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REVIEW

Research Advances in the Treatment of Allergic Rhinitis by Probiotics

Peng Liu[1], Tianyong Hu[2], Chenglin Kang[1], Jiangqi Liu[2], Jin Zhang[1], Hong Ran[1], Xianhai Zeng[2], Shuqi Qiu[2]

[1]Department of Graduate and Scientific Research, Zunyi Medical University Zhuhai Campus, Zunyi, People's Republic of China; [2]Department of Otolaryngology, Longgang E.N.T Hospital & Shenzhen Key Laboratory of E.N.T, Institute of E.N.T Shenzhen, Shenzhen, People's Republic of China

Correspondence: Shuqi Qiu; Xianhai Zeng, Email qiushuqi66858@163.com; zxhklwx@163.com

Abstract: Allergic rhinitis (AR) impairs the quality of life of patients and reduces the efficiency of social work, it is an increasingly serious public medical and economic problem in the world. Conventional anti-allergic drugs for the treatment of allergic rhinitis (AR) can cause certain side effects, which limit the quality of life of patients. Therefore, it makes sense to look for other forms of treatment. Several studies in recent years have shown that probiotics have shown anti-allergic effects in various mouse and human studies. For example, the application of certain probiotic strains can effectively relieve the typical nasal and ocular symptoms of allergic rhinitis in children and adults, thereby improving the quality of life and work efficiency. At the same time, previous studies in humans and mice have found that probiotics can produce multiple effects, such as reduction of Th2 cell inflammatory factors and/or increase of Th1 cell inflammatory factors, changes in allergy-related immunoglobulins and cell migration, regulate Th1/Th2 balance or restore intestinal microbiota disturbance. For patients with limited activity or allergic rhinitis with more attacks and longer attack duration, oral probiotics have positive effects. The efficacy of probiotics in the prevention and treatment of allergic rhinitis is remarkable, but its specific mechanism needs further study. This review summarizes the research progress of probiotics in the treatment of allergic rhinitis in recent years.

Keywords: allergy rhinitis, probiotics, immune tolerance, Th1/Th2 balance, Treg/Th17 balance, mucosal barrier

Introduction

AR is a global health problem, with significant burden and economic impact on various countries. The economic impact of AR is often underestimated, as indirect costs are often overlooked, and in the European Union, the impact of AR on job productivity is estimated at 30 billion to 50 billion euros per year.[1,2] AR is estimated to affect approximately 10 to 30% of adults and up to 40% of children,[3] and the prevalence is increasing year by year.[4] AR typical symptoms can have a significant negative impact on patients' quality of life (QoL), sleep quality, mood, learning efficiency and sexual function.[5] At present, traditional drug treatments for AR mainly include antihistamines, nasal mucosa decongestants, and glucocorticoids, the only one with disease immune regulation is allergen specific immunotherapy.[6] At present, the commonly used treatment of AR mainly focuses on conservative drug treatment, but drugs used to treat AR are often accompanied by adverse side effects (eg, dry mouth, drowsiness, dizziness), some of which can seriously affect quality of life, making it an urgent issue to find alternative treatments. At the same time, the use of probiotics as an alternative is increasing in the world, and consumption of probiotics is expected to modulate immune responses in AR patients, establish a more balanced gut microbiota, and make these patients more moderately responsive to inhaled allergens, and can reduce the damage caused by inflammation. Therefore, the use of probiotics is currently a popular strategy for adjuvant treatment of AR.

General Situation and Treatment of Allergic Rhinitis

Overview of Allergic Rhinitis

AR, a chronic inflammation of the nasal mucosa, is caused by a specific immunoglobulin E (IgE)-mediated response to type II helper T(Th2) cell-driven inhaled allergens and affects approximately one-sixth of the world's One of the people.[7,8] The etiology of AR is determined by multiple factors such as genetics, environment and family susceptibility, its typical symptoms

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include intermittent or persistent nasal itching and sneezing, rhinorrhea, nasal congestion and eyelid edema, these symptoms are often caused by seasonal or perennial allergies, it is a type I allergic disease, which affects patients' sleep, attention, study, work and leisure activities, reduces the quality of life, and is often associated with allergic conjunctivitis and asthma.[9,10]

When a patient is first exposed to an allergen, the allergic immune response is in the sensitization phase. Dendritic cells (DCs) in the nasal mucosa take up allergens, process them and transport them to the draining lymph nodes, and then present the allergens to naive CD4+T cells after secondary processing by the draining lymph nodes, naive CD4+T cells differentiate into allergen-specific Th2 cells, which in turn induce B cell activation to produce plasma cells, which further differentiate to produce specific IgE, which then undergo recirculation and interaction on the surface of effector cells such as mast cells and basophils, binds to IgE receptors (FcεRI) with high affinity. These processes simultaneously lead to the formation of memory allergen-specific Th2 cells and B cells.[11–16] Activation of Th2 plays an important role in the development and maintenance of AR, while mast cells, eosinophils and basophils are innate immune response cells and are considered to be the main effector cells of AR, at the same time, the reduction of basophils can also reduce the recruitment of eosinophils and reduce the Th2 response, afterwards, inflammatory mediators such as histamine, prostaglandins, leukotrienes, and tryptases are released, and most of the pathological processes in the nasal mucosa involve these mediators,[9,17,18] which is a key step in the occurrence of allergy. But when the nasal mucosa is exposed to various allergens sporadically, seasonally or chronically, it will become a process of repeated exposure to allergens. When a patient previously sensitized by exposure to an allergen is re-exposed to the allergen, the allergen binds to allergen-specific IgE on mast cells of the nasal mucosa, and then IgE and FcεRI are cross-linked, causing mast cell activation and degranulation, while releasing pre-stocked and newly synthesized mediators, including histamine, sulfinyl peptide leukotrienes, prostaglandin D2 and other products.[13] These mediators interact with the nasal sensory nerves, vasculature, and glands, resulting in AR symptoms (see Figure 1).

Treatment of Allergic Rhinitis

Appropriate treatment drugs are selected according to the specific severity of the disease, type of disease, and lifestyle (see Table 1).

Local treatment: Topical nasal corticosteroids act rapidly, especially to relieve nasal congestion. Topical steroids bind to specific cytoplasmic glucocorticoid receptors (GRs), activate anti-inflammatory gene transcription and inhibit pro-inflammatory

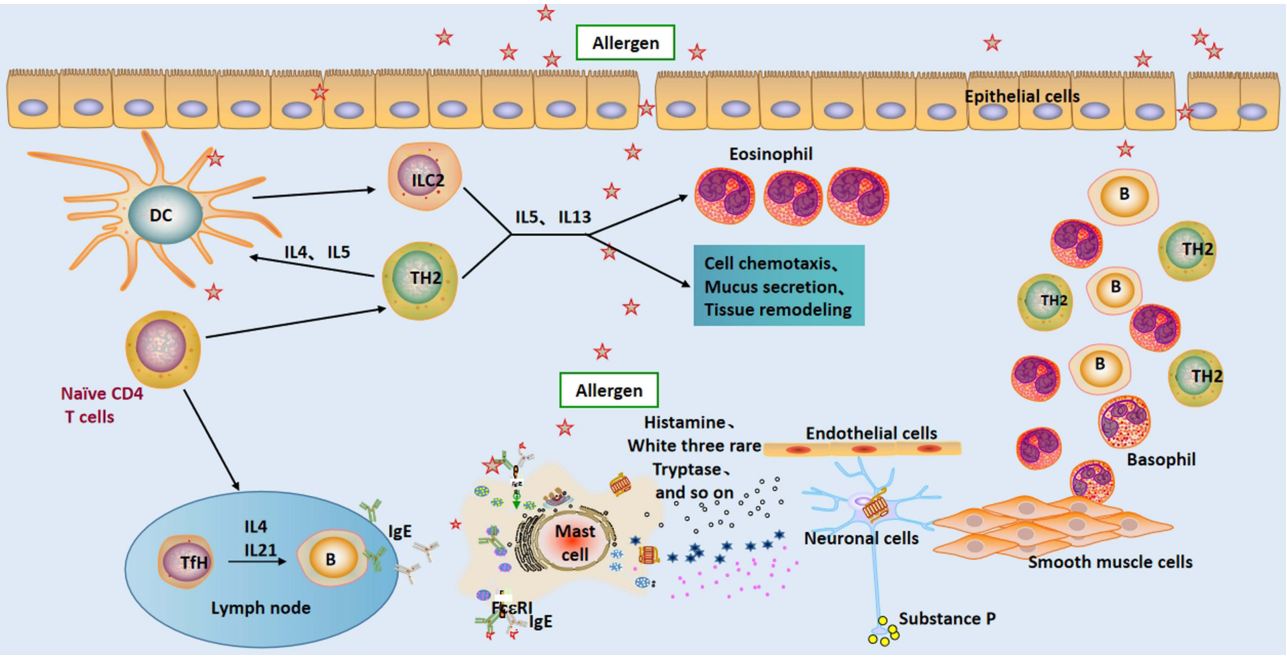

Figure 1 Pattern of pathogenesis of allergic rhinitis.
Abbreviations: DC, dendritic cell; B, B cell; IL, interleukin; ILC, type 2 innate lymphocytes; IgE, immunoglobulin E; TH2, type 2 helper T lymphocyte; TfH, follicular helper T lymphocyte.

Table 1 Treatment Options for Allergic Rhinitis[5,19]

Mode of Administration	Types of Drugs	Clinical Treatment	Degree of Recommendation
Oral	Oral corticosteroid	Second-line medication	Use as appropriate
	Oral H1-antihistamine	First-line medication	Recommended use
	Leukotriene receptor antagonist	First-line medication	Recommended use
	Mast cell membrane stabilizer	Second-line medication	Use as appropriate
Intranasal use	Intranasal corticosteroid	First-line medication	Recommended use
	Nasal decongestant	Second-line medication	Use as appropriate
	Nasal H1-antihistamine	First-line medication	Recommended use
	Intranasal corticosteroid plus H1-antihistamine	Second-line medication	Use as appropriate
	Intranasal anti-cholinergic agent	Second-line medication	Use as appropriate

gene transcription, and the anti-inflammatory effects of topical steroids reduce all nasal and ocular symptoms.[20] Topical steroids with combined antihistamines: MP Aze-Flu, a nasal spray consisting of azelastine hydrochloride and fluticasone propionate, was more effective in symptom scores and quality of life than placebo or fluticasone propionate alone valid.[21,22] Nasal congestion reducer: Because of the rebound effect and habituation effect of the nasal mucosa, continuous use is preferably not more than 7 days.[23] Most drugs can make alpha adrenergic receptors work, causing vasodilation and contraction, which can immediately relieve the symptoms of nasal congestion, mainly including pseudoephedrine, oxymetazoline, trichomazoline or phenylephrine. Nasal anticholinergics and cromolyn/mast cell stabilizers: Nasal cromolyn and anticholinergics, which primarily affect nasal secretions, have some older studies, but there is insufficient evidence to make an adequate recommendation.[23] Saline irrigation: Hyde et al[24] noted that increased nasal irrigation in children is beneficial compared to no nasal irrigation. It also appears to reduce nasal eosinophils and neutrophils.[25]

Systemic therapy: All mechanisms of systemic glucocorticoids are regulated by GR, which belongs to the ligand-regulated nuclear receptor superfamily, and the anti-inflammatory effects of steroids can be explained by three broad molecular mechanisms: decreased pro-inflammatory gene expression, anti-inflammatory increased inflammatory gene expression and non-genomic mechanisms.[26] Oral antihistamines: Four histamine receptors, H1 and H2 receptors, have been identified on a variety of cells, stimulating both the early and late stages of allergic reactions. Second-generation/third-generation non-sedating H1 receptor antagonists are the antihistamines of choice for AR.[27] Cetirizine has been shown to be efficacious in many studies, and cetirizine is superior to loratadine in symptom relief with a favorable safety profile.[28,29] Leukotriene Receptor Antagonists (LTRA): Leukotrienes are a family of inflammatory mediators, including LTA4, LTB4, LTC4, LTD4 and LTE4, by blocking the cysteine LT1 (CysLT1) receptor, LTRAs (such as Montelu sterol) can improve the symptoms of allergic rhinitis and asthma.[30] At present, the research on oral cromoglycate as a mast cell stabilizer is insufficient.

To date, allergen immunotherapy is the only immune-modifying and causal treatment currently available for patients with IgE-mediated allergic disease. The purpose of AIT is to reprogram the immune system to reduce the production of specific IgE, thereby inducing tolerance to allergens, it can be divided into subcutaneous and sublingual immunization methods through different routes of administration, patients can be desensitized by continuously increasing the allergen dose.[31] Meanwhile, Liu et al[32] published a population-wide study to investigate the effects of influenza vaccination and air pollution on allergic respiratory disease symptoms, and found that vaccination could improve the negative effects of long-term air pollution in allergic respiratory tract. A study by Dulny et al[33] showed that preventive immunization against rubella, typhoid, and smallpox showed a lower incidence of AR, while measles vaccine showed a higher incidence of AR.

Current treatment of AR is still based on allergen avoidance, symptom-relieving drugs, anti-inflammatory therapy, and allergy immunotherapy. At this stage, there are many adverse drug reactions in the treatment of AR and cannot be cured, the symptoms are easy to repeat, and the immunotherapy course is longer and the compliance is poor,[34] and at the same time reduce the quality of life. Probiotics can be used as immunomodulators and activators of the host defense pathway, in addition, oral probiotics can regulate the immune response of the respiratory system, and can prevent and treat upper respiratory diseases such as asthma, AR and other allergic diseases by modulating changes in the gut microbiota and immune response.[35] However, the research and application of probiotics as an alternative treatment

method in the world is increasing, and most of the studies suggest that probiotics can significantly improve the symptoms of AR patients.[36,37] Probiotics can activate Th1 or inhibit Th2, causing anti-inflammatory effects, and can also stimulate the production of immune factors such as interleukin 10 (IL-10), whose main role is to suppress inflammatory responses.[38,39] Probiotics have the advantages of safety and high cost performance, therefore, the basic research and clinical application of probiotics for AR treatment are increasing.

Probiotics

Introduction to Probiotics

Probiotics are active microorganisms that can improve the balance of intestinal flora in the body and have a beneficial effect on the body. The World Health Organization (WHO) defines probiotics as live microorganisms that, when administered in appropriate amounts, can have beneficial effects on the health of the host.[40] The best probiotics are human-derived, safe, and free from carriers that can create antibiotic resistance and pathogenic or virulent factors. In addition, probiotics have a strong ability to survive under intestinal conditions (acidic pH, enzymes, bile salts, etc.), and at the same time, probiotics show significant beneficial effects on the body by fighting pathogens and stimulating the immune system. It is also possible to maintain probiotic activity, growth efficiency, and function through technical treatments.[41,42]

There are many kinds of probiotics and about 400 kinds of in the human body, according to the reported probiotics, they are roughly divided into the following five categories: *Streptococcus, Lactobacillus, Bifidobacterium, Bacillus* and others, the common representative strains are shown in Table 2.[43–48] *Streptococcus, bifidobacteria* and *lactobacilli* can all produce lactic acid, so they can be classified into *lactic acid bacteria*, probiotics that do not produce lactic acid include *Bacillus*, propionic acid bacteria and yeast.[49] At present, more than 60 species and subspecies of *Streptococcus* have been reported and confirmed to be classified,[43] more than 50 species of *Lactobacillus* (of which more than 10 species are commonly used),[44] and more than 30 species of *Bifidobacterium* (14 of which are closely related to humans),[45] there are more than 150 species of *Bacillus* (more than 10 common species).[46]

Types of Probiotics Used to Treat Allergic Rhinitis

There have been a large number of clinical studies on probiotics in the treatment of AR. Ahmed et al[50] found that in the treatment of perennial AR, children taking *Lactobacillus paracasei* (LP-33) for 6 weeks had the same effect as taking cetirizine, and almost all children had the same effect baseline symptoms (rhinorrhea, sneezing, nasal congestion, cough, difficulty sleeping, and difficulty eating) all improved significantly. Similarly, a study evaluating the use of *Lactobacillus helveticus* SBT2171 (LH2171) to treat patients with mild to moderate AR for 16 weeks showed significantly improved nasal symptoms and significantly lower eosinophil counts in nasal fluid and peripheral blood in the LH2171 group in the placebo group.[51]

Gram-positive probiotic combinations have been extensively studied in AR. A 2017 study investigated the treatment of children with seasonal AR with a mixture of *bifidobacteria (B*. l*ongum* BB536, *B*. banfanit*s* M-63, *B*. b*reve* M-16V), symptoms and quality of life in children treated with a mixture of probiotics (QoL) was significantly improved.[52]

Table 2 Classification of Probiotics and Common Representative Strains

Classification	Representative Strains	Author
Streptococcus	*Viridans Streptococcus, Streptococcus thermophilus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus lactis, Streptococcus faecalis, Streptococcus platus*, etc.	Jin et al[43]
Lactobacillus	*Lactobacillus lactis, Lactobacillus paracasei, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus brevis, Lactobacillus bulgaricus, Lactobacillus plantarum*, etc.	Xie et al[44]
Bifidobacteria	*Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium adolescentis, Bifidobacterium thermophilus*, etc.	Liu et al[45]
Bacillus	*Bacillus licheniformis, Bacillus megaterium, Bacillus natto, Bacillus subtilis, Bacillus amyloliquefaciens, Bacillus anthracis, Bacillus sphaericus*, etc.	Cui et al[46]
Other classes	*Escherichia coli, Photosynthetic bacteria, Propionibacterium, Football bacteria, Escherichia coli*, yeast, etc.	Wang et al[47] Fei et al[48]

Efficacy of NVP-1703 probiotic mixture *(B. longum* IM55 and *Lactobacillus plantarum* IM76) compared with placebo for 4 weeks in a study in perennial adults with AR, treatment group TNSS and Rhinitis Control Assessment Test (RCAT) scores Significant improvement. At the same time, the level of dust mite-specific IgE was also significantly lower in the NVP-1703 group compared with the placebo group. At week 4, serum levels of IL-10 were significantly increased in the NVP-1703-treated group compared with the placebo group.[53] Another study included 250 AR-affected children aged 6 to 17, randomly assigned to intervention (150) or placebo (100), in addition to usual care (topical glucocorticoids and/or oral antihistamines) in addition to the drug), the intervention group took a mixture containing two *Bifidobacterium* strains (*Lactobacillus* BB12 DSM 15954 and *Enterococcus faecium* L3 LMG P-27496), and the results showed that the NSS of the intervention group was significantly reduced.[54] A preliminary study of 20 adult patients (18–65 years old) with allergic rhinitis caused by house dust mite allergy showed that adding five natural, non-genetically modified probiotic strains to bed sheets reduced symptoms, improve the quality of life.[55] At the same time, a study on compound lactic acid bacteria solid drinks *(Lactobacillus paracasei* GM-080TM, *Lactobacillus acidophilus, Lactobacillus fermentum* GM-090TM, *Lactobacillus paracasei* GMNL-133) can improve the quality of life of children with AR, the results suggest that the modified Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) score improved significantly.[56] Another clinical study on *Clostridium butyric* live capsules showed that the proportion of factors that can inhibit inflammation (IL-10, transforming growth factor-β1) in the serum of AR patients was significantly increased, and various scoring scales were significantly higher improvement.[57]

Probiotic-assisted combination therapy is also an important area of focus. In a study using a Gram-positive oral probiotic formulation (*Familact* capsules) in combination with budesonide, Jalali et al[58] found that the addition of probiotics significantly improved the quality of life of AR patients compared with budesonide alone (according to SNOT-22 and control test scores for allergic rhinitis and asthma). The benefits of combined treatment with probiotics and AIT have also been studied. One study compared four groups of placebo, dust mite-specific SCIT, *C. butyricum*, and *C. butyricum*-containing SCIT for the treatment of house dust mite-induced AR. Nasal symptoms were significantly reduced in the *C. butyricum* group and *C. butyricum*-containing SCIT group compared with the placebo group. Furthermore, combination therapy enhanced SCIT efficacy by improving nasal symptom scores and reducing specific IgE and TH2 cytokines.[59] The combined treatment of SLIT and probiotics has also been studied, and it has been suggested that probiotics combined with SLIT are effective in improving AR symptoms in children.[60] A 5-month randomized, controlled trial in 100 children (ages 5–12 years) to assess the efficacy of SLIT in combination with vitamin D, placebo, and *Lactobacillus rhamnosus* without SLIT in the control group. They observed a decrease in symptom drug scores in all groups treated with SLIT and found a significant increase in CD4 +CD25+Fox3+ cells in children treated with SLIT and *Lactobacillus rhamnosus* compared with children treated with SLIT and vitamin D.[61] As an add-on therapy that can effectively treat AR, probiotics are a valuable treatment option in the management of AR patients (see Table 3). Future studies will need to use validated AR models to evaluate probiotic therapy.

Mechanisms of Probiotic Treatment of Allergic Rhinitis

Effect of Probiotics on Serum Inflammatory Factors

A study in perennial adult AR evaluated the efficacy and safety of NVP-1703 probiotic mixture (*B. longum* IM55 and *Lactobacillus plantarum* IM76) intervention for 4 weeks, NVP-1703 group compared with placebo group, IL-4 The serum level of Dermatophagoides was not significantly changed, but the level of D. dust mite-specific IgE was significantly decreased in the NVP-1703 group. At week 4, the serum levels of IL-5 and IL-13 were decreased in the NVP-1703 group compared with the placebo group, while the serum levels of IL-10 were significantly increased.[53] In an earlier study, 60 AR patients were randomly divided into a *Broncho-vaxom* (BV) group and a control group. After BV treatment, the drug score of the treatment group was significantly lower than that of the control group, and both individual and total nasal symptom scores were significantly lower significantly decreased. The levels of IL-4 and IL-13 in the nasal lavage fluid of the BV group were significantly decreased, while the level of interferon gamma (INF-γ) was significantly increased, which made the ratio of IL-4/INF-γ significantly decreased, and eosinophils Cells were also significantly reduced, and the BV-induced benefits persisted for a longer period of time.[62] The increased rate/severity of respiratory viral infections in children with AR may be caused by

Table 3 Recent Investigations into the Use of Probiotics for Allergic Rhinitis

Author and Date	Type of Study	Probiotic Type	Dosage and Time of Exposure	Main Findings	Possible Mechanisms	Quality of Life and Symptoms, and so on
Xu et al 2016[59]	Randomized, double-blind, placebo-controlled crossover study with 15 adults	*Clostridium butyricum* (*Cb*)	Unclear dose for 7 months	IgE, B cells↓ Th2 cells↓ Treg, IL10↑	Inhibition of Th2 immune response	Add-on probiotic therapy enhanced SCIT in patients with AR
Jerzynska et al 2016[61]	Prospective and double-blind, randomized, placebo-controlled with 100 children	*L. rhamnosus* GG	1000 IU daily for 5 months	IL1, IL6↓ IL10, IL12, TGFβ↑ Th1 cells↑ CD4+CD25+Foxp3+↑	Enhance immune response	Add-on probiotic therapy enhanced SLIT in children with AR
Del et al 2017[52]	Randomized, double-blind, placebo-controlled study with 40 children	*B. longum* BB536, *B. infantis* M-63, *B. breve* M-16V	*B. longum* BB536 ($3x10^9$ CFU), *B. infantis* M-63 ($1x10^9$ CFU), and *B. breve* M-16 V ($1x10^9$ CFU) daily for 8 weeks	##	##	Improved AR symptoms and QoL
Berings et al 2017[55]	Randomized, double-blind, placebo-controlled crossover study with 20 adults	*B. subtilis, B. amyloliquefaciens, B. pumilus* strains	Bedding for house Purotex® covers 8 weeks	##	##	Improved AR symptoms and QoL
Qiao et al 2017[57]	Double-blind, placebo-controlled with 40 adults	*Clostridium butyricum* duplex viable	3 capsules/time Twice a day for 6 weeks	IL10, TGFβ↑	Inhibition of Th2 immune response	Improved AR symptoms and VAS, RQLQ
Juan et al 2017[66]	Randomized, double-blind, placebo-controlled study with 40 BALB/c mice	*Clostridium butyricum* CGMCC0313-1	$1×10^8$ CFU daily for 2 weeks	IL4, IL5, IL13, IL17↓ IgE/G1↓ IL10↑ CD4+CD25+Foxp3+↑	Th1/Th2 Cytokine balance	Alleviates inflammation
Harata et al 2017[121]	Double-blind, randomized, placebo-controlled study with 25 pollinosis patients	*Lactobacillus rhamnosus* GG *Lactobacillus gasseri* TMC0356	110g fermented milk daily for 10 weeks	Restore intestinal microbiota balance	Regulating blood lipids	Alleviates inflammation
Choi et al 2018[65]	Randomized, double-blind, placebo-controlled study with 35 BALB/c mice	*Lactobacillus plantarum* CJLP133 and CJLP243	$1×10^{10}$ CFU daily for 17 days	IL4, IL5, IL13↓ IgE, IgG1↓ IgG2a, IFNγ↑ Th1 cells↑	Th1/Th2 Cytokine balance	Reduce inflammation and symptoms
Ren et al 2018[72]	Randomized, double-blind, placebo-controlled study with # #BALB/c mice	*Bifidobacterium breve*	Unclear dose for 4 weeks	IL4, IL10↓ IgE↓ CD4+CD25+Tregs↑	Inhibition of Th2 immune response	Improved AR symptoms
Ahmed et al 2019[50]	Randomized controlled study with 212 children	*L. paracasei* LP33	$2x10^9$ CFU daily for 6 weeks	IgE↓	Promote Th1 immunity and inhibit Th2 response	As effective as cetirizine for perennial AR
Jalali et al 2019[58]	Randomized, double-blind, placebo-controlled crossover study with 152 adults	*L. acidophilus, L. casei, L. delbrueckii* subsp. *L. bulgaricus*, and *L. rhamnosus*	$11.5×10^{10}$ CFU daily for 8 weeks	##	##	Add-on probiotic therapy was more effective than budesonide
Meng et al 2019[62]	Randomized, placebo-controlled study with 60 patients	*Broncho-vaxom* (BV)	7mg daily for 10 days, resting 20 days, 3 courses	IL4, IL13↓ eosinophils↓ IFNγ↑	Th1/Th2 Cytokine balance	Improved TNSS and INSS score

Makino et al 2019[68]	Randomized, double-blind, placebo-controlled study with ## Ovalbumin (OVA)-specific TCR-transgenic DO11.10 mice	*L. helveticus* SBT2171	Unclear dose for 6 weeks	IL4, IL13↓ Leukocyte infiltration↓ IL10, IFNγ↑ Th1 cells↑	Th1/Th2 Cytokine balance	Alleviates allergic symptoms
Schaefer et al 2019[122]	Randomized, double-blind, placebo-controlled crossover study with 120 patients	*Enterococcus faecalis*	30 drops each time, 3 times daily for 8 weeks	Restore intestinal microbiota balance	Regulate immune response	Improved AR symptoms
Kim et al 2019[123]	Randomized, double-blind, placebo-controlled crossover study with 48 BALB/c mice	*Bifidobacterium longum* IM55 and *Lactobacillus plantarum* IM76	2×10^{9} CFU daily for 30 days	IL4, IL5↓ Th2 cells, Mast cells ↓ eosinophils, basophils↓ Bacteroides↓ Proteobacteria↑ Actinomycetes↑	Restoring Th2/Treg imbalance and gut microbiota disturbance	Improved AR symptoms
Yamashita et al 2020[51]	Randomized, double-blind, placebo-controlled study with 200 adults	*L. helveticus* SBT2171	10g daily for 12 weeks	IgE↓ eosinophils↓	Th1/Th2 Cytokine balance or Inhibition of Th2 immune response	Improved AR symptoms
Kang et al 2020[53]	Multi-center, double-blind, randomized, placebo-controlled with 97 adults	*B. longum* IM55, *L. plantarum* IM76	1×10^{10} CFU daily for 4 weeks	IL4, IL5, IL13↓ PDG2↓ Cysteine LTs↓ IgE↓ Mast cells↓ B cells↓ eosinophils↓ Th2 cells↓ Treg↑ IL10↑	Th1/Th2 Cytokine balance	Improved TNSS and RCAT score
Anania et al 2021[54]	Prospective and double-blind, randomized, placebo-controlled with 250 children	*Lactis* BB12, *Enterococcus faecium* L3	4×10^{10} CFU daily for 3 months	##	##	Improved NSS score
Bae et al 2021[67]	Randomized, double-blind, placebo-controlled crossover study with # #BALB/c mice	Fermented by probiotic bacteria (FRG)	Unclear dose for more than 2 weeks	IL4, eosinophils↓ basophils, IgE↓	Inhibition of Th2 immune response	Alleviates inflammation
Hu et al 2021[124]	Randomized, double-blind, placebo-controlled crossover study with 130 children	*Lactobacillus reuteri* GL-104, *Lactobacillus paracasei* GL-156, *Lactobacillus rhamnosus* MP-108	500mg each time, 3 times daily for 12 weeks	Restore intestinal microbiota balance	Restore intestinal barrier function	Alleviates inflammation
Yang et al 2022[71]	Randomized, double-blind, placebo-controlled crossover study with # #BALB/c mice	*Lactiplantibacillus plantarum* NR16	Unclear time and dose	IL12, IFNγ↑	Induce Th1 immune response and balance Th2/Th1 ratio	Improved AR symptoms

Abbreviations: AR, allergic rhinitis; QoL, quality of life; RCAT, rhinitis control assessment test; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; NSS, nasal symptom score; INSS, individual nasal symptom score; TNSS, total nasal symptom score; VAS, visual analogue score; RQLQ, rhinoconjunctivitis quality of life scale; ##, not mentioned or not applicable.

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multiple mechanisms, but IFN-γ deficiency may be one of them,[63,64] and probiotics can improve respiratory viral infections by raising IFN-γ levels.

Choi et al[65] found that oral administration of *Lactobacillus plantarum* reduced the number of infiltrating cells in the nasal cavity and lungs in an AR mouse model, while bronchoalveolar lavage fluid and draining lymph node samples showed decreased immune cell counts, IL-4, IL- 5, the levels of IL-13, serum IgE and specific serum IgG1 were decreased, while the secretion of IFN-γ and specific serum IgG2a were increased to improve allergic rhinitis. In addition, the study on the efficacy of oral *Clostridium butyricum* on ovalbumin-induced allergic airway inflammation in mice found that the *Clostridium butyricum* group significantly reduced lung resistance, pulmonary airway inflammation, mast cell degranulation, airway inflammation in mice remodeling and OVA-specific IgE/G1 expression. At the same time, it also reversed the Th1/Th2 imbalance and increased the anti-inflammatory serum factor IL-10.[66] Probiotics were used to ferment chemically transformed red ginseng (RG), in this study, the effect of probiotic-fermented RG (FRG) on ovalbumin (OVA)-induced allergic rhinitis model in mice was found to be FRG, it reduced IL-4 and IgE levels in bronchoalveolar lavage fluid, nasal fluid, and serum more effectively than RG, suggesting that FRG has a better immunomodulatory effect than RG. FRG also down-regulated immune cell levels (eosinophils, basophils) compared to RG, overall, the results suggest that FRG treatment reduces inflammation.[67] Another study demonstrated that *Lactobacillus helveticus* SBT2171 (LH2171) could induce cytokine production in naive mouse splenocytes stimulated by antigen in vitro, which could inhibit the production of IL-4 and IL-13, and increase IFN-γ and IL-10 generation.[68]

Combined with the study of probiotics in human and animal models of AR, most serum inflammatory factors have decreased to varying degrees, such as IL-4, IL-5, IL-13, IgE, specific serum IgG1, eosinophils and the level of basophils decreased, but some anti-inflammatory factors increased, such as IL-10, IFN-γ and specific serum IgG2a secretion increased.Therefore, probiotics can alleviate the inflammatory response of AR patients by improving the level of inflammatory factors in the serum, thereby alleviating their clinical symptoms.

Balance of Probiotics Against Allergic Rhinitis Th1/Th2

AR is a type I allergic disease, which is mainly caused by IL-4, IL-5 and IL-13 produced by Th2 cells, causing the Th1/Th2 balance to tilt towards Th2, thereby producing specific IgE, while mast cells release histamine and Leukotrienes.[69] On the other hand, Th1 suppresses the Th2 immune response by producing anti-inflammatory factors such as IFN-γ and IL10,[70] thereby alleviating AR symptoms.

Yang et al[71] found that *Lactobacillus plantarum* (NR16) extracted from fermented Korean kimchi was a powerful Th1 inducer, and when NR16 was co-cultured with immune cells, it could produce a large amount of IFN-γ and IL-12, and at the same time oral administration of NR16 reduces airway hyperresponsiveness and leukocyte infiltration in mice. Furthermore, oral administration of NR16 may alleviate AR symptoms by inducing a Th1 immune response, which in turn may rebalance the Th1/Th2 ratio by reducing the production of Th2 cytokines in specific mucosal lesions. Choi et al[65] found that *Lactobacillus plantarum* can increase the production of Th1-type cytokines (IFN-γ, specific serum IgG2a) in AR mouse model, Th2-type cytokines (IL-4, IL-5, IL-13) decreased and reached the balance of Th1/Th2.

Another randomized, controlled study showed that after *Broncho-vaxom* (BV) treatment, compared with the control group, the contents of IL-4 and IL-13 in the nasal lavage fluid of the BV group were significantly reduced, while the content of INF-γ was significantly increased high, which resulted in a marked decrease in the ratio of IL-4/INF-γ, and BV could modulate the Th1/Th2 cytokine balance as a potential cell signaling mechanism to improve overall mucosal immunity.[62] Ren et al[72] confirmed that oral administration of *Bifidobacterium breve* can inhibit Th2 response and induce CD4+CD25+Tregs activity, but does not cause Th1 response, but can regulate Th1/Th2 balance and has anti-allergic effect. Second, high doses of *Bifidobacterium breve* can significantly reduce the frequency of sneezing, while reducing serum IL-4 and specific IgE levels, increasing the number of CD4+CD25+ Tregs in the spleen, and significantly reducing the allergic reaction of nasal mucosa epithelial, low doses of *Bifidobacterium breve* provide only mild relief from allergic reactions.

Effects of Treg/Th17 Cell Balance

Treg acts as an immunosuppressive CD4+ T cell, while Th17 acts as an inflammatory CD4+ T cell, the balance between the two is a key condition for maintaining the stability of the human immune system.[73] In recent years, we have found in

some studies on autoimmune diseases that the occurrence and development of diseases are often accompanied by an increase in the number and function of Th17. A study in patients with allergic fungal sinusitis showed that the secretion of IL-1, IL-17, IL-21 and TGF-β in serum all increased to varying degrees, leading to a shift in the Th17/Treg balance Th17 direction is inclined.[74] Research data confirmed that the secretion of inflammatory factors such as IL-17, IL-35, and Th17 in the peripheral blood of AR patients increased,[75] and the increase in inflammatory factors caused Treg/Th17 imbalance, which in turn led to Th1/Th2 imbalance, resulting in a series of AR typical clinical symptoms and nasal mucociliary destruction, nasal gland hyperplasia and inflammatory cell infiltration.

Probiotics can modulate autoimmunity by affecting the balance of Treg and Th17. Fu et al[76] found that the induction of CD4+FoxP3+Treg cells by Clostridium spores could inhibit the pro-inflammatory response of Th17 cells. Ekmekciu et al[77] used the probiotic mixture VSL#3 to induce the proliferation of Treg cells. Cell experiments by Johansson et al[78] showed that the supernatant of lactic acid bacteria can reduce the activation of CD4+ T cells, CD8+ T cells, mucosa-associated constant T cells, etc., and the products of lactic acid bacteria can inhibit the proliferation and degranulation of these cells. Other studies have shown that changes in T cell metabolism caused by inflammation can affect the immune function of Treg cells. For example, enolase during glycolysis can regulate the binding variant of FoxP3 in exons, and changes in Treg metabolism caused by stress state, it is an important part of triggering an autoimmune response.[79] Wang et al[80] used *Lactobacillus casei* as an intervention control, and the results showed that the percentage of CD4+CD25+Foxp3+Tregs in the spleen of the intervention group increased, while the percentage of CD4+IL-17A+Th17 cells decreased, regulates the imbalance of Treg/Th17 cell ratio. Another study showed that *Lactobacillus rhamnosus* GG (LGG) extract could maintain Treg/Th17 homeostasis by reducing the ratio of IL-17+Th17 and increasing the ratio of CD25+Foxp3+Treg via the Toll receptor (TLR2) pathway.[81]

Probiotics can improve the immune regulation of allergy and immune diseases by regulating the balance of Treg/Th17, and have produced some targeted treatment methods with considerable results. Further exploration of the Treg/Th17 balance mechanism and its influencing factors will provide a more comprehensive understanding of the human body's autoimmune regulation mechanism, or provide theoretical support for the treatment of AR and the development of new drugs.

Influence on the Activity of Tolerant Dendritic Cells (Intestinal Immune Tolerance)

Dendritic cells (DCs) are the most efficient antigen-presenting cells (APCs) in the body, which can effectively induce antigen-specific immune responses by regulating tolerance and immunity to microbial antigens.[82] Tolerogenic DCs (TDCs) play a key role in regulating immune tolerance and are characterized by a semi-mature phenotype that expresses co-stimulatory molecules (CD80/CD86), which can be activated by TLR ligands or by exposure to specific cells, differentiation in a factor environment.[83] In addition, they also express immunoregulatory molecules and produce immunosuppressive factors, and semi-mature, co-stimulatory CD80/CD86 signaling affects the activation of Treg on T cells through the action of CD28 molecules, which in turn induces immune tolerance.[84] Currently, several clinical trials are underway to explore the effectiveness of TDC as an alternative treatment option for immune-mediated diseases.[85] These TDCs have a semi-mature phenotype, exhibit low levels of T-cell co-stimulatory properties, and a reduced ability to produce pro-inflammatory cytokines compared to anti-inflammatory molecules, especially through the expansion of regulatory T cells (Tregs) and/or or induction.[86] Other studies have also shown that TDCs secrete anti-inflammatory cytokines and regulate T cells to promote Foxp3+ Treg development in the mouse and human gut.[87,88] Globally, these data suggest that the DC/Treg/B regulatory axis plays a central role in the gut by re-establishing tolerance and regulating Tregs.

Recent evidence suggests that probiotics may affect immune regulation in vitro and in vivo by modulating DC maturation and TDC production, thereby suppressing inflammation.[89] The immunomodulatory effects of probiotics arise from the interaction of immune cells with intestinal DCs, thereby regulating the innate and adaptive immune systems.[90] Studies have shown that probiotics are able to react with pattern recognition receptors (PRRs) on DCs, which detect distinct evolutionarily conserved structures (pathogen-associated molecular patterns, PAMPs) on pathogens, or by producing soluble compounds, thereby inducing TDCs.[91] Different species and strains of probiotics may directly affect the maturation of DCs, and probiotics may regulate the levels of anti-inflammatory cytokines, such as transforming growth factor beta (TGF-β), IL-10, and induce Treg. A study targeting four strains of probiotics (including *Lactobacillus salivarius, Bifidobacterium, Bacillus coagulans*, and *Bacillus subtilis natto*) all induced stimulation of DC production of IL-10 and TGF-β, *Bifidobacterium* and *Bifidobacterium coagulans*

exhibited a stronger ability to induce IL-10 and TGF-β. Therefore, probiotic-induced DC activity to produce anti-inflammatory cytokines plays a key role in immunomodulatory functions.[92] TDCs are induced to produce TGF-β, IL-10, and stimulate Treg production, suppress effector T cell responses, and suppress allergic airway inflammation in mouse models, whereas depletion or blockade of CD25+ cells and TGF-β, IL-10 signaling can abolish this inhibitory effect, indicating that Treg is involved in the regulation of anti-inflammatory activity of TDC.[93] In conclusion, probiotics are potential targets for AR treatment by regulating TDC activity.

Stimulation of Toll Like Receptors?

Toll-like receptors (TLRs), as one of the main components of the body's immunity, are recognition receptors expressed on the surface of intestinal mucosal lymphocytes and epithelial cells, providing a defense barrier against invading pathogens and inflammatory responses. TLRs are located in the cytoplasmic membrane and also in intracellular endosomes, and can detect a series of pathogenic molecular patterns of bacteria, viruses and fungi, and TLR activation in dendritic cells can affect the adaptive immune response.[94]

Many microbial infections can activate TLR4 signaling, and probiotics, as part of the commensal gut microbiota, can affect TLRs, especially TLR4.[95,96] Probiotic-derived polysaccharide capsules can play a key role in controlling immune responses by modulating Th1/Th2 balance, inducing T regulatory cell differentiation, and activating DCs, which then interact with gut microbiota through TLRs.[97] In a study of probiotics (*Lactobacillus rhamnosus* GG) combined with sublingual immunotherapy (SLIT), the between-group analysis showed that the induction rate of CD4+CD25+Foxp3+ was significantly increased in the SLIT probiotic group, compared with the SLIT vitamin D group, in contrast, the percentage reduction in the TLR-positive cell group was higher.[61] The study by Marschan et al[98] showed that the transient protein produced by probiotics can induce TLR production, and this protein can alleviate allergic reactions caused by specific IgE. In addition, some TLRs can stimulate DC activation, which in turn leads to increased Treg cell production. Previous studies have pointed out that TLR may be a potential target for probiotics to affect the proliferation and differentiation of Treg cells.

In the study of Wu et al,[99] the regulatory effect of probiotics on the TLR4/NF-kB pathway in the regulation of host defense against lipopolysaccharide ovalbumin (LPS OVA)-induced lung injury and airway inflammation was elucidated. Allergic infantile asthma and TLRs have effects. Similarly, Li et al[100] studied the in vitro macrophage model, with live and inactive *Lactobacillus acidophilus* (*La* KLDS 1.0738) strains and TLR4 inhibitors, miR-146a inhibitors were treated with β Milk protein (β-Lg)-induced macrophages. The results showed that β-Lg stimulation caused increased transduction of the TLR4/NF-κB signaling pathway in macrophages. Similar to the TLR4 signaling pathway inhibitor, *La* KLDS 1.0738 intervention significantly reduced allergic inflammation by inhibiting the TLR4 pathway, which was superior to the control group, especially the live *Lactobacillus acidophilus* treatment group. In addition, *La* KLDS 1.0738 strain could significantly reduce TLR4 transduction and inflammatory cytokine production, which were closely associated with upregulation of miR-146a levels. Taken together, these observations suggest that probiotics can modulate allergic inflammation dependent on the TLR4/NF-κB pathway.

Probiotics Affect Type 2 Innate Lymphocytes

Innate lymphocytes (ILCs) are innate immune cells that are difficult to identify, and are divided into five subtypes, NK cells correspond to CD8+ T cells, and Th1, Th2, and Th17 cells correspond to ILC1s, ILC2s, and ILC3s, respectively. Related ILC and T cell subsets have similar functions and similarly similar regulatory pathways.[101] Type 2 innate lymphocytes (ILC2s) correspond to Th2 cells in adaptive immunity and are closely related to allergic disease development and systemic immune regulation.[102] Th2 cells and ILC2s play a role in the development of type II immune responses by releasing cytokines such as IL-4, IL-5, IL-9, and IL-13.[103] Although the number of ILC2s is small in various diseases, they are indispensable for various allergic diseases, in-depth study of the impact of ILC2s on different allergic diseases will help to better understand the relationship between allergic response and immune system, the relationship between them is important.

AR is an IgE-mediated inflammation that results in increased numbers of Th2 cells and type II cytokines in the nasal mucosa.[104] Peng et al[105] identified the distribution of ILC2s on the nasal mucosa by immunohistochemistry and found that the number of ILC2s in the nasal mucosa was positively correlated with AR clinical visual analog scale (VAS) scores. Multiple lipid receptors have been reported to be upregulated in AR patients, including CysL1R (LTD4 ligand) and PGD2. Although LTD4 was shown to activate IL-4 production in ILC2s, IL-4 levels in nasal secretions of

AR patients were not significantly changed.[106] Ozone aggravates AR symptoms by inducing the release of IL-5 and IL-13 from ILC2s.[107] Children with HDM-AR had significantly higher levels of ILC2 in peripheral blood than children without HDM-AR.[108] All these findings suggest that ILC2s play an important role in regulation in AR. Meanwhile, in a study of papain-induced BL6 mice, treatment with the probiotic *Escherichia coli* strain Nissle 1917 (ECN) resulted in a smaller decrease in IL-5, a significant decrease in IL-13, and a significant decrease in IL-33 levels. ECN-treated mice had significantly lower CD3+CD4+IL5+ and IL13+ cell frequencies compared to untreated controls. Data suggest that ECN is able to inhibit the activation of Th2 and ILC2s and the production of prototypical sensitizing IL-5 and IL-13.[109] Therefore, probiotics can control the occurrence and development of AR by inhibiting the activation of ILC2s, but the current research is relatively limited, and more basic and clinical studies are needed to evaluate the long-term therapeutic effect in the future.

Regulation of the Gut Microflora (Regulation of Metabolism?)

As the largest digestive organ in the human body, the gut contains hundreds of microbiota.[110] The microbiota in the human gut is closely related to the physiological functions of the body, is an important part of human life activities, and is mostly considered to be beneficial to the human body, the microbiota can not only improve the efficiency of life activities related to energy metabolism, but also participate in human immunity, system activation, while maintaining the homeostasis of human immunity.[111,112] Under normal circumstances, the interaction between the microbiota and the body is the basis for determining the health of the body, and if one of these links is damaged, it may cause intestinal flora imbalance.[113] Dysregulation of the gut microbiota significantly affects the metabolism between the microbiota and the host, and suppresses the host immune system.[114,115] Most allergic diseases are associated with an imbalance of gut microbiota, such as AR.[116,117] Alterations in microbial diversity in early infancy relative to school age (6–8 years) predispose to the development of AR and asthma. Elevated serum IgE levels are a risk factor for allergen sensitization in children, and some studies have found that decreased gut microbiota diversity may be closely related to increased serum IgE levels.[118] In summary, the imbalance of the body's microbiota may be beneficial to the occurrence and development of AR.

As an important means to regulate the balance of intestinal flora, probiotics include a wide variety of bacteria, and their main role is to promote the production of pro-anti-inflammatory factors, maintain the balance of the immune system, improve the structure of the flora, restore the balance of the flora, and at the same time, it can alleviate the local mucosal inflammatory response in the intestinal tract, restore the mucosal barrier, and block the invasion of foreign pathogens.[119] Studies have shown that the addition of probiotics can modulate the immune response of AR by restoring intestinal flora disturbances.[120] Another study pointed out that after treatment with probiotic fermented milk, the serum-specific IgE in patients with hay fever was significantly reduced, the immune function was significantly improved, the structure of intestinal flora in the body was improved, and the balance of intestinal flora was restored, symptoms were also significantly relieved. As an adjuvant therapy for AR, probiotics can not only restore the intestinal microbiota disturbance of the body from a deeper level and relieve the typical symptoms of nasal allergy, but also have the advantages of high cost performance and low risk.[121] In a study on the efficacy of probiotics in the treatment of AR, Schaefer et al[122] found that the allergic symptoms of patients were not significantly relieved, but the nasal mucosa microenvironment of some patients was improved compared with before treatment. Kim et al[123] found that AR treatment with a probiotic mixture (PM) of *Bifidobacterium longum* and *Lactobacillus plantarum* isolated from human feces and kimchi could alleviate AR by controlling intestinal flora disturbance (significantly inhibited deformation bacteria, increasing the composition of *Bacteroides* and *Actinomyces*). The results of Hu et al[124] showed that probiotics and L-glutamine can effectively regulate the level of gastrointestinal peptides in the treatment of children with AR, restore the balance of intestinal microflora, and restore the barrier function of the intestinal mucosa for the purpose of treatment.

Based on the above research results, it can be seen that probiotics can regulate and restore intestinal microbiota disorders to treat AR. Currently, as a new direction of clinical allergic disease research, it is expected to become a potential new target for AR control and treatment. The possible mechanisms of probiotics for AR treatment is shown in Figure 2.

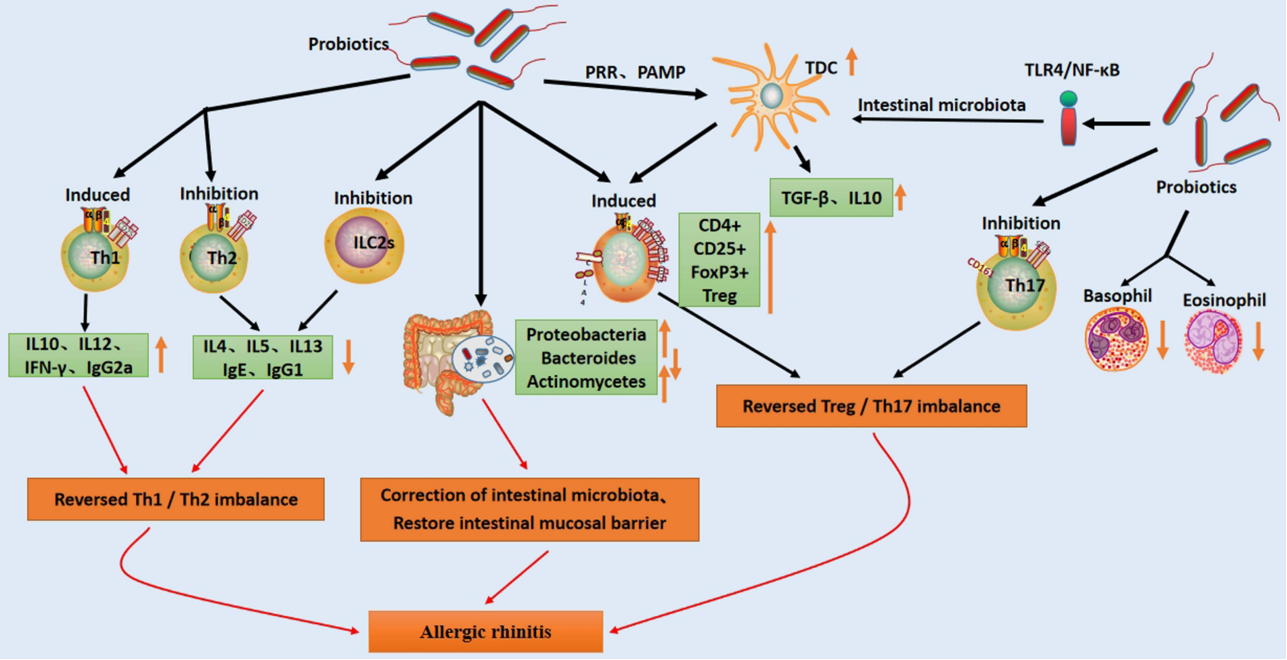

Figure 2 Brief mechanism of probiotic treatment of allergic rhinitis. Probiotics protect against allergic rhinitis by reducing serum pro-inflammatory factors, increasing the number of immune cells, regulating Th1 and Th2 balance, increasing Treg numbers, and inhibiting Th17. In addition, probiotics can directly stimulate the formation of TDCs or activate the TLR pathway to indirectly stimulate DC, thereby inducing the formation of Tregs. Probiotics can improve AR by increasing the level of beneficial bacteria to regulate the stability of the gut microbiota, restoring the intestinal mucosal barrier.

Abbreviations: TDC, tolerogenic dendritic cell; IL, interleukin; ILC2s, type 2 innate lymphocytes; IgE, immunoglobulin E; IgG2a, immunoglobulin G2a; IgG1, immunoglobulin G1; Th1, type 1 helper T lymphocyte; Th2, type 2 helper T lymphocyte; Th17, type 17 helper T lymphocyte; TGF-β, transforming growth factor-β; IFN-γ, interferon-γ; TLR4/NF-κB, toll like receptor-4/nuclear factor-κB; Foxp3, forkhead box protein p3; Treg, T regulatory cells.

Conclusion

Probiotics have clear benefits for clinical AR patients and can represent an aspect of future management of AR therapy. Probiotics have excellent immune regulation effects. A large number of research data show that probiotics play a vital role in regulating the immune system of the body, and also have an impact on various stages of autoimmune-related diseases, it has great potential in related diseases, especially for the treatment of AR. At present, clinicians have an increasing understanding of how probiotics can affect the immune regulation of the body, and the research on the basic mechanism of using probiotics to treat AR is increasing, mainly focusing on how probiotics regulate the balance and influence of Th1/Th2 and Treg/Th17 cells Tolerance dendritic cell activity, stimulation of Toll-like receptors, regulation affecting type 2 innate lymphocytes and gut microbiota, and associated immune cells and immune factors. At the same time, probiotic fusion proteins may be a new way to improve the therapeutic effect of AR. The optimal strain, dosage and duration of probiotics need to be further explored, and further research should clarify the clinical efficacy of probiotics, the selection scheme, the design of appropriate study populations, and the safety of using probiotics. Fundamental research in this area is underway and will hopefully provide better insights into how probiotics can help treat AR and even allergy-related diseases.

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Disclosure

The authors report no conflicts of interest in this work.

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