MECHANISMS OF PROBIOTIC ACTION ON IMMUNE CELLS AND THEIR HEALTH BENEFITS IN HUMANS

Bazarova Gulnora Rustamovna

Associate Professor at the "Alfraganus" university's medical faculty

g.bazarova@afu.uz

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Abstract: Intestinal immune cells and commensal microorganisms continuously interact to maintain immune homeostasis. This relationship involves complex pathways that regulate the balance between immune tolerance and activation. Probiotic bacteria influence intestinal immune cells and resident microbiota, thereby modulating immune responses and supporting normal immune function. Growing evidence highlights their health-promoting and immunomodulatory properties, suggesting that probiotics may offer a promising approach to improving immune regulation. However, research has focused mainly on their metabolic and nutritional effects, while their interactions with host immune cells remain only partially understood. This review summarizes current evidence on the mechanisms through which probiotics interact with immune cells and contribute to improved immune function.

Keywords: immune cells, probiotics, human health, gut microbiota, beneficial microorganisms, microbiome, immune modulation, immune response

I. Introduction

The intestine is a complex and continuously changing ecosystem whose immune system has adapted to constant exposure to dietary antigens and potentially pathogenic microorganisms. Different intestinal immune cell populations protect against infections while maintaining tolerance to commensal bacteria and food antigens. These functions are strongly influenced by resident microorganisms with beneficial immunomodulatory properties. Interactions among immune cells, commensal microbes and nutrients help maintain immune homeostasis and regulate both innate and adaptive immune responses.

The intestinal environment provides favorable conditions for beneficial microorganisms to establish and exert their effects. Throughout life, humans coexist with diverse microbial populations in the gastrointestinal tract. These microorganisms have adapted to intestinal conditions, and their interactions with the host contribute to immune development and protection against infectious and inflammatory diseases. However, changes in microbial composition can disrupt immune regulation and potentially contribute to autoimmune disorders.

According to the Food and Agriculture Organization and World Health Organization, probiotics are live microorganisms that provide health benefits when administered in adequate amounts. These microorganisms are commonly consumed through foods and supplements and can influence intestinal microbial composition and interact with various immune cell populations. Through these activities, probiotics may support immune function, help prevent certain disorders and offer potential applications in disease management.

Despite growing recognition of their beneficial effects, the mechanisms underlying probiotic interactions with host immune cells remain incompletely understood. Much of the existing research has focused on their metabolic and nutritional properties, with comparatively less attention given to their immunomodulatory activities. Further investigation is also needed to identify new probiotic strains with beneficial immune-regulating properties.

This review summarizes current findings on the interactions between probiotic bacteria and host immune cells, with particular emphasis on the mechanisms through which probiotics regulate immune responses and support host immune function.

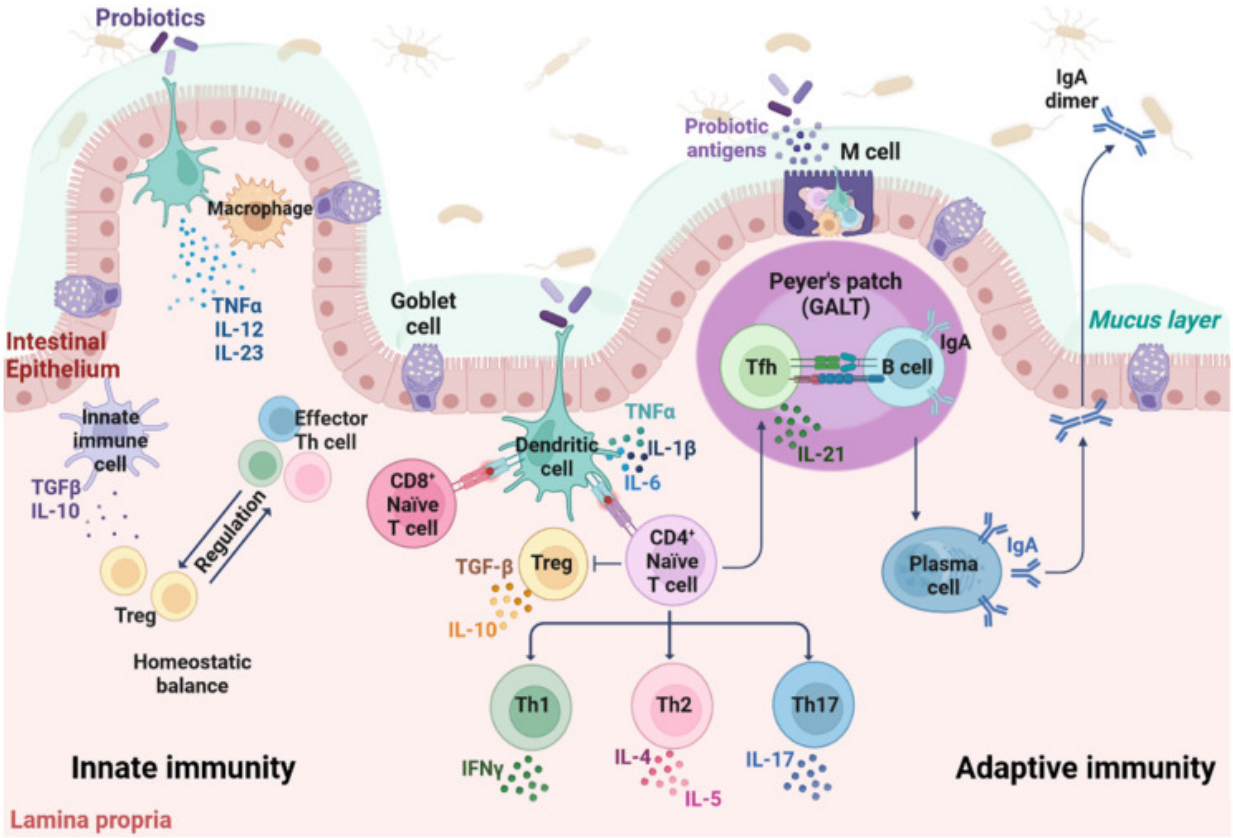
II. The Gut Immune System

The intestinal immune system consists of physical barriers, including the epithelial layer and the underlying connective tissue, known as the lamina propria, which contains immune effector cells. Gut-associated lymphoid tissue (GALT), another essential component of intestinal immunity, forms part of the mucosa-associated lymphoid tissue (MALT) and represents the largest component of the body's overall immune system. It serves as a major reservoir of T and B lymphocytes, which migrate to effector sites to initiate immune responses. GALT also contains various populations of dendritic cells (DCs).

An important structural component of GALT is the Peyer's patches, which are lymphoid structures associated with the follicle-containing epithelium and distributed throughout the intestinal mucosa. They contribute to immune surveillance by monitoring intestinal bacteria and protecting against pathogenic infections. Functionally, the intestinal epithelium acts as the first line of defense against external stimuli, whereas GALT is primarily involved in adaptive immune responses. Dendritic cells capture antigens transported through the epithelium and microfold (M) cells, subsequently presenting them to T lymphocytes to initiate antigen-specific immune activation.

Figure 1. Schematic representation of the interaction between host intestinal immune cells and probiotics. Probiotics play a role in host innate and adaptive immune responses by modulating immune cells such as dendritic cells (DCs), macrophages, and B and T lymphocytes. Interactions between host intestinal cells and probiotics mainly occur at the surface of the intestinal barrier, including the intestinal epithelium and the underlying lamina propria. Intestinal microbiota is separated from the intestinal epithelium by a mucus layer secreted by goblet cells. Consumed probiotic bacteria adhere to intestinal epithelial cells and activate them by pattern recognition receptors (PRRs). Cytokines stimulated by probiotic bacteria lead to the activation of T regulatory (Treg) cells, which maintain immune homeostasis in the intestinal mucosa.

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Tregs are effective suppressors of the immune response and play a key role in limiting immune response. Intestinal antigens are transferred to DCs via specialized enterocytes known as microfold cells (M cells), which are located in the epithelium overlying Peyer's patch. Probiotics are processed directly by DCs in lamina propria in the intestinal lumen. Intestinal DCs can activate CD8+/CD4+ naïve T cells and direct helper T cell responses towards Th1, Th2, Th17, or regulatory patterns. The Th1 immune response is mainly characterized by interferon (IFN)-γ production and is involved in cell-mediated immunity. The Th2 immune response includes interleukin (IL)-4, IL-5 release, thus inducing humoral immunity. The Th17 immune response is characterized by IL-17 production. Induction of Tregs releases IL-10 or transforming growth factor (TGF)-β. In addition, probiotics induce maturation of B cells into immunoglobulin (Ig)A-producing plasma cells. Intestinal epithelial cells release cytokines and chemokines, creating a microenvironment in the lamina propria of the intestine that allows the clonal expansion of B cells to produce IgAs. IgAs migrate through the epithelium into the mucus layer where they control bacterial adhesion to the host tissue.

III. The Intestinal Immune System and Its Interaction with the Microbiota

Owing to its cellular composition and complex histological organization, the intestine is regarded as the body's largest immunological organ. Approximately 70–80% of all IgA-producing B cells are located within this organ. Immunoglobulin A (IgA) represents a protease-resistant antibody produced locally in mucosal effector tissues and plays a central role in mucosal defense. It protects mucosal surfaces by binding to and neutralizing foreign antigens, including those derived from pathogens and toxins. Through this mechanism, IgA prevents microorganisms from attaching to intestinal epithelial cells and subsequently penetrating the epithelial barrier. Nevertheless, emerging evidence indicates that IgA may also contribute to inflammatory processes in both mucosal and extra-mucosal tissues.

Intestinal defense relies on the coordinated activity of two major branches of immunity: innate and adaptive. Adaptive immunity includes both humoral, antibody-mediated responses and cell-mediated mechanisms. Innate immunity provides the initial, non-specific defense against potentially harmful external agents. Its principal components include physical and chemical barriers, such as the skin and mucous membranes; immune cells, including dendritic cells (DCs), monocytes, macrophages, neutrophils and natural killer (NK) cells; and signaling molecules such as cytokines.

In contrast, adaptive immunity provides a highly specific response and involves two main lymphocyte populations: B cells and T cells. B lymphocytes produce immunoglobulins (Igs), mediating antibody-dependent protection, whereas T lymphocytes participate in cell-mediated immune responses. The interaction between major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs) and T-cell receptors on CD4+ helper T lymphocytes is essential for their activation, differentiation and maintenance. T-cell-mediated responses also involve CD8 and CD4 co-receptors, which recognize antigens presented by MHC class I and class II molecules, respectively.

Dendritic cells, which express MHC class II molecules,

serve as important antigen-presenting cells linking innate and adaptive immunity. Following antigenic stimulation, naïve CD4+ T cells can differentiate into distinct helper T-cell subsets according to the cytokine environment and specific signals provided by APCs. Cytokines are small regulatory proteins that coordinate immune activity. Anti-inflammatory cytokines, particularly interleukin-10 (IL-10), help regulate immune responses by limiting pro-inflammatory signaling. Important pro-inflammatory mediators involved in intestinal inflammation include interferon-γ (IFN-γ), IL-12, IL-1β and tumor necrosis factor-α (TNF-α).

The intestinal surface is covered by a viscoelastic mucus layer that works together with antimicrobial peptides, proteins and antigen-specific mucosal immune cells to protect the underlying tissues. This barrier limits the access of potentially harmful agents to the intestinal epithelium and lamina propria. Mucus is primarily composed of mucins, which are large glycoproteins containing O-linked glycans and are secreted by goblet cells distributed throughout the intestinal epithelium.

Under normal physiological conditions, the host and intestinal microbiota maintain a mutually beneficial relationship. The host provides microorganisms with nutrients and a stable protective environment, while the microbiota contributes to nutrient metabolism and supports the physiological integrity of the intestinal mucosa. The gut can therefore be viewed as a complex microbial ecosystem containing approximately 10^{14} bacteria that contribute to host metabolic processes.

The intestinal microbiota supports digestion and the absorption of dietary nutrients, while also participating in the breakdown of cellular debris and other host-derived materials. It additionally contributes to the metabolism of drugs and xenobiotic compounds. Commensal microorganisms support host nutrition by producing short-chain fatty acids (SCFAs), vitamins and certain essential amino acids through the degradation of complex polysaccharides and proteins that cannot be digested by the host alone. Collectively, these activities help preserve the structural integrity and barrier function of the intestinal mucosa. Another essential function of commensal bacteria is the maintenance of immune homeostasis, with numerous beneficial microbial species contributing to the regulation of intestinal immune activity.

One of the key characteristics of intestinal immunity is its ability to distinguish beneficial commensal microorganisms from potentially harmful pathogens. Immunological tolerance prevents unnecessary immune reactions against resident bacteria, even when some of their cellular components resemble those of pathogenic microorganisms. Similarly, oral tolerance is an active regulatory process that prevents excessive immune responses to harmless dietary antigens through immune exclusion and immunosuppressive mechanisms.

These processes are regulated partly by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), expressed on intestinal immune surveillance cells such as macrophages and dendritic cells. By detecting microbial components, these receptors contribute to intestinal defense and regulate the production of pro- and anti-inflammatory cytokines. Nucleotide-binding oligomerization domain (NOD)-like receptors, in contrast, are located intracellularly and monitor microbial signals within the cytoplasm. Together, these recognition systems enable the immune system to distinguish commensal microorganisms from harmful pathogens.

The balance between immunological tolerance and immune activation is essential for maintaining intestinal mucosal homeostasis. Intestinal epithelial cells also contribute to this balance by regulating interactions between the host immune system and the microbiota. While immune mechanisms control microbial colonization and limit bacterial attachment to the mucosal surface, intestinal microorganisms and their metabolites can, in turn, influence immune function.

The immunomodulatory effects of probiotics and other beneficial microorganisms involve several mechanisms, including the activation of macrophages, stimulation of IgA-producing cells and neutrophils, enhancement of peripheral immunoglobulin production, promotion of mucus secretion and suppression of pro-inflammatory cytokine release.

IV. Probiotic Bacteria

The concept of probiotics as beneficial microorganisms naturally inhabiting the gastrointestinal tract emerged in the late nineteenth century, following observations of microbial populations in healthy individuals without gastrointestinal symptoms. Today, probiotics are widely recognized as beneficial microorganisms found in various foods and within the human digestive system. They can compete with potentially harmful microorganisms, establish themselves in the intestinal environment and support health by improving or restoring the composition and functional activity of the gut microbiota.

Most probiotic microorganisms are Gram-positive bacteria, particularly members of the genera Lactobacillus and Bifidobacterium. Other microorganisms with recognized probiotic properties include selected strains of Escherichia coli, Enterococcus and Pediococcus, as well as certain yeasts, such as Saccharomyces boulardii. Some commensal intestinal bacteria, including Streptococcus oralis and Streptococcus salivarius, have also been associated with beneficial health effects.

Probiotics contribute to intestinal homeostasis through several mechanisms. These include: (i) strengthening innate and adaptive immune responses while supporting antimicrobial and anti-inflammatory activities; (ii) improving the availability and absorption of certain biologically active compounds and essential nutrients; and (iii) reducing food intolerance in susceptible individuals. Similar to naturally occurring commensal bacteria, dietary probiotics may therefore support overall health by promoting digestive function and immune regulation.

The beneficial activities of probiotics involve diverse molecular mechanisms, reflecting the wide range of compounds they produce and release. These microorganisms interact with intestinal cells through metabolic cross-feeding processes and direct cell-to-cell contact. They also release numerous bioactive substances into the intestinal environment, facilitating communication between the gut microbiota, epithelial cells and immune system. Their molecular mediators include surface-associated or secreted proteins, small peptides and amino acids, bacterial DNA, and short-chain fatty acids (SCFAs). In addition, probiotic antigens and bacterial cell components may cross the intestinal barrier and interact with

immune cells, contributing to the regulation of host physiological processes.

Unlike conventional supplements that generally target particular physiological functions or body systems, probiotics may exert beneficial effects across multiple tissues and organs. Their potential health applications have been investigated in various conditions, including allergic disorders, diarrhea, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), infections, infantile colic and certain types of cancer. Selected probiotic strains may also complement antibiotic treatment by reducing treatment-associated adverse effects and supporting mucosal immune function. In patients receiving broad-spectrum antibiotics, probiotics may help restore a balanced intestinal microbial community. Further research is ongoing to clarify their additional therapeutic applications and broader effects on human health.

V. The Gut–Brain and Gut–Lung Axes

The intestinal microbiota exerts important immunomodulatory effects at both local and systemic levels. Through complex biochemical signaling pathways, the gastrointestinal tract communicates with various organ systems, particularly the central nervous system (CNS) and respiratory system. These interactions are commonly described as the microbiota–gut–brain axis and the microbiota–gut–lung axis. Although commensal microorganisms primarily reside in the intestine, their effects can extend to distant organs, including the brain and lungs. Consequently, alterations in microbial composition caused by disturbances in intestinal homeostasis, specific pathological conditions or dietary changes may influence immune regulation and physiological balance within the CNS and respiratory tract.

The gut–brain axis involves an intricate network of neural and hormonal pathways that enables continuous, bidirectional communication between the gastrointestinal tract and the brain under both physiological and pathological conditions. Experimental studies have demonstrated that intestinal microorganisms contribute to the development and maturation of the enteric nervous system and the hypothalamic–pituitary–adrenal (HPA) axis. The absence of commensal bacteria has also been associated with disturbances in neurotransmitter expression and metabolism. Furthermore, gut microbiota influences sensory signaling from the intestine and produces metabolites capable of interacting directly with nervous system cells.

Through these mechanisms, probiotics may contribute to the regulation of neuroendocrine and immune functions. For example, experimental administration of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 has been shown to reduce HPA-axis and autonomic nervous system activity. Probiotic supplementation has also been associated with enhanced hippocampal neurogenesis and altered expression of hypothalamic genes involved in synaptic plasticity. Communication also occurs in the opposite direction, as the CNS can influence intestinal physiology by modifying mucus and biofilm production, gastrointestinal motility, epithelial permeability and local immune responses.

Although the respiratory tract was traditionally considered sterile, research has established that healthy individuals possess distinct microbial communities throughout the respiratory system, with considerable differences between the upper and lower airways. The predominant microbial groups vary according to anatomical location: Firmicutes and Actinobacteria are commonly found in the nasal cavity, Firmicutes, Proteobacteria and Bacteroidetes predominate in the oropharynx, while Bacteroidetes and Firmicutes are characteristic of the lung microbiota. These microbial populations maintain continuous interactions with local host immune cells, contributing to respiratory immune regulation.

In addition to the activity of microorganisms residing within the respiratory tract, intestinal microbiota also plays an important role in maintaining pulmonary homeostasis. This gut–lung communication may involve the production and systemic transport of microbial molecules, including pathogen-associated molecular patterns (PAMPs), from the intestine to the lungs, where they can influence local immune responses. Thus, microbial metabolites represent important immunomodulatory mediators and may offer potential therapeutic opportunities for managing certain respiratory diseases.

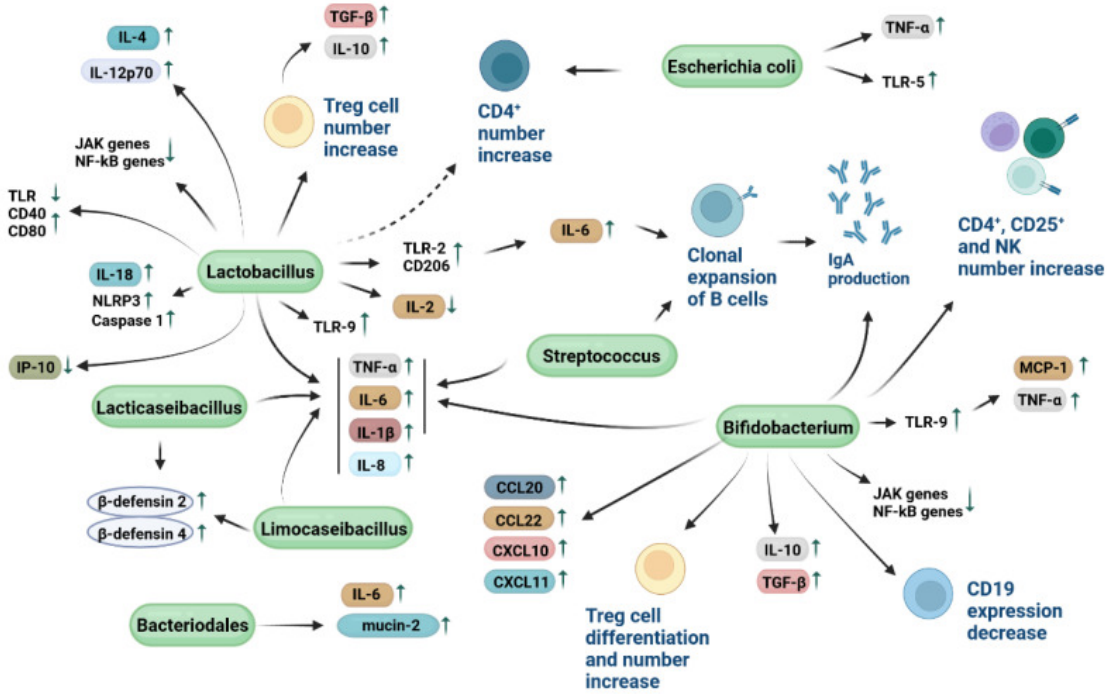
VI. Immunomodulatory Mechanisms of Probiotic Bacteria

Immunomodulation represents one of the principal biological functions of probiotic microorganisms. This activity is mediated through their interactions with various immune cell populations, including lymphocytes, monocytes, macrophages and dendritic cells (DCs), as well as intestinal epithelial cells. One important mechanism by which probiotics strengthen intestinal immunity is the stimulation of B lymphocytes to produce immunoglobulin A (IgA).

Oral administration of several probiotic strains, including Lactobacillus casei, L. acidophilus, L. rhamnosus, L. delbrueckii subsp. bulgaricus, L. plantarum and L. lactis, together with Streptococcus thermophilus, has been associated with a dose-dependent increase in the population of intestinal IgA-producing cells. These microorganisms can promote the clonal proliferation of B lymphocytes and enhance IgA secretion without causing a corresponding increase in CD4+ T-cell numbers. Other investigations have similarly demonstrated that probiotic supplementation stimulates the production of secretory IgA, thereby contributing to mucosal immune protection.

The underlying mechanism has been further investigated using Lactobacillus casei CRL 431 and Lactobacillus helveticus R389. Their oral administration was associated with increased IL-6 production through a Toll-like receptor 2 (TLR2)-dependent pathway. This cytokine response was accompanied by an expansion of intestinal IgA-producing cells without a significant change in the number of CD4+ T lymphocytes. These findings suggest that lactobacilli may enhance B-cell clonal expansion and promote intestinal IgA production through IL-6-mediated signaling.

Figure 2. Mechanisms of action of probiotic bacteria. Lactobacillus can (i) stimulate T cell regulatory cells (Treg cells) to produce TGF-β, interleukin-10 (IL-10), and IL-8, (ii) increase levels of secreted IL-6 secreted in a Toll-like receptor (TLR)-2-dependent manner, thereby inducing the clonal expansion of all IgA-producing B cells, while also stimulating



the expression of macrophage mannose receptor CD206, (iii) inhibit the expression of Janus kinase (JAK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) genes, (iv) increase the release of IL-12p70 and IL-4, (v) reduce the TLR expression and increase CD40 and CD80 expressions, (vi) degrade the proinflammatory chemokine IFN-γ-inducible protein 10 (IP-10), (vii) increase the expression of TLR-9, and (viii) favor the expression of nucleotide binding oligomeric domain-like receptor protein 3 (NLRP3), cysteine proteinase-1 (Caspase-1), and IL-18. Lacticaseibacillus and limocaseibacillus can induce β-defensins 2 and 4 and IL-8 expressions. Distinct studies reported opposing data on TLR expression. Bifidobacterium can (i) inhibit the expression JAK and NF-κB genes, (ii) favor the overexpression of IL-10 and TGF-β, while, at the same time, stimulate the production of IgAs, (iii) favor Treg cell differentiation, (iv) increase the total helper (CD4+) and activated (CD25+) T lymphocytes and NK cells, (v) reduce the expression of CD19 on B cells, (vi) induces the production of monocyte chemoattractant protein 1 (MCP-1) and TNF-α through TLR-9 stimulation, and (vii) increase the number of Foxp3(+) T regulatory cells and the release of CCL20, CCL22, CXCL10, and CXCL11. Escherichia coli can induce the expression of TLR-5 and TNF-α as well as increase the number of CD4+ cells. Bacteroidales stimulates the release of IL-6 accompanied by the expression of mucin-2 and claudin-1. Lactobacillus, lacticaseibacillus, limocaseibacillus, bifidobacterium, and streptococcus can favor the release of TNF-α, IL-6, IL-1β. Streptococcus can induce clonal expansion of B cells stimulated to release IgAs. Dash arrow: conflicting data have been reported on the effect of lactobacilli in increasing CD4+ T cell number.

VII. Immunomodulatory Effects of Probiotic Bacteria on Mucosal and Systemic Immunity

Probiotic microorganisms enhance mucosal and systemic immune protection by stimulating the secretion of immunoglobulin A (IgA) into the intestinal lumen. Secretory IgA is released in substantial quantities and helps prevent harmful bacteria from reaching the intestinal epithelium, thereby limiting their attachment and colonization. Probiotics also contribute to antimicrobial defense by modifying the composition and properties of the viscoelastic mucus layer through the regulation of mucin expression. Furthermore, they inhibit the adhesion and proliferation of pathogenic microorganisms on mucosal surfaces, protecting intestinal epithelial cells (enterocytes) and the underlying lamina propria.

The ability of probiotics to attach to intestinal mucus involves both non-specific physical interactions, such as hydrophobic binding, and specific adhesion mechanisms mediated by bacterial surface structures. These include mucus-binding proteins containing mucus-binding (Mub) or mucin-binding (MucBP) domains; fimbriae and pili, including type IV pili and Spa-A, Spa-B and Spa-C pilus components; as well as fibronectin-binding proteins (FBPs) and surface-layer proteins (SLPs). Through these interactions, probiotics can occupy mucosal binding sites, interfere with pathogen attachment and support the establishment of beneficial commensal microorganisms. Consequently, their immunological benefits are associated with changes in both intestinal immune-cell activity and the composition of the microbial community.

Oral probiotic supplementation has also demonstrated potential immunological benefits in older individuals. Studies have reported improved immune parameters in elderly subjects consuming Bifidobacterium lactis HN019. One proposed mechanism involves increased interferon-alpha (IFN-α) production following stimulation of peripheral blood mononuclear cells (PBMCs) isolated from healthy volunteers. Similarly, consumption of milk containing viable Bifidobacterium animalis DN-173 010 has been associated with increased leukocyte counts in elderly individuals, suggesting enhanced immune activity.

Probiotic supplementation may also influence immune

function in individuals particularly susceptible to gastrointestinal infections. For example, consumption of yogurt containing Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 has been associated with increased CD4+ T-cell counts. Certain probiotic strains have additionally been suggested to help regulate inflammatory responses in these patient populations.

Rotavirus is a major cause of gastroenteritis and diarrhea in children worldwide and contributes substantially to diarrhea-related infant mortality, particularly in developing countries. The immunomodulatory potential of Lactobacillus reuteri ATCC 55730 was demonstrated in children with rotavirus-associated diarrhea. Its administration increased intestinal IgA secretion and reduced the duration of diarrhea in a dose-dependent manner. Similarly, Lactobacillus casei and Lactobacillus rhamnosus GG have shown the ability to enhance immune responses against rotavirus in children with acute diarrhea. The role of probiotics in modulating immunity against rotavirus has subsequently received considerable research attention. Various probiotic preparations are also used in the management of diarrhea, infantile colic and other gastrointestinal disorders, with lactobacilli among the most extensively investigated microorganisms for these conditions.

Growing evidence indicates that intestinal microbiota can influence the effectiveness of vaccination. Oral vaccines have often demonstrated reduced efficacy in developing countries, where children may have intestinal dysbiosis or diminished populations of beneficial commensal microorganisms required for appropriate immune responses. Disruption of the intestinal microbial balance can also contribute to inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, which are characterized by chronic intestinal inflammation. In children, alterations in the gut microbiota and impaired mucosal immune regulation may be associated with inflammatory complications and increased susceptibility to allergic sensitization.

Among probiotic-derived proteins, surface-layer proteins (SLPs) play an important role in the interaction between lactobacilli and dendritic cells (DCs). In particular, SLPs facilitate the binding of Lactobacillus acidophilus NCFM to the dendritic cell-specific receptor DC-SIGN. This interaction promotes the secretion of several cytokines, including IL-12p70, TNF-α and IL-1β. Furthermore, T cells activated by DCs exposed to L. acidophilus NCFM have been shown to stimulate IL-4 production. Other bacterial surface structures associated with the peptidoglycan (PG) layer, such as flagella, pili and fimbriae, can also be specifically recognized by host immune cells. Among these structures, the Spa-CBA pilus fibers of Lactobacillus rhamnosus GG have been particularly well characterized for their ability to mediate adhesion to host cells.

Secreted probiotic proteins also contribute to the regulation of interactions between microorganisms and immune cells. For example, Lactobacillus plantarum produces serine- and threonine-rich proteins (STp) that promote bacterial aggregation. These proteins may additionally influence dendritic cell phenotypes in patients with ulcerative colitis. Exposure of DCs to STp has been associated with reduced TLR expression and increased expression of the costimulatory molecules CD40 and CD80. Another example is Bifidobacterium longum, whose immunomodulatory activity is partly mediated by the secretion of serine protease inhibitor (serpin). This protein binds to and inhibits human neutrophil and pancreatic elastases. Similarly, Lactobacillus paracasei produces the protease lactocepin, which may help maintain intestinal immune homeostasis through anti-inflammatory activity. Lactocepin selectively degrades the pro-inflammatory chemokine IFN-γ-inducible protein 10 (IP-10), a mediator involved in lymphocyte recruitment.

Among non-protein probiotic components, lipoteichoic acids (LTAs) and exopolysaccharides (EPS) have attracted considerable attention because of their immunomodulatory properties. Teichoic acids derived from Lactobacillus plantarum have demonstrated anti-inflammatory effects in studies examining their influence on monocytes and peripheral blood mononuclear cells (PBMCs). LTAs are linear polymeric structures associated either with the peptidoglycan layer of the bacterial cell wall or with the cytoplasmic membrane. Experimental research using animal models of colitis has shown that administration of L. plantarum LTA can improve disease outcomes. Its immunomodulatory activity appears to depend on TLR2 signaling, indicating that these bacterial components can directly influence host immune responses.

Exopolysaccharides produced by Lactobacillus and Bifidobacterium species also contribute to protection against pathogen invasion. Several strains with immunomodulatory EPS activity have been identified. For instance, EPS from Lactobacillus plantarum N14 interacts with the TLR-associated RP105/MD1 receptor complex. Similarly, EPS produced by Bifidobacterium breve UCC2003 and Bifidobacterium animalis subsp. lactis may facilitate beneficial host–microbial interactions by regulating immune responses and providing protection against pathogens.

Epigenetic mechanisms, including differences in bacterial DNA methylation, may represent another pathway through which probiotics influence host immunity. Unmethylated CpG motifs present in Bifidobacterium DNA can activate TLR9 signaling in macrophages, promoting the production of monocyte chemoattractant protein 1 (MCP-1) and TNF-α. This signaling response may subsequently favor the development of a T-helper 1 (Th1)-oriented immune response.

Pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs), represent important molecular targets through which probiotics interact with host cells. These interactions regulate intracellular signaling pathways, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, thereby influencing immune mediator production. Studies have demonstrated that Lactobacillus casei CRL 431 and Lactobacillus paracasei CNCM I-1518 can interact with intestinal epithelial cells through TLR-dependent mechanisms. This interaction stimulates IL-6 secretion and monocyte chemoattractant protein 1 expression. Activated epithelial cells can subsequently influence immune cells within the lamina propria, promote cytokine release by T lymphocytes and initiate innate immune responses.

Several probiotic strains, including Lactobacillus helveticus IMAU70129, Lactobacillus rhamnosus GG, Lactobacillus rhamnosus KLSD and Lactobacillus casei IMAU60214,

have demonstrated the ability to enhance innate immune activity in vitro. Their effects include increased phagocytic and bactericidal functions of human monocyte-derived macrophages, elevated reactive oxygen species (ROS) production and enhanced nuclear translocation of NF-κB p65. These responses are also associated with TLR2-dependent signaling. Similarly, experiments involving Lactobacillus johnsonii NBRC 13952 have demonstrated increased macrophage phagocytic activity, together with enhanced expression of IL-1β and the costimulatory molecule CD80 following probiotic exposure.

VIII. Host Cytokine Release and Probiotics

Interactions between intestinal immune cells, epithelial cells, and probiotic bacteria can initiate signaling pathways that regulate the secretion of pro- and anti-inflammatory cytokines, thereby influencing immune function.

Different probiotic strains can modify inflammatory responses by acting as immunoregulatory agents and stimulating innate, nonspecific immune mechanisms. They may affect cytokine production either directly or indirectly through immune cells, including dendritic cells (DCs), lymphocytes, macrophages, mast cells, and granulocytes, as well as intestinal epithelial cells. The cytokines involved include interleukins (ILs), interferons (IFNs), transforming growth factors (TGFs), tumor necrosis factors (TNFs), and chemokines. Immunoregulatory probiotics can promote IL-10 secretion and regulatory T-cell (Treg) development, whereas immunostimulatory strains may enhance IL-12 production, supporting Th1-cell differentiation and natural killer (NK) cell activation. These distinct effects suggest potential applications in controlling autoimmune disorders, allergies, inflammatory bowel disease (IBD), and inflammation, as well as strengthening immune responses against infections and cancer cells.

For example, Lactobacillus casei CRL 431 has been shown to support intestinal homeostasis by stimulating IL-10 production in Th2 lymphocytes and macrophages. In vitro studies using colorectal adenocarcinoma cells co-cultured with peripheral blood mononuclear cells (PBMCs) demonstrated that Lactobacillus sakei can induce the secretion of pro-inflammatory cytokines, including IL-1β, IL-8, and TNF-α. These findings suggest that interactions between immunocompetent cells and intestinal epithelial cells may facilitate the recognition of non-pathogenic bacteria through soluble signaling molecules rather than direct cell-to-cell contact. In the same experimental setting, Lactobacillus johnsonii stimulated the production of the anti-inflammatory cytokine TGF-β.

Studies involving intestinal mucosal samples from patients with Crohn's disease have also demonstrated that exposure to L. casei, L. bulgaricus, L. crispatus, and even Escherichia coli can reduce TNF-α expression while increasing CD4+ cell numbers. These observations indicate that different bacterial strains can influence mucosal immune activity through local regulation of inflammatory cytokines. Furthermore, L. casei has been associated with increased expression of innate immune markers, particularly CD206 and TLR2, without altering T-cell numbers. Other experimental findings show that intestinal epithelial cells exposed to various Lactobacillus and Bifidobacterium strains increase the expression of IL-6, IL-10, and TGF-β while promoting immunoglobulin A (IgA) production.

Co-culture experiments involving human colon cells, colorectal cancer cells, and PBMCs exposed to Streptococcus thermophilus, L. rhamnosus, L. casei, L. acidophilus, Bifidobacterium bifidum, and B. longum have demonstrated increased TNF-α and IL-1β production, accompanied by changes in the secretion of other cytokines. Research investigating immune tolerance to intestinal commensal bacteria has further shown that exposure of dendritic cells and T lymphocytes to Lactobacillus reuteri 100-23 increases the production of the anti-inflammatory cytokines IL-10 and TGF-β while reducing IL-2 levels. This response may contribute to the expansion of Treg populations and the maintenance of intestinal immune tolerance.

A meta-analysis of eight studies examining probiotic consumption and salivary cytokine and immunoglobulin levels suggested that locally administered strains, including L. casei Shirota, L. fermentum, L. rhamnosus, and Bifidobacterium animalis, may influence salivary immune mediator production. In addition, Lacticaseibacillus paracasei SD1, L. rhamnosus SD4 and SD11, and Limosilactobacillus fermentum SD7 have been reported to stimulate the expression of human β-defensins 2 and 4, IL-1β, IL-6, IL-8, and TNF-α in gingival epithelial cells.

Experimental research using human colorectal adenocarcinoma cell lines has also indicated that sonicated preparations of Lactobacillus and Bifidobacterium can downregulate genes involved in the NF-κB signaling pathway, including JAK genes, TIRAP, IRAK4, NEMO, and RIP. Reduced IL-6 production has been observed in some experimental models following probiotic stimulation, although other studies have reported increased IL-6 secretion. Differences in experimental conditions and cellular models may account for these contrasting findings.

Collectively, these observations suggest that probiotic supplementation may help regulate intestinal inflammation, potentially contributing to the management of inflammatory conditions such as IBD. Probiotics may also influence gene expression in human cells and modify macrophage activity. For instance, Lactobacillus rhamnosus GG has been shown to interact with macrophages and potentially improve their ability to distinguish pathogenic microorganisms from beneficial bacteria through interferon-mediated regulation of TLR-related genes.

Other bacterial groups, including members of the order Bacteroidales, may contribute to intestinal immune regulation by stimulating IL-6 production and promoting the secretion of mucin-2 and claudin-1. Since IL-6 is involved in B-cell clonal expansion, this mechanism may also support B-cell activity. Similarly, in vitro studies have demonstrated that Bifidobacterium breve IPLA 20004 and B. bifidum LMG13195 can enhance intestinal barrier function and stimulate chemokine production. Co-culture experiments using these strains and human colorectal adenocarcinoma cells have shown increased Treg differentiation and the release of CCL20, CCL22, CXCL10, and CXCL11, which are involved in recruiting immune effector cells.

Among these chemokines, CCL20, also known as macrophage inflammatory protein-3α (MIP-3α), plays an important role in attracting CCR6-expressing lymphocytes and dendritic cells to mucosal tissues. It also contributes to the organization of lymphoid structures, including Peyer's patches, mesenteric lymph nodes, and gut-associated lymphoid tissue (GALT). By increasing CCL20 expression, probiotic-stimulated intestinal epithelial cells may facilitate communication between innate and adaptive mucosal immune responses.

IX. Animal Model-Based Studies with Probiotics

In vivo experimental studies have demonstrated that certain probiotic strains may support immune homeostasis, regulate host immune responses, and contribute to the prevention or treatment of various diseases. For example, oral administration of Lactobacillus gasseri SBT2055 (LG2055) in mice has been shown to stimulate IgA production and increase the proportion of IgA-positive cells in Peyer's patches and the small intestinal lamina propria. This effect may be mediated by enhanced TGF-β expression and activation of TLR2 signaling. Similarly, supplementation of healthy newborn mice with Lactobacillus reuteri DSM 17938 increased Foxp3-positive regulatory T-cell (Treg) populations and promoted greater gut microbial diversity.

The immunological effects of probiotics have also been investigated in piglets. Administration of Streptococcus faecalis, Clostridium butyricum, and Bacillus mesentericus was associated with increased numbers of CD4+ and IgM-positive cells in the liver, alongside a reduction in CD4+CD8+ T cells in Peyer's patches. Enhanced phagocytic activity of MHC class II-positive liver cells was also observed.

Probiotic-mediated regulation of cytokine production has been repeatedly demonstrated in animal models. Strains of Bacillus subtilis and Bacillus velezensis isolated from Tibetan yaks improved blood parameters associated with immune function and inflammation in mice. Their administration increased IgA, IgG, and IgM production, upregulated IL-10, and reduced the expression of TNF-α, IL-6, and IL-8. Other experiments have reported decreased production of pro-inflammatory cytokines, particularly TNF-α and IFN-γ, by splenic cells and Peyer's patch lymphocytes following probiotic treatment.

In IL-10-deficient mice with colitis, Lactobacillus salivarius and Bifidobacterium infantis significantly reduced disease severity while increasing systemic and mucosal Th1-type cytokine production. Murine colitis models have therefore become important experimental systems for investigating probiotic–host interactions. Studies using these models have shown that Lactobacillus casei CRL 431 can exert anti-inflammatory effects and stimulate the expression of the macrophage mannose receptor CD206 and TLR2 in gut-associated immune cells.

Administration of Lactobacillus acidophilus NCFB 1748 and Lactobacillus paracasei subsp. paracasei in BALB/c mice and Fischer-344 rats has been associated with increased polymorphonuclear cell chemotaxis, phagocytic activity, and TNF-α production. Both strains interacted with gut-associated lymphoid tissue (GALT), activating TLR2- and TLR4-dependent signaling pathways and promoting the secretion of IL-6, IL-10, IFN-γ, and TNF-α.

Further research in BALB/c mice demonstrated that L. casei can activate intestinal mucosal immunity through innate immune mechanisms. Following administration, CD206 and TLR2 expression increased in mononuclear cells isolated from Peyer's patches. Although the numbers of T cells and IL-5-positive cells remained unchanged, an increase in IgA-positive cells and IL-6-producing cells was observed. These findings suggest that L. casei can enhance innate immune activity without substantially altering T-cell populations. In another mouse study, Lactobacillus reuteri administration increased β-defensin-1 and secretory IgA levels while reducing Staphylococcus aureus colonies in the vaginal mucosa.

The effects of probiotics on inflammasome-related pathways have also been investigated. In a mouse model of ulcerative colitis, Lactobacillus casei ATCC 393 increased the expression of NLRP3, caspase-1, IL-1β, and IL-18. NLRP3 is an inflammasome complex involved in recognizing various microbial stimuli. Conversely, a combination of L. paracasei and L. reuteri reduced mucosal pro-inflammatory cytokine levels and attenuated colitis in IL-10-deficient mice infected with Helicobacter hepaticus. One proposed mechanism involves the inhibition of intestinal NF-κB activation by lactobacilli, resulting in reduced IL-12 expression. However, the absence of IL-10 may influence IFN-γ regulation, since IL-10 can directly suppress IFN-γ-producing T and NK cells.

Studies in rats treated with Lactobacillus and Bifidobacterium have reported reduced TNF-α and IL-6 expression, together with changes in IL-10 levels and increased IgA and IgG production. Administration of Bifidobacterium bifidum MIMBb23sg also reduced IL-10 levels in the mouse ileum and downregulated colonic cyclooxygenase-2 (COX-2), suggesting a potential anti-inflammatory regulatory effect. In another experimental model, rats exposed to acrylamide developed increased systemic levels of IL-1β, IL-6, and TNF-α. Administration of a probiotic combination containing L. casei, L. acidophilus, L. rhamnosus, L. bulgaricus, B. infantis, B. breve, and Streptococcus thermophilus was associated with attenuation of this inflammatory response.

The immunological effects of probiotic-enriched milk have also been assessed in animal models. Milk supplemented with Lactobacillus casei DN 114001 promoted IL-6 release and increased the populations of macrophages, IgA-positive B lymphocytes, and goblet cells. This strain also activated calcineurin, which subsequently stimulated nuclear factor of activated T cells (NFAT), a transcription factor involved in several immune processes, including T-cell development, anergy, apoptosis, and immune system aging. Comparable findings were reported in mice receiving L. acidophilus strains CRL 1462 and A9, L. casei CRL 431, and Escherichia coli strains 129 and 13-7. The two L. acidophilus strains and L. casei CRL 431 increased TLR9 expression, while all tested probiotics increased the number of calcineurin-expressing cells in the lamina propria.

Another study examined the immunomodulatory properties of Lactiplantibacillus plantarum strains CJLP243, CJW55-10, and CJLP475 in immunodeficient mice. Bone marrow-derived macrophages isolated from treated animals

showed increased secretion of IL-6, IL-12, and IFN-α, accompanied by enhanced expression of the co-stimulatory molecules CD80 and CD86. Increased NK-cell proliferation and cytotoxic activity were also reported. In a separate mouse model of autoimmune dry eye, a five-strain probiotic mixture known as IRT5, containing B. bifidum, L. acidophilus, L. casei, L. reuteri, and S. thermophilus, altered the expression of proteins associated with antigen presentation in splenic CD11b-positive and CD11c-positive cells.

X. Probiotics in Experimental Models of Immune-Mediated Diseases

Animal studies have demonstrated promising effects of probiotics in several immune-mediated disorders. Formulations containing L. acidophilus, L. casei, L. reuteri, S. thermophilus, and B. bifidum have been investigated in experimental models of IBD, atopic dermatitis, and rheumatoid arthritis. Their proposed immunomodulatory mechanisms include an increase in CD4+Foxp3+ regulatory T cells and a reduction in Th1-, Th2-, and Th17-associated cytokine responses. The differentiation of T cells into Foxp3-positive Treg cells may be mediated by regulatory dendritic cells expressing high levels of IL-10, TGF-β, COX-2, and indoleamine 2,3-dioxygenase.

A review of more than 30 animal-based studies, including 28 investigations of probiotic therapy and nine examining commensal-based interventions, highlighted the potential of several multispecies formulations. Among the most promising preparations for experimental multiple sclerosis were VSL#3, containing three Bifidobacterium strains, four Lactobacillus strains, and one S. thermophilus strain, as well as L. paracasei, B. animalis, E. coli Nissle 1917, and Prevotella histicola.

VSL#3 has also been reported to reduce sickness-like behavior in mice with liver inflammation, although it did not alter disease severity, gut microbiota composition, or intestinal permeability. These effects were accompanied by reduced microglial activation, decreased cerebral monocyte infiltration, and lower TNF-α levels. In addition, administration of Lactobacillus and Bifidobacterium strains has been associated with reduced anxiety-like behavior in mice and rats. Another study investigating probiotic effects on microbiota-related degenerative changes and cognitive function found that Lactobacillus fermentum JDFM216 improved behavioral outcomes, enhanced macrophage phagocytic activity, increased secretory IgA production, and stimulated immune cell activity.

XI. Antitumor and Antiallergic Effects of Probiotics

In vivo research has also explored the potential antitumor properties of probiotics. The Lactobacillus casei BL23 strain was investigated in a mouse allograft model of HPV-induced cancer. In tumor-bearing animals receiving BL23, local Foxp3 expression was negatively associated with tumor size and T-cell subpopulations. Probiotic administration was additionally associated with local NK-cell recruitment and increased cytotoxic activity, indicating a potential antitumor effect.

The potential benefits of probiotics in allergic disorders have also been examined, particularly their ability to influence IgE production, an important component of allergic immune responses. In sensitized mice, administration of probiotic-fermented milk containing Lactobacillus bulgaricus, Streptococcus thermophilus, and L. paracasei CNCM I-1518 shifted the immune response from a Th2-dominant toward a Th1-associated profile. This was accompanied by increased IgG production, reduced IgE-associated responses, and elevated IL-10 and IFN-γ levels, with IFN-γ production attributed to Th1 cells.

Similarly, mice treated with a combination of L. rhamnosus and Lactococcus lactis showed increased TGF-β levels and Treg responses, accompanied by reduced IgE production and attenuation of allergic reactions. However, findings from an ovalbumin-induced mouse model of allergic airway disease, used to investigate asthma-related mechanisms, showed that six probiotic strains—Bifidobacterium breve M-16V, B. infantis NumRes251, B. animalis NumRes252 and NumRes253, Lactobacillus plantarum NumRes8, and L. rhamnosus NumRes6—were associated with improved lung function and changes in eosinophil numbers and IgE, IL-4, IL-5, and IL-10 levels in bronchoalveolar lavage fluid.

Combined administration of B. animalis, B. breve, L. helveticus, and L. paracasei has also been reported to alleviate allergic responses and associated clinical manifestations. In another murine allergy model, supplementation with B. breve AH1205 and B. longum AH1206 produced a protective effect that was associated with an increased population of Foxp3-positive regulatory T cells.

XII. Concluding Remarks

Accumulating evidence suggests that dietary probiotics interact with intestinal immune cells and may contribute to maintaining immune homeostasis and enhancing host immune function. Despite the long history of probiotic research, however, relatively few studies have thoroughly investigated the molecular pathways responsible for their immunomodulatory effects and the mechanisms through which they communicate with host immune cells.

Probiotics can influence both innate and adaptive intestinal immunity through several mechanisms. These include regulating the production of cytokines and chemokines by dendritic cells, lymphocytes, macrophages, mast cells, granulocytes, and intestinal epithelial cells, as well as promoting the differentiation and activity of IgA-producing cells and subsequent IgA secretion.

Through these immunomodulatory activities, probiotics may support host immune defense and contribute to the prevention or management of various inflammatory and immune-related disorders. Their potential applications have been investigated in inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), intestinal inflammation, diarrhea, infectious diseases, infantile colic, and certain types of cancer.

Nevertheless, despite considerable progress in this field, the precise mechanisms underlying interactions between ingested probiotics and intestinal immune cells remain incompletely understood. Further preclinical and clinical investigations are therefore necessary to clarify these biological pro-

cesses. More detailed molecular and mechanistic evidence will be essential for understanding probiotic–immune cell interactions and explaining how specific probiotic strains contribute to improved immune regulation and host health.

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