA can lead to dysbiosis, where the balance of gut bacteria is disturbed [3]. For instance, in IgA-deficient mice, this imbalance manifests as altered microbial diversity and composition, characterized by the overgrowth of segmented filamentous bacteria in the intestine, which in turn triggers spontaneous enteritis [2, 4]. Beyond restraining microbial overgrowth, mucosal IgA actively shapes the intestinal environment by mediating immune responses through M cells. IgA also interacts with the colonization factor MAFF in *Bacteroides thetaiotaomicron*, helping to prevent excessive inflammation and mediating the adherence of *Bacteroides fragilis* to intestinal epithelial cells [5–7]. Moreover, IgA profoundly influences the population levels of *Bifidobacterium*, *Lactobacillus*, and Gamma Proteobacteria, while also promoting the development of *Escherichia coli* biofilms [8, 9].

Conversely, metabolites produced by the gut microbiota stimulate macrophages and intestinal epithelial cells to release cytokines that enhance IgA production in B cells [10]. For instance, short-chain fatty acids (SCFAs) boost intestinal IgA production through the retinoic acid (RA) and GPR43 signaling pathways [11–14]. In addition, SCFAs lowered inflammation risk, and improved gastrointestinal function [15]. Acetate, a major SCFA, further induces Aldh1a2 expression, converting vitamin A into its active form, retinoic acid, which promotes IgA production [16]. Beyond SCFAs, polyunsaturated fatty acids (PUFAs) are vital for brain development, cognitive function, inflammation regulation, and immune response [17, 18]. Reduced PUFA levels in patients with IgA nephropathy (IgAN) are associated with increased kidney inflammation and fibrosis [19]. Long-chain n-3 PUFAs in fish oil, with their anti-inflammatory effects, can slow kidney function decline in IgAN patients. Together, these findings suggest that gut microbiota metabolites and PUFAs are essential in regulating IgA expression in the intestine and maintaining kidney health [20].

In this study, we performed a diversity analysis

of human gut microbiota samples. Following this, we conducted an in-depth investigation into the effects of the *Prevotella* genus and its metabolites on serum IgA levels in mice using a high-IgA (HIgA) mouse model. Our comprehensive study was further strengthened by metabolomics analysis, offering a multifaceted approach to explore the complex interactions between gut microbiota and immune responses. In summary, this research elucidates the dynamic interactions between intestinal mucosal IgA and the gut microbiota, identifying IgA-sensitive bacteria and their abundance shifts associated with IgA expression. It also deciphers the molecular interactions between IgA and bacterial metabolites, revealing significant correlations with secondary metabolites produced by the microbiota. This study advances our understanding of gut microbiota's role in IgA regulation and provides a foundation for further investigation into its regulatory mechanisms.

MATERIALS AND METHODS

Main consumables and animals

The reagents and consumables used are all commercial products, including Human IgA ELISA Kit (Abcam, UK, Ab196263-1x96 tests), Mouse IgA ELISA Kit (Abcam, Ab157717-1x96 tests), Columbia blood agar plate (Oxoid, UK, PB0123A), Brain-Heart Infusion broth medium (BHI, Solarbio, China, B8130), Bovine Serum Albumin (BSA, Aidisheng, China, ADS218C0), carbon tetrachloride (CCl_4, Sigma, USA, 65805I), castor oil (Abmole, USA, M31309-100mL), lipopolysaccharide (LPS, Sigma, L2880-10MG), and incomplete Freund's adjuvant (Sigma, F5506). MBP-20PADSA, maltose-binding protein-20-Peptide cellular Antigen Determinant of the *Staphylococcus aureus* membrane surface, were meticulously synthesized by Abcam (Beijing) Biotechnology Co., Ltd., based on publicly available protein sequence data (NVGGDNVDIHSIVPVGQDPH) from the literature [21]. For animal experiments, the strain of specific pathogen free (SPF) mice used was Balb/c (sex: male, age: 5–6 weeks, weight: 20 ± 2 g, $n = 6$ per group), which were purchased from the Veterinary Institute at the Chinese Academy of Agricultural Sciences.

Collection and preparation of samples

Fecal and blood samples were randomly collected from healthy volunteers and adult IgAN patients. In total, this study included a total of 39 healthy volunteers and 13 patients with IgAN. Among them, 13 healthy volunteers and 9 patients were within the age range of 18 to 50 years. Samples were selected based on the concentration of serum IgA (for patients, C(IgA) $\geqslant$ 3.80 mg/ml; for healthy individuals, 0.80 mg/ml $\geqslant$ C(IgA) $\geqslant$ 3.80 mg/ml), and a portion of the corresponding fecal samples was immediately placed in liquid nitrogen for 15 min, then transferred to −80 °C for storage. Another portion was placed in a microbiological anaerobic incubator (BACTRON anaerobic workstation, USA) for at least 1 h to establish oxygen equilibrium. In the anaerobic environment, the samples were weighed and mixed at a ratio of 0.1 g of sample to 0.5 ml of sterile PBS buffer, and finally filtered through a membrane with a pore size of 40 μm to collect the filtrate for later use.

Isolation, cultivation, and identification of intestinal bacteria

An appropriate amount of the aforementioned filtrate was inoculated onto Columbia blood agar plates, then cultivated at 37 °C for 48–72 h. Subsequently, single colonies were picked and transferred to BHI liquid medium for continued incubation at 37 °C. After a certain period, the monoclonal and culture supernatant was collected. The 16S rRNA sequencing for the single colonies was conducted by Entrust Beijing Tsingke Biotech Co., Ltd., China. The supernatant was stored at −20 °C.

Construct a high-expression IgA mouse model

All protocols were approved by the licensing committee of Second Hospital & Clinical Medical School, Lanzhou University (Approval number D2023-218), Lanzhou, China, in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no.85-23, revised 1996). All methods involved in the animal experiments were carried out in accordance with relevant guidelines and regulations (ARRIVE guideline (https://arriveguidelines.org).

Mice aged 5–6 weeks were selected. In the early stages of our study, the mice were immunized with either MBP-20PADSA or BSA via intraperitoneal injection [21–23]. The grouping and immunization procedures are described in Table 1 and Fig. 3, with six mice in each group. For the MBP-20PADSA induction model, MBP-20PADSA serves as the specific immunogen to induce sustained high serum IgA levels and IgAN-like pathological changes, while incomplete freund's adjuvant (IFA) acts as an adjuvant to form an immune depot, slow antigen release, and enhance the humoral immune response against the target antigen. For the BSA-based induction model, the high-IgA (HIgA) mouse model was established using modified protocols. Briefly, BSA was administered by intragastric gavage every other day (800 mg/kg) as a persistent antigen to trigger chronic mucosal immune activation and sustained serum IgA overproduction. A mixture of CCl_4 and castor oil (1:5) was injected subcutaneously once weekly to induce mild hepatic impairment, thereby reducing the clearance of circulating IgA and immune complexes. LPS (50 μg) was injected intravenously twice at weeks 6 and 8 to enhance systemic innate immune responses, promote B-cell IgA class switching, and exacerbate renal mesangial injury.

In subsequent model experiments, BSA was selected as the primary adjuvant for immunizing mice. In the later stages of model construction, collect the blood from the mouse's tail vein and detect the IgA content in the mouse's blood by ELISA. When the IgA content is significantly higher than that of the control group and can be maintained in a stable state, we consider the model construction successful.

Effect of gut microbiota cultures on serum IgA levels

The experimental design allocated the mice into 5 groups: HIgA (sterile PBS buffer), IB (BHI bacterial medium containing inactivated bacteria), AB (BHI bacterial medium containing active bacteria), M (metabolites of bacterial culture obtained by filtration through a 0.22 μm sterile filter membrane), and BF (bacterial culture fluid containing active bacteria). All mice underwent gavage administration, which were administered under conditions of a 4-h fast both before and after the procedure. The infusions were conducted once every 3 days, with each dose being 0.10 ml of a suspension containing a concentration of 10^9 ($1 \pm 5\%$) CFU/ml. The intervention lasted for approximately 24 days, commencing during the 7th to 8th week of the model establishment phase.

Multi-omics analysis of murine intestinal content

After successfully constructing the model, mice were anesthetized by intraperitoneal injection of pentobarbital sodium (1% solution), euthanized by cervical dislocation, and samples of their intestinal contents were collected. The intestinal content samples were entrusted to Shanghai Meiji Biomedical Technology Co., Ltd., China, for non-targeted metabolomic and proteomics analysis.

For 16S rDNA sequencing, microbial diversity was analyzed using the Shannon index, and intergroup comparisons were performed using t-tests. For differential metabolite identification, $|\log_2 \mathrm{FC}| \geqslant 1$ and $p < 0.05$ were used as primary thresholds. Key metabolites were further screened with $|\log_2 \mathrm{FC}| \geqslant 1$ and $p < 0.001$, in accordance with conventional standards for untargeted metabolomics.

Data statistical analysis

This study analyzed differences between sample groups using T-tests and parametric tests. No significant differences were found when p-values were greater than 0.05; p-values of 0.05, 0.01, and 0.001 indicate significant, highly significant, and extremely significant differences, respectively. We denote the level of significance with asterisks: * for significant, ** for highly significant; and ***/**** for extremely significant.

RESULTS

Analyzing gut microbiota

Diversity profiling of the gut microbiota revealed that *Bacteroides*, *Faecalibacterium*, *Roseburia*, *Prevotella*, and *Megamonas* were the dominant genera in the samples, collectively accounting for 61.68% of total abundance (Fig. 1A). Additionally, the Shannon diversity index of fecal microbiota in the patient group (Pts.) was much lower than that in the healthy control group (HC), showing a highly significant difference ($p < 0.001$) (Fig. 1B).

Based on clinical examination diagnostic criteria (the normal serum IgA concentration range for healthy adults is 0.80–3.80 mg/ml), this study selected fecal and blood samples from 25 volunteers, categorizing them into two groups (Fig. 1C): The HC with levels ranging from 0.80 to 3.80 mg/ml (16 volunteers), and the Pts. with levels exceeding 3.80 mg/ml (9 volunteers).

Correlation between gut microbiota abundance and IgA concentrations

Species composition analysis showed that among the dominant species (TOP 20), there was no significant difference in species composition between the HC and Pts. groups; however, the relative abundances difference of some genus was relatively significant ($p < 0.05$; Fig. 2A,B). Among the taxa with significant differences in species abundance between groups at the genus level (Fig. 2C), the abundance of *Prevotella*, *Phascolarctobacterium*, and *Blautia* shows a negative correlation with serum IgA levels. *Prevotella* shows the strongest negative correlation, with a correlation coefficient (r) of 0.732. The species abundance of *Lactobacillus*, *Ruminococcus*, and *Alistipes*, on the other hand, shows a positive correlation with serum IgA levels, with *Alistipes* having the highest correlation coefficient of 0.273.

In conclusion, the analysis of the correlation between species abundance and serum IgA levels has revealed a close association between serum IgA levels and the structure of the intestinal microbiota. Notably, *Prevotella* stands out among dominant species with its significant negative correlation with serum IgA levels. This insight has directed our research focus, prompting us to investigate the role and functionality of *Prevotella* in animal models.

Construction and efficacy evaluation of the HIgA mouse model

Male SPF Balb/c mice aged 4–5 weeks were used to establish a HIgA mouse model by induction with MBP-20PADSA or BSA (Table 1, Fig. 3). Model evaluation (Fig. 4A) demonstrated that both approaches effectively elevated serum IgA levels compared with HC and PBS controls ($p < 0.001$). However, the BSA-induced HIgA model exhibited a more pronounced

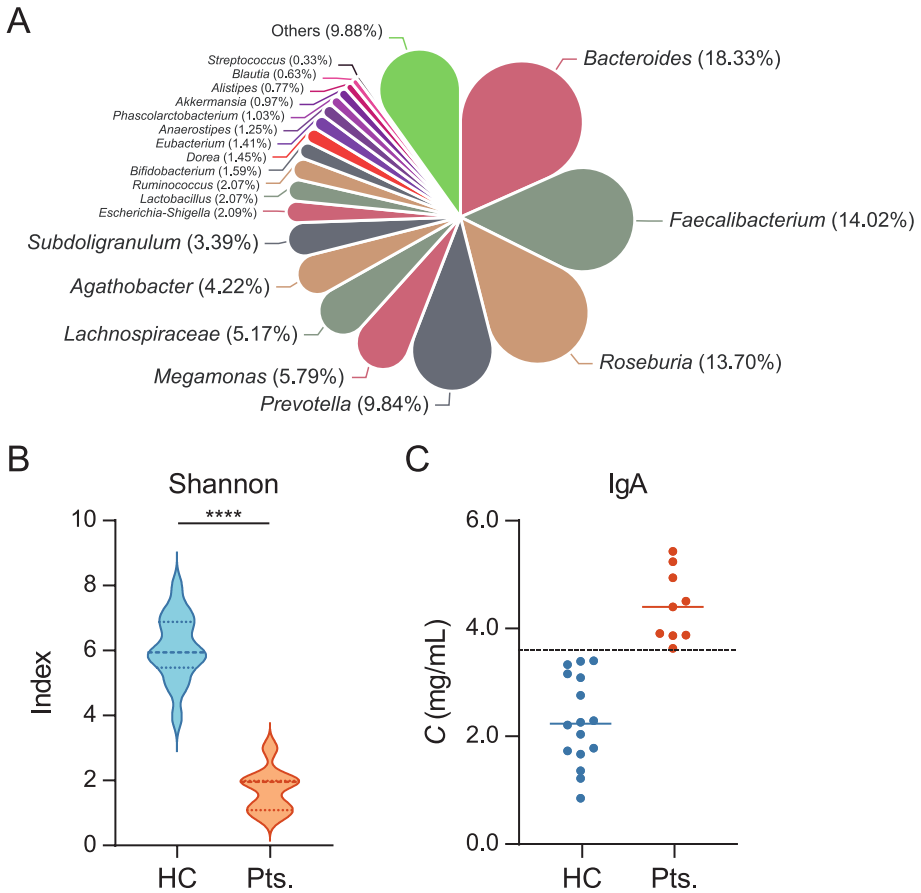

Fig. 1 Human gut microbiota composition, alpha diversity, and association with serum IgA levels. (A) Pie chart showing the composition of human gut microbiota. (B) The Shannon diversity index for gut microbiota samples from the HC and Pts. Groups shows a significant difference in microbial diversity, with a statistically significant difference between the two cohorts (****, $p < 0.0001$). (C) Based on clinical examination diagnostic criteria, the normal serum IgA concentration range for healthy adults is 0.80–3.80 mg/ml. The 25 volunteer samples were categorized into two groups based on their serum IgA concentrations.

Table 1 Grouping of HIgA mouse model construction.

Group	HC	PBS	MBP-20PADSA	BSA
1	+	−	−	−
2	−	+	−	−
3	−	−	+	−
4	−	−	−	+

HC denotes a group of healthy mice that received no specific treatment, only standard feeding. The PBS group (control) received intraperitoneal injections of PBS under consistent feeding conditions. The MBP-20PADSA and BSA groups, serving as experimental groups, received intraperitoneal injections of specific inducers. + indicates the selected treatment methods, and − denotes those not chosen.

increase in serum IgA, together with greater stability and consistency, and achieved these features within 12 weeks, whereas the MBP-20PADSA model required more than 20 weeks. Consequently, considering the efficiency and reliability of the model, we have selected the BSA-induced HIgA model for functional verification analysis.

During the model establishment, the isolation and screening of *Prevotella* were performed simultaneously. A representative bacterial monoclonal colony is shown in Fig. 4B. The functional validation of the model, as illustrated in Fig. 4C, reveals that under conditions characterized by elevated IgA levels in mouse serum, gavage administration of either active bacterial suspensions (AB group), sterile metabolites (M group), or a combination of both (BF group), significantly reduced serum IgA levels. The AB group is defined by its use mixture of active bacterial and sterile BHI medium, whereas the M group comprises metabolites derived from bacterial culture after filtration through a 0.22 μm sterile filter membrane. In contrast, the impact of inactivated bacterial suspension (IB group), which was also prepared with fresh, sterile BHI medium, on serum IgA levels in mice is found to be negligible. It is particularly noted that in the treatment groups containing active gut bacterial metabolites, the down-regulation of IgA levels in mouse serum was more pronounced

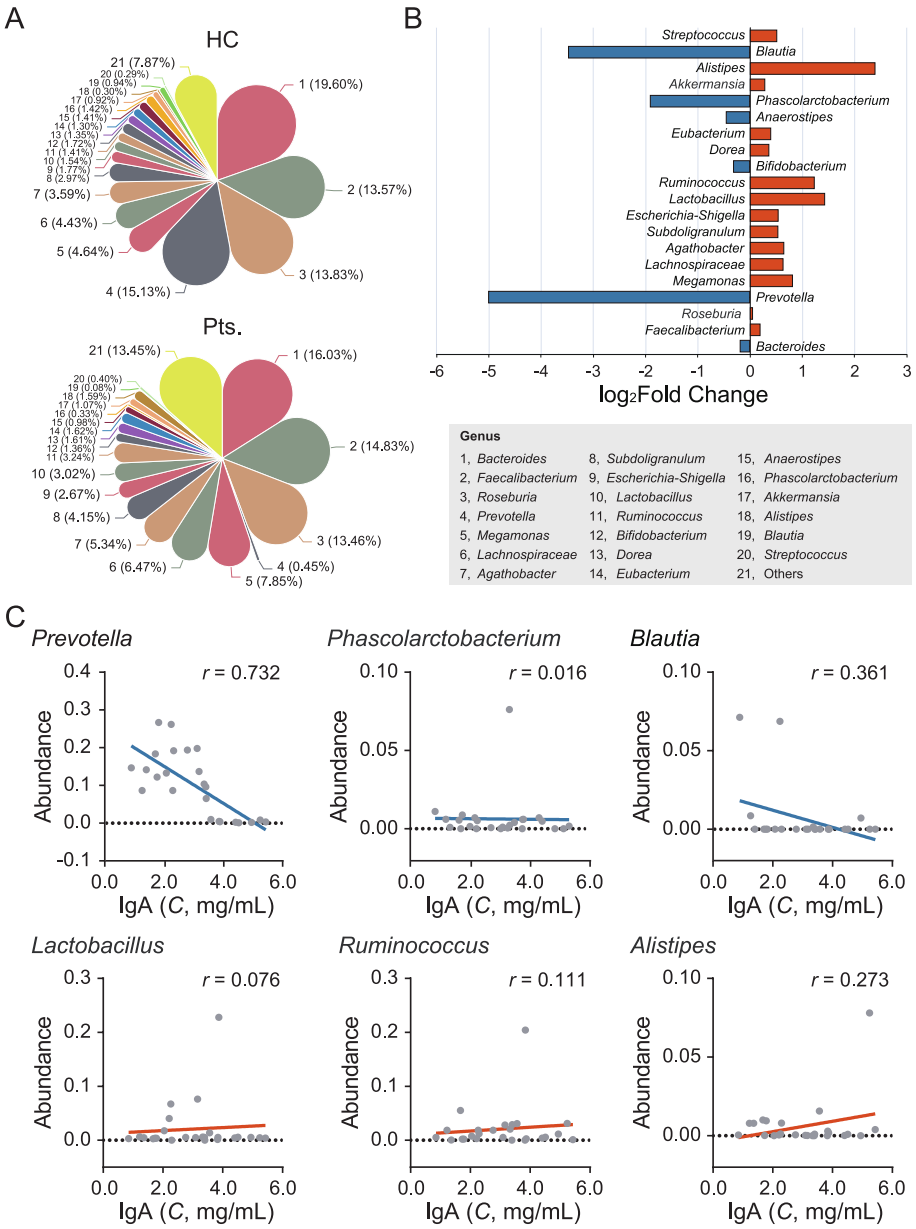

Fig. 2 Dominant genus-level species abundance and serum IgA correlation. (A) Pie chart showing the gut microbiota composition of HC and Pts. group. (B) Fold change in dominant species (Pts. vs. HC). (C) Correlations between genus abundance and serum IgA levels ($|\log_2 \mathrm{FC}| > 1$). The graph illustrates the correlation, denoted by '*r*', with serum IgA levels on the X-axis and microbiota abundance on the Y-axis. A positive '*r*' value signifies a direct correlation, whereas a negative '*r*' indicates an inverse relationship, and the strength of the correlation is represented by the absolute value of '*r*', with larger values suggesting a stronger link.

($p < 0.0001$).

This finding further confirms that the substances primarily responsible for the reduction in IgA levels are the metabolic products of the *Prevotella* strain, rather than the live bacteria themselves or the components of the culture medium. In subsequent studies, we will conduct metabolomic and proteomics analyses of fecal samples from mice, providing a solid foundation for a deeper understanding of the functional metabolism of the intestinal microbiota.

Multi-omics analysis reveals key molecules and pathways

HIgA mice were deprived of water and fasted for 4 h, and then euthanized by the cervical dislocation method. The contents of the cecum were collected into a 2.0 ml aseptic centrifuge tube, and 0.2 g collected for each mouse. The samples were immediately

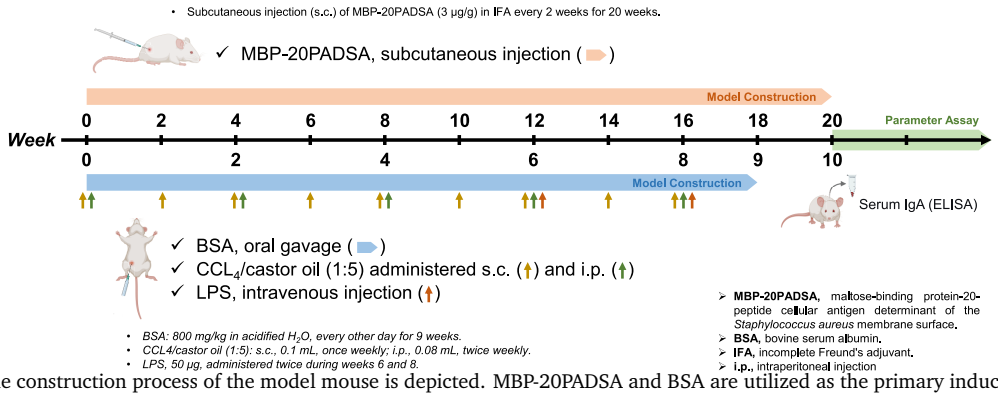

Fig. 3 The construction process of the model mouse is depicted. MBP-20PADSA and BSA are utilized as the primary inducers for the establishment of the model. In each step of the process, six male Balb/c mice are employed.

flash-frozen in liquid nitrogen for 15 min, labeled and then transferred to −80 °C for 24 h. Untargeted metabolomics and proteomics analyses of cecal contents were subsequently performed by Shanghai Meiji Biomedical Technology Co., Ltd.

In the differential volcano plot (Fig. 4D), the metabolomic analysis revealed significant differences in the expression levels of 596 intestinal microbial metabolites between the TEST and PBS groups ($p < 0.05$), accounting for 4.51% of the total metabolites. Specifically, 395 metabolites were upregulated and 201 were downregulated, constituting 66.28% and 33.72% of the significantly different metabolites, respectively. Through further screening with a fold change threshold (Fold Change, FC) of 2 (FC $\geqslant$ 2 or FC $\geqslant$ 0.5), we identified 12 upregulated intestinal bacterial metabolites, specifically fatty alcohols/purines, fatty acyl glycosides, indolecarboxylic, phenylpyruvic acid derivatives, flavonoids and stilbenes; as well as 5 downregulated metabolites, specifically purines and purine derivatives, amino acids/peptides/analogues. The largest fold changes were observed in fatty alcohols/purines (53.167) and purine derivatives (0.235) among metabolites with a clear HMDB subclass. These results suggested that fatty alcohols and purines and purine derivatives may be key metabolites regulating the expression levels of serum IgA.

KEGG enrichment analysis (Fig. 4E) revealed significant differences in the enrichment levels of metabolites from 10 pathways between the HC and HIgA groups. Particularly, the lysine degradation and arginine biosynthesis pathway showed the highest enrichment of intestinal bacterial metabolites, while in terms of functional regulation, the penicillin pathway and the cholinergic and anticholinergic drugs pathway tend to be upregulated and downregulated, respectively. Differential protein expression analysis further identified 30 signature proteins that showed highly significant differences between groups ($|\log_2 \mathrm{FC}| > 1$, $p < 0.001$; Fig. 4F). Among them, KRT82, KRT86, and UNC13B were upregulated proteins, while all others were downregulated. Notably, UNC13B (unc-13 homolog B) and CNTNAP1 (contactin associated protein 1), which are related to nerve signal transmission speed, showed the most significant changes among upregulated and downregulated proteins, with fold changes of 2.391 and 0.210, respectively.

Based on these findings, it is suggested that fatty alcohols, purines, and purine derivatives may be the key intestinal microbial metabolites influencing serum IgA expression, while the penicillin pathway and the cholinergic and anticholinergic drugs pathway may represent critical signaling pathways in this regulatory process. In addition, UNC13B and CNTNAP1 are key proteins that influence how efficient signals are transmitted.

DISCUSSION

The profound and multifaceted interplay between the human immune system and the rich tapestry of the gut microbiota continually unearths novel insights into the frontiers of health and disease. In this study, we investigated the relationship between serum IgA levels and the gut microbiota to elucidate underlying regulatory mechanisms. This exploration provides a foundational framework for understanding the interaction between the immune system and the gut microbiota. Our findings indicate that, among dominant species, the abundance of *Prevotella* bacteria shows a significant negative correlation with serum IgA levels. A primary factor for the decrease in IgA levels, as further validated in animal models, is the metabolites produced by *Prevotella* strains, rather than the live bacteria or the medium's components.

Mechanistically, serum IgA reduction by *Prevotella* intervention is mediated via a microbe-metabolite-host signaling axis. *Prevotella* shows a strong negative correlation with serum IgA and reduces IgA levels through its secreted metabolites rather than bacterial cells or medium components. Using metabolomic analysis, we identified fatty alcohols, purines, and their derivatives as key intestinal microbial metabolites that regulate serum IgA expression. KEGG enrichment further demonstrated that the penicillin-associated metabolic

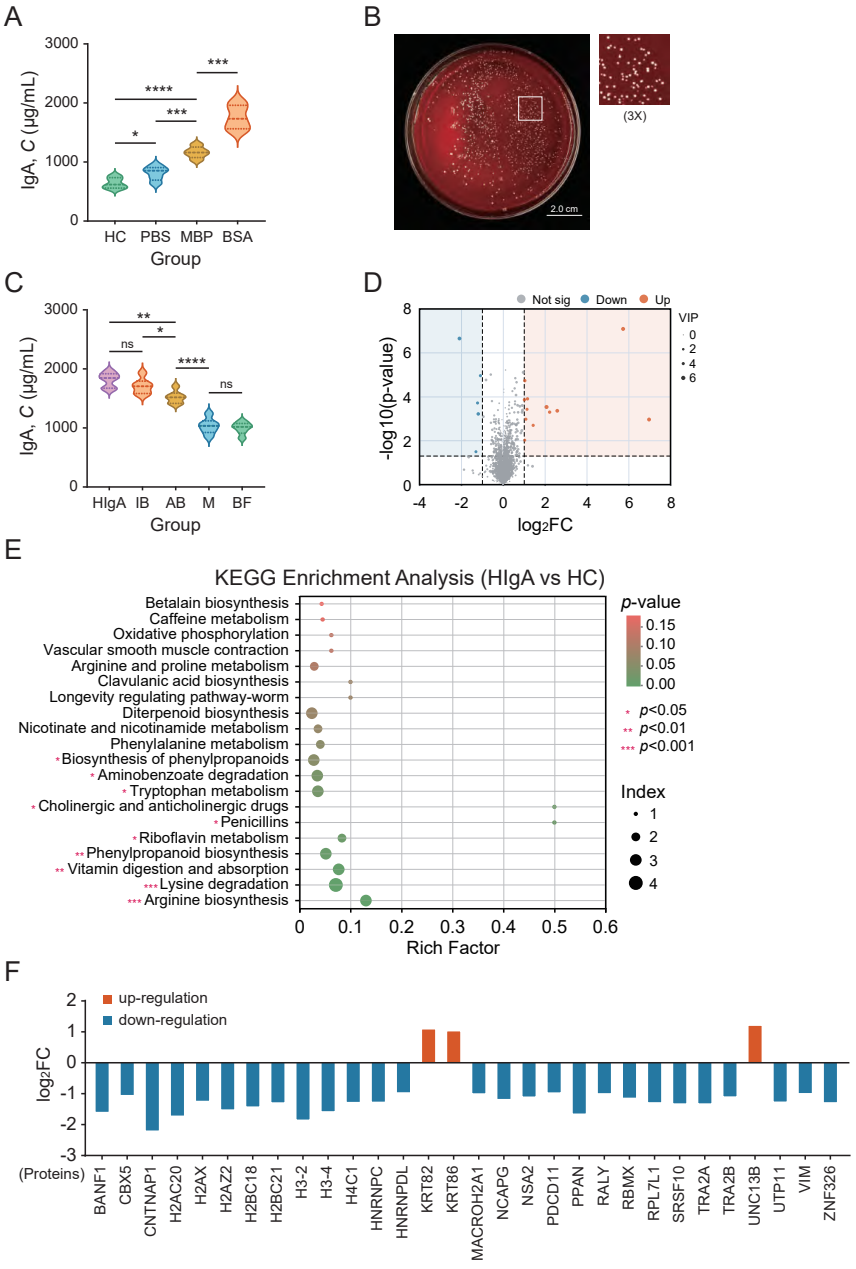

Fig. 4 Evaluation of a High-IgA mouse model and the effect of *Prevotella* intervention on serum IgA and gut markers. (A) Evaluation of the HIgA mouse model. (B) Photograph of a *Prevotella* colony exhibiting monoclonal morphology on a Columbia blood agar plate. (C) Effect of *Prevotella* on mouse serum IgA concentration. Data shown are from day 21 of the intervention. (D) Volcano plot of differentially expressed metabolites. (E) KEGG pathway enrichment analysis of differential metabolites. Bubble size reflects metabolite enrichment ratio, while bubble color represents the enrichment significance (p-value). (F) Log2 fold change of differential proteins in gut contents ($|\log_2 \mathrm{FC}| > 1$).

pathway and cholinergic/anticholinergic pathways are critically involved in this regulatory process, while proteomics revealed UNC13B and CNTNAP1 as key dysregulated neural-immune signaling proteins in HIgA states. Together, these findings delineate a molecular cascade whereby *Prevotella*-derived metabolites modulate metabolic pathways and neuro-immune crosstalk to restrain serum IgA production.

The field of gut microbiota research is rapidly gaining momentum, capturing global attention. This

complex community of microbes is crucial for maintaining intestinal health, facilitating digestion, and supporting nutrient absorption. It is also instrumental in the management of critical diseases, including intestinal inflammation, obesity, diabetes, and autoimmune disorders. Previous research underscores its vital role in fostering a robust intestinal immune system [24, 25]. The gut microbiota's interaction with the host is profound, affecting mucosal balance through the synthesis of metabolites, modulation of immune responses, and regulation of host gene expression.

According to existing literature, evidence suggests that acetate, a SCFA, is pivotal in B cell IgA class switching and IgA production, with the RA signaling pathway playing a significant role in these processes [16]. The cholesterol metabolite 25-hydroxycholesterol has been identified as a regulator that restricts IgA plasma cell differentiation in the intestinal mucosa by inhibiting SREBP2 activation in germinal center B cells [26]. *Bacteroides*, a key bacterial strain in gut microbiota research, is recognized for its role in enhancing intestinal IgA levels and bolstering mucosal immune function through the upregulation of polymeric immunoglobulin receptor (PIgR), BAFF, and AID [10]. Furthermore, *Lactobacillus*, *Bifidobacterium*, and other beneficial bacteria are known to enhance host immune function by modulating immune responses, promoting regulatory T cells (Tregs), and reducing the levels of pro-inflammatory cytokines [27].

Recent studies have revealed that carotenoids, along with their metabolite RA, stimulate immune system responses via the RAR/RXR nuclear receptor pathway [28, 29]. Notably, research has shown that supplementing the diet of pregnant mice with β-carotene (at a dosage of 50 mg/kg) from the onset of gestation through postnatal day 14 leads to a marked increase in IgA expression in both the intestinal tract and serum of their progeny [30, 31]. It is also noteworthy that mice exhibit a significantly higher efficiency in converting β-carotene into vitamin A compared to humans [32]. Astaxanthin and RA have emerged as potent regulators of IgA expression. Animal studies have illustrated that the dietary inclusion of these compounds can notably reduce the *Helicobacter pylori* load within the mouse gastrointestinal tract and mitigate intestinal mucosal inflammation [33]. Furthermore, clinical studies have confirmed that supplementation with astaxanthin or RA in humans can lead to a significant decrease in blood neutrophil levels, while concurrently enhancing IgA expression in the gastrointestinal tract and serum [34].

In this study, we set out to scrutinize the variations in gut microbiota composition between healthy controls and individuals exhibiting elevated serum IgA levels, utilizing clinical samples for our analysis. Through meticulous correlation analysis, we pinpointed *Prevotella* as a pivotal bacterial species that may modulate IgA levels, corroborating existing literature on *Prevotella* [35]. Capitalizing on these insights, we established a murine model that emulates the HIgA phenotype, thereby substantiating the role of *Prevotella* in modulating serum IgA expression. Extending our investigation, the metabolomics profiling indicates that fatty alcohols, purines, and their respective derivatives could be instrumental gut microbial metabolites in the regulation of serum IgA levels. Moreover, we posit that the penicillin pathway, alongside the cholinergic and anti-cholinergic drug pathways, and some proteins related to nerve signal transmission may exert considerable influence on this intricate regulatory mechanism.

CONCLUSION

Our study aimed to explore the effects of gut microbiota metabolites on serum IgA levels, utilizing a HIgA mouse model. Our findings offer empirical evidence, highlighting the role of gut microbiota in modulating host immune responses through its metabolites. This lays a groundwork for ongoing research. It is essential to recognize the limitations of our study, notably the model's representativeness and the need for a more profound understanding of how metabolites affect immunity. Given the physiological and immunological disparities between humans and mice, further studies are necessary to evaluate the impact on additional immune components, such as IgM and IgG. Moreover, a thorough analysis of the gut microbiota's diversity and complexity is crucial for a comprehensive understanding of its immunological implications. Such an approach will deepen our insights and facilitate the development of targeted strategies for immune modulation.

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