Review

Protein-Mediated Interactions Between Gut Microbiota, Probiotics and Host Immunity

Mohamed Hammad Aaqib Katiyan , Balu Alagar Venmathi Maran * , Hideaki Unno , Masanari Kimura

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Review

Protein-Mediated Interactions Between Gut Microbiota, Probiotics and Host Immunity

Mohamed Hammad Aaqib Katiyan [1,2], Balu Alagar Venmathi Maran [3,*] , Hideaki Unno [3,4] and Masanari Kimura [4]

[1] Department of Biomedical Sciences, School of Biosciences and Technology, Vellore Institute of Technology, Vellore 632-014, India
[2] Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4, Sakamoto, Nagasaki 852-8523, Japan
[3] Organization for Marine Science and Technology, Graduate School of Integrated Science and Technology, Nagasaki University, 1-14 Bunkyomachi, Nagasaki 852-8521, Japan
[4] Graduate School of Engineering, Graduate School of Integrated Science and Technology, Nagasaki University, 1-14 Bunkyomachi, Nagasaki 852-8521, Japan
* Correspondence: bavmaran@nagasaki-u.ac.jp

Abstract

The human gut microbiota plays a central role in shaping host immunity, metabolic homeostasis and resistance to infection. Beyond microbial metabolites, increasing evidence highlights the importance of microbial and probiotic-derived proteins as key mediators of host-microbe communication. These proteins participate in immune signalling, epithelial barrier regulation and competitive interactions with intestinal pathogens. This review synthesizes current knowledge on the protein biochemistry of gut microbes and probiotics, emphasizing their mechanisms of immune modulation and roles in host-pathogen interactions. We discuss surface-associated proteins, secreted effectors, peptides and extracellular vesicle associated proteins that influence innate and adaptive immune responses. Furthermore, we explore how probiotic strains counteract pathogenic microbes through protein-mediated mechanisms and immune training. Finally, we highlight translational implications, emerging technologies and future directions for protein focussed microbiome research. This integrative perspective aims to advance the mechanistic understanding of gut microbiota-immune interactions and inform the development of next generation probiotic and therapeutic strategies.

Keywords: gut microbiota; probiotics; immune modulations; protein biochemistry; host-microbe interactions; host-pathogen interactions; microbial proteins; gut immunity

1. Introduction

The human gastrointestinal tract houses an extraordinarily complex microbial community, trillions of microorganisms that have co-evolved with their human hosts over millennia [1]. This ecosystem, collectively termed the gut microbiota, extends far beyond passive residency; it actively shapes fundamental aspects of human physiology, from nutrient metabolism and vitamin synthesis to immune system education and pathogenic resistance [2]. When this delicate microbial balance is disrupted and a state known as dysbiosis occurs. The consequences can be profound, contributing to inflammatory bowel disease, metabolic disorders, autoimmune disease and increased susceptibility to infections [3].

Much of the existing literature has focussed on microbial metabolites as the primary mediators of microbiota-host communication. Short-chain fatty acids like butyrate, secondary bile acids and tryptophan derivatives have been extensively studied for their immunomodulatory properties [4]. However, this metabolite-centric view, while valuable, overlooks an equally important class of

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effector molecules: proteins. Microbial and probiotic proteins possess unique characteristics that metabolites simply cannot replicate the structural specificity, enzymatic catalytic activity and the ability to direct engage host cell receptors with remarkable precision [5]. These properties enable highly specific, often strain-dependent interactions that can profoundly influence immune outcomes.

Consider that different strains of the same bacterial species can elicit completely different immune responses, an observation frequently attributed to variations in their repertoires rather than metabolic outputs [6]. Similarly, heat-killed probiotic preparations often retain beneficial effects, suggesting that stable proteinaceous components, rather than live metabolic activity, mediate certain therapeutic outcomes [7]. In the pathogenic realm, bacteria deploy sophisticated protein effector systems to manipulate host immunity and it stands to reason that commensal and probiotic organisms may use analogous or antagonistic protein-based strategies [5,8].

This review takes a deliberately protein-centric approach to understanding gut microbiome-host immune interactions. We will comprehensively examine gut microbiota and probiotics with a particular focus on protein biochemistry and immune modulation, exploring both microbial and host-derived proteins, peptides and protein-containing structure that mediate host-pathogen interactions, along with emerging mechanistic insights and therapeutic implications. By synthesizing this perspective, we aim to illuminate underappreciated mechanisms of microbiota function and inspire novel microbiome-based therapeutic approaches.

2. Gut Microbiota and Immune System Crosstalk

2.1. The Intestinal Immune Landscape

The intestinal immune system faces a remarkable challenge: it must maintain tolerance to trillions of commensal bacteria and harmless dietary proteins while simultaneously defending against genuine threats [9]. This balancing act occurs within the gut-associated lymphoid tissue (GALT), the body's largest immune compartment, which includes organized structures like Peyer's patches and isolated lymphoid follicles, as well as diffuse populations of immune cells scattered throughout the lamina propria [10].

At the frontline site the intestinal epithelium, which is a single-cell-thick barrier serves dual roles as both physical partition and active immunological interface [11]. Specialized epithelial cells contribute to this function in distinct ways: enterocytes from tight junction and secrete antimicrobial peptides, goblet cells produce protective mucus layers, Paneth cells release α-defensins and lysozyme, and microfold (M) cells actively sample luminal antigens for immune presentation [12]. Beneath this epithelial layer, dendritic cells extend dendrites between epithelial cells to T cell populations which includes regulatory T cells (Tregs), T helper 17 (Th17) cells and innate lymphoid cells. They orchestrate context-appropriate responses [13,14].

Critically, the composition and functional output of these immune populations are not predetermined but rather continuously shaped by microbial signals [15]. Among these signals, proteins serve as particularly important mediators, capable of delivering specific molecular information that fine-tunes immune responses.

2.2. Microbial Protein Recognition by Pattern Recognition Receptors

The innate immune system employs pattern recognition receptors (PRRs) to detect conserved microbial structures known as pathogen-associated molecular patterns (PAMPs) [16]. While much attention has been paid to lipopolysaccharide (recognized by TLR4), peptidoglycan (sensed by NOD1/NOD2) and microbial nucleic acids (detected by TLR3, TLR7/8, TLR9 and cytosolic sensors), bacterial proteins themselves represents important PAMP molecules [17].

Flagellin provides perhaps the clearest example. This structural protein, which forms bacterial flagella, is recognized by TLR5 on intestinal epithelial cells and immune cells [18]. Upon flagellin binding by TLR5 activates NF-κB and MAPK signalling cascades, triggering production of pro-inflammatory cytokines and chemokines [19]. Interestingly, the immunogenicity of flagellin varies

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considerably among bacterial species based on the subtle protein sequence variations, demonstrating how protein structure dictates immune outcomes [20].

Beyond flagellin, bacterial lipoproteins are sensed by TLR2 in combination with TLR1 or TLR6, depending on lipid modifications [21]. The protein component of these lipoproteins contributes to recognition specificity and downstream signalling patterns. Some secreted bacterial proteins can also activate intracellular inflammasome complexes; for example, certain pore-forming toxins trigger NLRP3 inflammasome activation through membrane disruption and potassium efflux [22].

Remarkably, commensal and probiotic bacteria express proteins that modulate, rather than simply activate, PRR signalling. Certain probiotic surface proteins have shown to interface with TLR4 signalling by competing for receptor binding or altering downstream adaptor proteins recruitment [23]. Others engage alternative receptors that promote anti-inflammatory or tolerogenic signalling [5]. These molecular details like protein structure, post translational modifications, receptor binding kinetics ultimately helps to determine whether a microbial encounter promotes inflammation, tolerance or balanced immunity.

2.3. Shaping Adaptive Immunity Through Protein Antigens

Microbial proteins also function as antigens that fundamentally shape adaptive immune responses in the gut [24]. Dendritic cells constitutively sample intestinal contents, processing microbial proteins and presenting resulting peptides on MHC class II molecules to naive $CD4^+$ T cells in mesenteric lymph nodes [13]. The nature of the presenting dendritic cell, the costimulatory signals provided and the cytokine milieu all influence whether T cells differentiate into effector or regulatory phenotypes [25].

Under homeostatic conditions, presenting of commensal bacterial protein antigens predominantly induces regulatory T cells, which suppress inflammatory responses and promote tolerance [26]. This retinoic acid, drive $Foxp3^+$ Treg differentiation [27]. Remarkably, certain commensal species have been shown to express particular proteins that preferentially induce Treg responses, representing an apparent evolutionary adaptation to peaceful coexistence [28].

The antigen-specific nature of these responses has important implications. Different bacterial strains expressing distinct surface protein repertories will induce different T cell clones, potentially explaining strain-specific immunological effects observed with probiotics [6]. Moreover, the gut contains population of effector memory T cells specific for commensal bacterial antigens, maintained in a state of controlled immune activation, allowing rapid response to epithelial barrier breaches without pathological inflammation [24].

B cells and antibody responses represent another dimension of protein antigen-driven immunity. The gut produces vast quantities of secretory IgA, much of it specific for commensal bacterial surface proteins [29]. This IgA coating serves multiple functions: it limits bacterial penetration of the mucus layer, neutralizes bacterial toxins and enzymes and promotes beneficial bacterial colonization while restricting potential pathogens all through protein-specific recognition [30]. The specificity of these antibody responses underscores the importance of microbial protein diversity in shaping personalized immune landscape.

(**A**) Probiotic bacteria utilize surface proteins including S-layer proteins, pili and adhesins for epithelial adhesion and deliver secreted proteins (p40, proteases) and extracellular vesicle-packaged protein cargo to modulate epithelia and immune cell function. Surface proteins engage pattern recognition receptors (TLR2, TLR5, DC-SIGN) on epithelial cells, triggering intracellular signaling cascades (NF-κB, MAPK) that enhance barrier integrity, promote antimicrobial peptide production and create a tolerogenic immune environment. Dendritic cells sample bacterial protein antigens by extending dendrites between epithelial cells and present them to T cells, inducing regulatory T cell (Treg) differentiation. B cells produce secretory IgA that coats bacteria and limits their penetration of the mucus layer (Figure 1). (**B**) Pathogenic bacteria deploy adhesins such as intimin for epithelial attachment and inject effector proteins (SopE, SopB, OspG) via type III secretion systems (T3SS) to

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manipulate host cell cytoskeleton, disrupt tight junctions and suppress inflammatory signaling pathways including NF-κB. This enables bacterial invasion and survival while evading initial immune response. Probiotics can completely exclude pathogens through superior binding affinity or steric hindrance at epithelial attachment sites. Pathogen presence triggers recruitment of pro-inflammatory immune cells (neutrophils, M1 macrophages) and production of inflammatory cytokines (TNF-α, IL-1β, IL-6) (Figure 1). (**C**) Net immune outcomes depend on the balance between regulatory and inflammatory signals. Probiotic protein exposure (left) promotes Treg expansion, anti-inflammatory cytokine production (IL-10↑↑, TGF-β ↑), epithelial barrier integrity and mucosal IgA responses, establishing homeostasis. Pathogen protein exposure (right) triggers pro-inflammatory cytokine production (TNF-α↑↑↑, IL-1β↑↑, IL-6↑↑), barrier compromise with bacterial translocation, neutrophil infiltration and tissue inflammation. The balance scale represents the shift in immune tone from anti-inflammatory (homeostasis) to pro-inflammatory (inflammation) based on microbial protein signals (Figure 1).

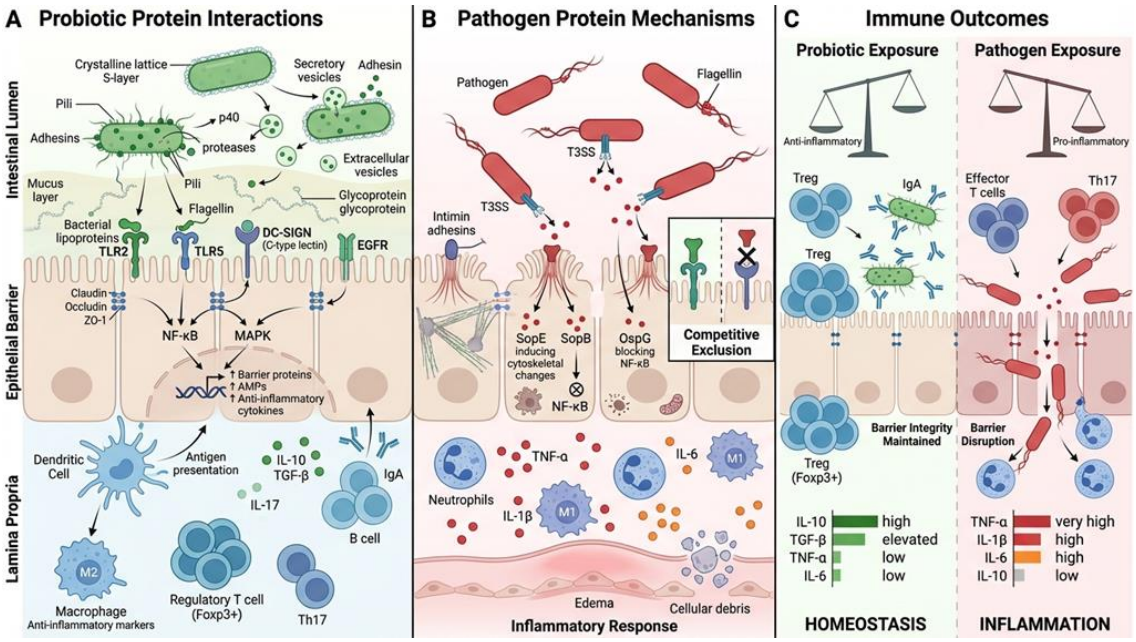

Figure 1. Protein-mediated interactions between gut microbiota and host immune system.

3. Protein Biochemistry of Gut Microbes

3.1. Surface-Associated Proteins: Adhesins and S-Layer Proteins

The bacterial cell surface represents the primary interface for host interactions and surface-displayed proteins play crucial roles in colonization, immune recognition and signalling [31]. Among probiotic lactobacilli and bifidobacteria, surface-layer (S-layer) proteins from crystalline arrays that cover the cell wall, serving both structural and functional roles [32]. S-layer proteins exhibit remarkable diversity in structure and function across different strains. In *Lactobacillus acidophilus*, the S-layer proteins (SLPs) mediates adherence to intestinal epithelial cells through interactions with glycoproteins and glycolipids on the cell surface [33]. This adhesion is not merely mechanical; it triggers intracellular signalling cascades in epithelial cells that modulate tight junction permeability, cytokine secretion and antimicrobial peptide production [34]. Interestingly, SLPs from different *L. acidophilus* strains can exhibit significant sequence variation, correlating with differential immunomodulatory properties such strains with certain SLPs variants preferentially induce anti-inflammatory cytokine profiles [35].

Pili and fimbriae represents another important class of surface proteins, particularly in bifidobacteria [36]. These hair-like proteinaceous appendages extend from the bacterial surface, mediating adhesion to mucin, epithelial cells and extracellular matrix components. *Bifidobacterium*

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bifidum express multiple types of pili, each composed of distinct pilin protein subunits with different binding specificities [36]. Some pili preferentially bind to mucin MUC2, facilitating colonization of the mucus layer, while others interact directly with epithelial cell surface receptors, triggering immunomodulatory responses [37].

Adhesins represents a broader category of surface proteins specialized for binding host structure. The sortase-anchored adhesins found in many lactobacilli contain specific domains that recognize and bind to extracellular matrix proteins like fibronectin, collagen and laminin [38]. Beyond simple adhesins, these protein-protein interactions can initiate bidirectional signalling where the bacteria sense their local environment and modify gene expression accordingly, while host cells respond to bacterial binding with altered cytoskeletal organization, signalling pathway activation and changes in genes transcription [5].

3.2. Secreted Proteins and Enzymatic Effectors

While surface proteins mediate contact-dependent interactions, secreted proteins extend bacterial influence into the surrounding microenvironment and beyond [39]. Probiotic bacteria secrete a diverse array of proteins, including enzymes, chaperons and regulatory factors that can modulate host physiology (Table 1).

Extracellular proteases and peptides represent an important functional class. *Lactobacillius* species secrete various peptidases capable of degrading dietary proteins, generating bioactive peptides and processing bacterial surface proteins [40]. Some of these peptidases have been shown to cleave host inflammatory mediators or active latent anti-inflammatory molecules, contributing to the amelioration of intestinal inflammation [41]. For example, certain probiotic-derived proteases can degrade pro-inflammatory chemokines, reducing neutrophil recruitment to inflamed tissue [42] (Table 1). This table summarizes key bacterial proteins from both probiotic and pathogenic organisms that modulate host immune responses. Probiotic proteins generally promote anti-inflammatory responses and barrier protection, while pathogenic proteins facilitate invasion and immune evasion.

Table 1. Key microbial and probiotic proteins involved in immune modulation.

Bacterial Species/strains	Protein/protein class	Function	Immune Effect	Reference
Lactobacillus acidophilus NCFM	S-layer protein (SlpA)	Adhesion to epithelial cells	Induces Treg differentiation: anti-inflammatory cytokine production	[35]
Lactobacillus rhamnosus GG	Pili (SpaA, SpaB, SpaC)	Adhesion to epithelial binding	Enhances barrier function; reduces inflammation	[43]
Lactobacillus rhamnosus GG	P40 (secreted proteins)	EGFR activation	Epithelial cell survival; barrier protection	[42]
Bifidobacterium bifidium PRL2010	Sortase-dependent pili	Mucus binding; colonization	Modulation DC function; promotes tolerance	[36]
Feacalibacterium praunsnitzii	MAM (microbial anti-inflammatory molecule)	NF-κB inhibition	Potent anti-inflammation effects	[44]
Lactobacillus spp.	Bacteriocins	Antimicrobial activity	Microbiota modulation; indirect immune effects	[45]
Pathogenic Bacteria				

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Bacterial Species/strains	Protein/protein class	Function	Immune Effect	Reference
Salmonella spp.	SopE, SopB (T3SS effectors)	Cytoskeleton manipulation	Invasion; immune evasion	[46]
Shigella spp.	OspG (effector protein)	NF-κB pathway interference	Suppresses inflammatory responses	[47]
E. coli (EHEC)	Intimin (adhesins)	Intimate attachment	Facilitates colonization and T3SS delivery	[8]
Clostridioides difficile	Toxins A and B	Cytotoxicity	Epithelial damage; inflammation	[48]

Bacteriocins, antimicrobial peptides synthesized ribosomally by bacteria, represent another important class of secreted proteins [45] (Table 1). While classically viewed as weapons for inter-bacterial competition, bacteriocins also interact with host cells. Some of them can modulate host immune responses by binding to cell surface receptors or by altering the composition of the local microbiota, indirectly influencing immune signalling [49] (Table 1). The narrow or broad spectrum of bacteriocin activity determines their impact on microbial community structure, which in turn shapes immune responses.

Probiotic bacteria also secrete molecular chaperons and stress response proteins, particularly under environmental stress condition [50]. Heat shock proteins (HSPs) and chaperonins secreted by *Lactobacillus* and *Bifidobacterium* species have been shown to interact with host immune cells, in some cases promoting anti-inflammatory cytokine production and Treg induction [51]. The immunomodulatory properties of bacterial HSPs appear context-dependent, with outcomes influenced by concentration, cellular localization and the presence of other microbial components.

3.3. Microbial Peptides and Post Translational Modifications (PTMs)

Beyond full-length proteins, bacterial-derived peptides generated through proteolysis or specialized biosynthetic pathways can exert profound biological effects [52]. These bioactive peptides may originate from dietary protein degradation by bacterial proteases, from processing of bacterial proteins or from dedicated biosynthetic machinery for non-ribosomal peptides.

Certain probiotic lactobacilli produce peptides with opioid like activity through fermentation, which can influence intestinal motility and secretion [53]. Other bacterial peptides possess anti-hypertensive, immunomodulatory or antioxidant activities, generated through strain-specific proteolytic systems [54]. The peptide sequences, length and amino acid composition all contribute to biological activity, making this a highly structure dependent phenomenon.

The gut microbiota also produces enzymes capable of modifying host proteins through PTMs. Bacterial proteases can cleave or modify host receptors, signalling molecules and structural proteins, while bacterial kinases and phosphates can alter phosphorylation states of host protein involved in signalling cascades [55]. These modifications represent direct biochemical mechanisms by which microbial proteins reshape host cell function.

3.4. Bacterial Extracellular Vesicles and Protein Cargo

Extracellular vesicles (EVs) released by gut bacteria have emerged as important vehicles for protein delivery and intracellular communication [56]. Both Gram-negative and Gram-positive bacteria produces EVs from outer membrane and membrane vesicles respectively, that packages proteins, nucleic acids, lipids and metabolites into membrane-enclosed particles [57].

The protein cargo of bacterial EVs is highly diverse and functionally significant. EVs from probiotic bacteria contain immunomodulatory proteins, adhesins, enzymes and toxins that can be delivered to host cells, sometimes crossing epithelial barriers to underlying immune cells [56]. For example, EVs from *Lactobacillus plantarum* carry surface-layer proteins and adhesins that maintain

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immunomodulatory activity when separated from the parent bacterium [58]. These vesicles-associated proteins can engage in host cell receptors, be internalized through endocytosis and influence intracellular signalling pathways. Importantly, EVs may protect protein cargo from proteolytic degradation in the harsh intestinal environment, extending the functional range and stability of microbial proteins [59]. They also enable bacteria to deliver proteins across physical barriers, potentially reaching the immune cells in the lamina propria that would otherwise be inaccessible to intact bacteria. The biogenesis, composition and uptake mechanisms of bacterial EVs remain areas of active investigation, but their role as protein delivery vehicles is increasingly recognized.

4. Probiotics as Immunomodulatory Agents

4.1. Protein-Based Mechanisms of Probiotic Action

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host [60]. While much research has focused on probiotics metabolism and metabolites production, protein-mediated mechanisms are equally central to probiotic function.

Probiotic surface proteins facilitate colonization through adhesion to intestinal epithelium, mucus and extracellular matrix, a prerequisite for exerting local effects [61]. *Lactobacillus rhamnosus* GG, one of the most extensively studied [43]. Deletion of pilus genes significantly reduces the strain's ability to adhere and to exert immunomodulatory effects, demonstrating the functional importance of these protein structure [62].

Probiotic-derived soluble proteins also contribute significantly to health effects. Culture supernatant from various *Lactobacillus* and *Bifidobacterium* strain contain secreted proteins that, when isolated and purified, retain anti-inflammatory or immunoregulatory activities [63]. These include secreted enzymes that degrade inflammatory mediators, chaperons that modulate immune cell function and as yet uncharacterized proteins that influence epithelial barrier integrity [23].

One well-characterized example is p40, a soluble protein secreted by *Lactobacillus rhamnosus* GG that activates EGFR (epidermal growth factor receptor) in intestinal epithelial cells [42]. This activation promotes cell survival, enhances barrier function and protects against cytokine-induced apoptosis. The protective effects of p40 have been demonstrated in multiple models of intestinal injury and inflammation, highlighting the therapeutic potential of individual probiotic proteins [64].

4.2. Strain-Specific Protein Profiles and Differential Effects

A remarkable feature of probiotics is that even closely related strains can exhibit dramatically different health effects as a phenomenon largely attributable to variations in proteins repertoires [6]. Comparative genomics and proteomics have revealed that strains within the same species often differ substantially in their surface protein genes, secreted protein profiles and protein modification systems [65]. For instance, different *Lactobacillus plantarum* strains possess distinct combinations of surface adhesins, resulting in variable adhesion capabilities to different intestinal cell types and differential abilities modulate immune responses [66]. Some strains preferentially induce anti-inflammatory IL-10 production by dendritic cells, while others more strongly activate pro-inflammatory pathways which differences that map to specific surface protein variants [67]. Similarly, *Bifidobacterium* species and strains vary considerably in their exopolysaccharide biosynthesis and surface protein expression, which influence both immune recognition and functional outcomes [68]. Strains with certain pili variants show enhanced ability to adhere to mucus and to persist in the gut, while others excel at immunomodulation despite lower colonization efficiency [37].

This strain specificity has important practical implications: probiotic selection for specific applications must consider the protein-level characteristics of candidate strains, not just their taxonomic identity. Mechanistic understanding of which proteins drive which effects enables rational probiotic selection and potentially, engineering of improved strains with optimized protein profiles.

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4.3. Interactions with Epithelial Cells: Barrier Function and Signalling

The intestinal epithelium serves as the primary interface between probiotic and the host, and protein-mediated interactions at this barrier are fundamental to probiotic function [69]. Probiotic adhesion to this epithelial cells, mediated by surface proteins, initiates a cascade of cellular responses that extend far beyond simple attachment.

Upon binding, probiotic proteins can trigger activation of epithelial cell signalling pathways including MAPK, PI3K/Akt and NF-κB cascades [70]. Depending on the specific proteins involved and receptors engaged, these pathways can promote epithelial cell survival, enhance tight junction integrity, stimulate mucin production or induce secretion of antimicrobial peptides and cytokines [71]. For example, certain *Lactobacillus* surface proteins activate PKC and MAPK pathways that increase expression of tight junction proteins ZQ-1, occluding and claudins thereby strengthening the epithelial barrier [72].

Probiotic proteins can also modulate epithelial cell pattern recognition receptor signalling. Some probiotic surface proteins have been shown to interact with TLR2, triggering the cytoprotective heat shock protein expression and anti-apoptotic signalling [73]. Others influence TLR signalling indirectly by modulating receptor trafficking, adaptor protein recruitment or downstream transcription factor activation [74].

Beyond signalling, probiotic proteins influence epithelial cell gene transcription. Microarray and RNA-seq studies have revealed that probiotic exposure alters expression of hundreds of genes in intestinal epithelial cells many involved in immune regulation, barrier function and stress responses [5]. While metabolites contribute to these transcriptional changes, protein-protein interactions and receptor engagement by probiotic properties are critical initiating events [75].

4.4. Modulation of Immune Cell Populations

Probiotics shape not only epithelial cell responses but also the composition and function of intestinal immune cell population, with proteins playing central roles in these interactions [76]. Dendritic cells, as professional antigen-presenting cells (APCs) and key orchestrates of adaptive immunity, are major targets of probiotic immunomodulation.

Probiotic bacteria and their surface proteins can be sampled by dendritic cells through multiple mechanisms: direct uptake of bacteria that have breached the epithelium, sampling of bacterial components transported across M cells or interaction with dendritic cell dendrites extended between epithelial cells [13]. Once internalized or engaged, probiotic proteins influence dendritic cell maturation and cytokine production. Many probiotic strains bias dendritic cells towards a tolerogenic phenotype characterized by low expression of costimulatory molecules and high production of IL-10 and TGF-β [77].

The molecular details matter: specific surface proteins from *Lactobacillus* and *Bifidobacterium* strains have been shown to engage DC-SIGN, a C-type lectin receptor on dendritic cells or to modulate TLR signaling in dendritic cells, skewing their functional phenotype [78]. These protein-primed dendritic cells subsequently induce regulatory T cell differentiation when presenting antigens to naive T cells, establishing a tolerogenic immune environment [79].

Probiotic protein also directly influences macrophage polarization. In vitro studies have demonstrated that probiotic surface proteins can shift macrophages from a pro-inflammatory M1 phenotype towards an anti-inflammatory M2 phenotype, characterized by IL-10 production and tissue repair functions [80]. This reprogramming involves changes in TLR signaling, altering in intracellular metabolic pathways and epigenetic modifications as they all initiated by protein-protein interactions at the cell surface.

Regulatory T cells, crucial mediators of intestinal immune homeostasis, are expanded and activated by many probiotic strains through protein-dependent mechanism [26]. Specific bacterial protein antigens presented by dendritic cells can induce antigen-specific Treg populations, while

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probiotic surface proteins that engage epithelial or immune cell receptors promote production of Tregs-inducing factors like TGF-β and retinoic acid [81].

4.5. Clinical Applications and Evidence

The protein-mediated immunomodulatory mechanisms of protein translate into clinical benefits across diverse condition. In inflammatory bowel disease, certain probiotic strains have demonstrated efficacy in maintaining remission of ulcerative colitis, with mechanistic studies revealing that their surface proteins and secreted factors reduce inflammatory cytokine productive cytokine production, enhance barrier integrity and promote mucosal healing [82]. The VSL#3 probiotic mixture, for example, exerts anti-inflammatory effects partly through secreted proteins that modulate NF-κB signaling in intestinal epithelial cells [83].

In allergic diseases, oral administration of specific probiotic strains has been associated with reduced allergic sensitization and symptoms, effects linked to their ability to promote Th1 responses and induce regulatory T cells through protein-mediated interactions [84]. *Lactobacillus rhamnosus* GG proteins, for instance, have been shown to modulate dendritic cell function in ways that reduce Th2-biased allergic responses [74].

Probiotic proteins may also contribute to protection against infection. By competitively excluding pathogens through surface protein-mediated adhesion, secreting bacteriocins that inhibit pathogen growth and enhancing host immune defences through immunostimulatory proteins, probiotics can reduce infection incidence and severity [5,85].

5. Host-Pathogen Interactions in the Gut

5.1. Pathogenic Protein Effectors and Immune Evasion

Intestinal pathogens have evolved sophisticated protein-based strategies to colonize the gut, evade immune defences and causes diseases [55]. Understanding these pathogenic mechanisms provides context for appreciating how probiotics and commensals counteract them through their own protein effectors.

Enteric pathogens such as *Salmonella*, pathogenic *Escherichia coli* and *Shigella* utilize type III secretion systems (T3SS) to inject effector proteins directly to host cells [86]. These effectors manipulate virtually every aspect of the host cell biology: they remodel the cytoskeleton to promote bacterial invasion, interfere with vesicular trafficking, modulate inflammatory signaling and disable antimicrobial defences [87]. For example, *Salmonella* SopE and SpoB proteins activate Rho GTPases to induce membrane ruffling and bacterial uptake, while SptP subsequently reverses these changes, erasing evidence of invasion [46].

Pathogenic bacteria can also deploy proteins that directly target immune signaling. *Shigella* OspG protein interferes with ubiquitin-dependent NF-κB activation, dampening inflammatory responses during early infection [47]. *Yesrinia* YopJ is an acetyltransferase that inactivates MAPK and NF-κB pathway components, suppressing cytokine production [88]. These examples illustrate how pathogens use protein effectors to create permissive environments for colonization and replication.

Surface-exposed pathogen protein also enable immune evasion. Some pathogens express proteins that bind complement regulators, preventing complement-mediated killing [89]. Others produce proteases that cleave immunoglobulins, antimicrobial peptides or cytokines, disabling humoral and innate defences [90]. The molecular arms race between pathogen proteins and host immune defences has driven remarkable evolutionary innovations on both sides.

5.2. Competitive Exclusion: Probiotic vs Pathogen Adhesion

One important mechanism by which probiotics protect against the pathogen is competitive exclusion by occupying ecological niches and binding sites that would otherwise be exploited by pathogens [91]. This competition often occurs at the molecular level through protein-protein and protein-glycan interactions.

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Probiotic and pathogenic surface proteins frequently compete for the same host cell receptors or extracellular matrix binding sites. For example, both *Lactobacillus* and enteropathogenic *E. coli* bind to fibronectin through specific adhesins and probiotic pre-colonization can block subsequent pathogen attachment [92]. Similarly, probiotic pili that bind mucus glycoproteins can prevent pathogen access to the epithelial surface, creating a protective microbial lever [36].

The molecular basis of competitive exclusion has been elucidated for several probiotic-pathogens pairs. *Lactobacillus acidophilus* surface proteins block adhesions of exterotoxigenic *E. coli* to intestinal epithelial cells through steric hindrance and competition for binding sites [93]. Some probiotics secrete proteins that aggregate pathogens, preventing their adherence and promoting their clearance through peristalsis [94].

Beyond simple competition, probiotic proteins can actively displace already-adhered pathogens. Certain probiotic surface proteins bind more strongly that pathogen adhesins, enabling probiotics to outcompete and displace pathogens from epithelial surfaces [95]. The kinetics and thermodynamics of these protein-mediated adhesion process determine competitive outcomes, with higher-affinity binding generally conferring advantage.

5.3. Immune Training and Enhanced Pathogen Resistance

Probiotic exposure can enhance host resistance to subsequent pathogen challenge through a process sometimes termed “immune training” [96]. This phenomenon involves probiotic proteins priming immune cells in ways that accelerate or enhance responses to future threats, without necessarily inducing classical immunological memory.

Probiotic proteins can enhance innate immune cell function through epigenetic programming. Exposure to certain probiotic surface proteins has been shown to induce chromatin remodeling and histone modification in monocytes and macrophages, rendering these cells more responsive to subsequent pathogen encounters [97]. This This “trained immunity” involves enhanced cytokine production, improved phagocytosis and more efficient pathogen killing upon re-stimulation which effects that can persist for weeks or months after the initial probiotic exposure [98].

The molecular mechanisms underlying immune training involve metabolic reprogramming triggered by probiotic protein-receptor interactions. Engagement of specific PRRs by probiotic proteins shifts cellular metabolism towards glycolysis and increases production of metabolic intermediates that serve as substrates for histone-modifying enzymes [99]. These metabolic and epigenetic changes create a cellular “memory” of probiotic exposure that enhances subsequent responses to pathogens, even though classical adaptive immune memory is not involved.

Probiotic proteins can also enhance adaptive immune responses to the pathogens. By promoting development of robust Th17 and Th1 responses while maintaining regulatory T cell population, certain probiotics create a balanced immune environment capable of mounting effective anti-pathogen responses without excessive inflammation [14]. The protein antigens from probiotics may also elicit cross-reactive antibody responses that recognize and neutralized pathogenic organisms, providing a form of molecular mimicry-based protection [100].

5.4. Pathogen-Specific Examples: Molecular Mechanisms

Examining specific pathogen-probiotic interactions at the molecular level reveals the sophistication of protein-mediated competition and protection. In the case of *Clostridiodes difficile* infection, a leading cause antibiotic-associated diarrhea, several mechanisms involving probiotic proteins have been identified [48]. Certain *Lactobacillus* and *Saccharomyces boulardii* strains produce proteases that degrade *C. difficile* toxins A and B which are the primary virulence factors, thereby neutralizing their cytotoxic effects [101]. Additionally, probiotic surface proteins can bind to the same intestinal epithelial receptors targeted by *C. difficile* toxins, providing competitive protection.

In enterohemorrhagic *E. coli* (EHEC) infection, the pathogen’s primary virulence mechanism involves intimate attachment to intestinal epithelium mediated by intimin, a surface adhesins protein

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and injection of effector proteins via T3SS [8]. Several *Lactobacillus* species interfere with this process through multiple protein-mediated mechanisms: their surface proteins compete for epithelial bindings sites, their secreted proteins modulate epithelial cell signaling to reduce expression of EHEC receptors and their bacteriocins directly inhibit EHEC growth [102]. Some probiotics also secrete proteins that aggregate EHEC bacteria, preventing their dispersal and attachment.

Salmonella enterica invasion of intestinal epithelium relies on T3SS effector proteins SopE, SopB and others that manipulate host cell cytoskeleton and signaling [103]. Probiotic interference with this invasion process can occur through several protein-independent mechanisms. *Lactobacillus rhamnosus* GG secretes soluble factors, including protein that stabilize the epithelial cytoskeleton and make cells more resistant to pathogen-induced rearrangements [104]. Additionally, probiotic activation of epithelial innate immune responses upregulates expression of antimicrobial peptides such as β-defensins which exerts direct bactericidal activity against invading enteric pathogens including *Salmonella* [105].

These pathogen-specific examples demonstrate that probiotics employ diverse, protein-mediate strategies tailored to the particular virulence mechanisms of different pathogens. Understanding these molecular interactions enables rational selection of probiotic strains for prophylaxis or treatment of specific infections.

Table 2. Comparison of Metabolite Vs Protein-mediated immune modulation. Microbial metabolites and proteins represent complementary mechanisms of host-microbe communication, with distinct physicochemical properties and biological functions. Both contribute synergistically to microbiota effects on host immunity and health.

Feature	**Microbial metabolites (eg. SCFAs)**	**Microbial proteins**
Molecular size	Small molecules (<500 Da)	Large macromolecules (10-100+ kDa)
Diffusion	Rapid; systemic distribution possible	Limited; primarily local effects
Receptor interaction	GPCRs, nuclear receptors, HDAC inhibition	PRRs, specific protein receptors, enzymatic
Strain specificity	Moderate (similar metabolite across strains)	High (unique protein repertoires per strain)
Stability	Moderate (pH, temperature sensitive)	Variable (some highly stable, others labile)
Primary mechanism	Signaling molecules, epigenetic modulation	Enzymatic activity, receptor engagement, structural
Range of action	Local + systemic	Primarily local (unless packaged in EVs)
Heat stability	Generally stable	Variable (many inactivated by heat)
Therapeutic delivery	Can be synthesized/administered directly	Requires live bacteria or EVs for delivery
Examples	Butyrate, acetate, propionate, secondary bile acids	P40, SlpA, pili proteins, MAM, bacteriocins

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5.5. Complementary Mechanisms of Action

While this review emphasizes protein-mediated mechanisms, it would be incomplete without acknowledging that metabolites and proteins often work synergistically rather than independently to shape host immunity [4]. Short-chain fatty acids (SCFAs), particularly butyrate, acetate and propionate are produced through bacterial fermentation of dietary fibres and represent the most extensively studied class of microbiota-derived metabolites [106] (Table 2). SCFAs and microbial proteins exert immunomodulatory effects through fundamentally different mechanisms. SCFAs primarily function as signaling molecules that bind to G-protein-coupled receptors (GPR41, GPR43, GPR109A) on immune and epithelial cells, triggering intracellular signaling cascades [107] (Table 2). They also serve as histone deacetylase (HDAC) inhibitors, directly influencing gene transcription through epigenetic mechanisms [108]. In contrast, microbial proteins typically engage specific protein receptors, possess enzymatic activities or function as structural components that physically interact with host cells (Table 2).

The kinetics of action also differ. Metabolites like SCFAs can rapidly diffuse through tissues, even entering systemic circulation to exert effects beyond the gut [106] (Table 2). Proteins, being larger and less diffusible, generally exert more localized effects, through bacterial EVs enable some protein-based long-range signaling [56] (Table 2). Metabolites may provide broad, systemic immune modulation, while proteins deliver more specific, targeted signals.

Importantly, metabolite and protein effects often synergize. For example, butyrate enhances intestinal barrier function by promoting tight junction assembly and mucin production, while probiotic surface proteins simultaneously strengthen barriers through direct epithelial cell engagement and signaling [109] (Table 2). The combination produces more robust barrier enhancement than either mechanism alone. Similarly, while SCFAs promote Treg differentiation through HDAC inhibition, bacterial protein antigens provide the specificity that determines which T cell clones expand and what antigens they recognize [110].

6. Therapeutic and Translational Implications

6.1. Protein-Based Probiotic Therapies

The mechanistic understanding of probiotics opens exciting therapeutic possibilities beyond traditional whole-organism probiotic supplementation. Purified or recombinant probiotic proteins could serve as therapeutic agents themselves, offering potential advantages over live bacteria including improved safety profiles, easier formulation and storage, more precise dosing and regulatory hurdles [111]. Recent advances in probiotic engineering and delivery systems have further expanded these possibilities, enabling precise control of protein expression, improved stability in the GIT and targeted interaction with the host [112].

Several proof of concept studies have demonstrated efficacy of isolated probiotic protein. The p40 protein from *L. rhamnosus* GG, when administered as a purified recombinant protein, protects against intestinal injury and promotes mucosal healing in experimental models, recapitulating key benefits of the live probiotic [42]. Similarly, purified S-layer proteins from lactobacilli retain immunomodulatory and barrier-protective properties when administered independently [35].

Protein-based therapeutics could be particularly valuable in clinical situations where live bacteria pose risks, such as in several immunocompromised patients, critically ill individuals or those with central venous catheters where bacteremia risk is elevated [113]. Heat-killed or lysed probiotics preparations that retain protein activity while eliminating viability concerns represents another application of this principle and several such products are in clinical development.

Bacterial EVs represents another protein-based therapeutic platform with significant recent momentum. EVs from beneficial bacteria can be purified, standardized and administered to deliver protein cargo without live organisms [114]. Early studies suggest that probiotic-derived EVs retain immunomodulatory and protective properties, potentially offering advantages over both purified individual proteins (which lack the natural protein cocktail) and live bacteria (which carry safety

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concerns). The development of portable microstructure electrochemical devices for EV isolation from raw samples is making clinical translational more feasible [115]. Furthermore, EVs from minimalistic bacteria like Mollicutes are revealing new mechanisms of immune modulation and horizontal gene transfer that could be harnessed therapeutically [116].

6.2. Precision Nutrition and Personalized Probiotic Selection

The protein-centric view of microbiota function also informs precision nutrition approaches the dietary and probiotic interventions to individual microbiome compositions and host characteristics [117]. Since different individuals harbor distinct microbial communities with varying protein expression profiles and since host genetics influence receptor expression and immune responsiveness, optimal probiotic selection likely varies by individual. Recent comprehensive reviews and meta-analysis have demonstrated the potential of personalized probiotic approaches for metabolic health and body weight management [118], while emerging frameworks for personalized therapeutics based on gut microbiome profiles are being developed [119].

Emerging diagnostic approaches could profile both an individual's microbiome protein expression (through metaproteomics) and their host receptor/immune status to identify which probiotics strains are most likely to successfully colonize and exert desired effects [120]. For instance, individuals with low baseline expression of certain beneficial microbial proteins might benefit from supplementation with strains that produce those proteins, while others with adequate expression might require different interventions.

Host genetic polymorphisms affecting pattern recognition receptors, cytokine receptors and signaling pathways components influence how individuals respond to specific microbial proteins [121]. Personalized probiotic selection could account for these genetic factors, matching probiotic protein profiles to host receptor genotypes to maximize bacterial interactions. While still largely theoretical, this precision approach represents a logical extension of mechanistic understanding.

6.3. Engineered Probiotics with Enhanced Protein Functions

Synthetic biology approaches enable engineering of probiotic strains with augmented or novel protein functions, creating "designer probiotics" optimized for specific therapeutics applications [122,123]. Several strategies are being pursued, each leveraging protein-level modifications, with significant advances reported in recent years.

One approach involves overexpressing beneficial endogenous proteins. Probiotic strains could be engineered to produce higher levels of anti-inflammatory proteins, adhesins that enhance colonization or antimicrobial proteins that more effectively exclude pathogens [124]. For example, *Lactococcus lactis* has been engineered to overproduce and secrete human IL-10, demonstrating therapeutic efficacy in inflammatory bowel disease models [125].

Another strategy introduces heterologous proteins into probiotic chassis organisms. Proteins could be engineered to produce therapeutic human proteins (growth factors, cytokine, enzymes), vaccine antigens or proteins from other beneficial microbes [126]. These engineered organisms serve as living factories that deliver therapeutic proteins directly to the intestinal mucosa, achieving high local concentrations while minimizing systemic exposure.

Surface display of therapeutic proteins on probiotic cells wells represents yet another approach. Proteins with antimicrobial, immunomodulatory or protein-binding proteins can be anchored to the bacterial surface, creating whole-cell biotherapeutics with enhanced functional properties [127]. This strategy has been used to create probiotics that display pathogenic-binding proteins, effectively functioning as live "pathogen sponges" that capture and remove pathogens from the gut.

Safety considerations are paramount for engineered probiotics. Strategies to prevent horizontal gene transfer, ensure biology containment and enable controlled elimination of engineered strains are essential for clinical translation [128]. Despite these challenges, engineered probiotics with optimized protein functions represents a promising frontier in microbiome-based therapeutics.

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6.4. Diagnostic and Biomarker Applications

Microbial proteins also hold promise as diagnostic biomarkers and therapeutics targets. Proteomics analysis of fecal or intestinal samples can identify microbial protein signatures associated with health or disease states [129]. For instance, elevated levels of certain pathogenic effector proteins or reduced expression of beneficial commensal proteins might serve as biomarkers for disease risk or progression.

Antibody responses to specific microbial proteins could also serve as diagnostic indicators. Individuals with inflammatory bowel disease often exhibit altered antibody profiles commensal bacterial proteins compared to health controls [130]. These antibody signatures might provide diagnostic or prognostic information and could potentially guide therapeutic decisions.

Therapeutically targeting pathogenic bacterial proteins represents another translation opportunity. Small molecules or antibodies that inhibit pathogens adhesins, neutralize toxins or block effector protein injection could serve as anti-virulence that disarm pathogens without necessarily killing them [131]. This approach might reduce selection pressure for antibiotic resistance while preserving beneficial microbiota.

7. Challenges and Future Directions

7.1. Technical and Methodological Challenges

Despite significant advances, several technical challenges limit our understandings of microbial protein functions in the gut. Metaproteomic analysis reveals the comprehensive characterization of microbial proteins in complex samples and remains technically demanding due to the enormous protein diversity, wide dynamic range of protein abundances and presence of host protein that can mask microbial signals [120]. Advances in mass spectrometry sensitive and bioinformatics tools are gradually overcoming these limitations, but comprehensive protein-level characterization of the gut microbiota remains more challenging than metagenomic or metatranscriptomic approaches. Recent development in extracellular vesicle research have added another layer of complexity, requiring standard [132,133]

Studying protein post-translational modification in the gut microbiota presents additional challenges. Many bacterial PTMs are poorly characterized and detection them requires specialized analytical approaches [134]. Yet these modifications can profoundly influence protein function and host interactions, making their characterization important for mechanistic can profoundly influence protein function and host interactions, making their characterization important for PTMs in the gut microbiota presents additional challenges. Development of enrichment strategies and detections methods for bacterial PTMs represents an important technical frontier.

Establishing causality between specific microbial proteins and host phenotypes requires sophisticated experimental approaches. While correlative metaproteomic data can identify can identify candidate proteins, demonstrating that a specific protein is necessary and sufficient for a particular effect requires genetic manipulation, protein purification and controlled experimentation [135]. For fastidious or unculturable gut bacteria, these studies remain extremely challenging.

In vivo imaging and tracking of protein-mediated interactions in the gut represents another methodological frontier. Observing how specific bacterial proteins interact with host cells in real time, within the complex three-dimensional architecture of the intestine, could provide insights impossible to obtain through in vivo studies or endpoint analyses [136]. Development of fluorescent protein reports, advanced microscopy techniques and appropriate animals' models continues to push this field forward.

7.2. Knowledge Gaps and Unanswered Questions

Numerous fundamental questions about microbial proteins in the gut remain unanswered. What is that complete protein repertoire expressed by the gut microbiota under different physiological and pathological conditions? How do microbial protein expression patterns change

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during development, aging, diet shifts or disease? We have only scratched the surface of this complexity.

The specificity of host immune responses to microbial proteins deserves deeper investigation. How many distinct microbial protein antigens do individuals develop immune responses to? What determines whether a particular bacterial protein induces tolerance, immunity or immunopathology? How stable are these responses over time and what factors drive their evolution?

The role of microbial proteins in inter-kingdom signaling beyond bacteria-host interactions merits exploration. Do fungal and archaeal proteins in the gut contribute significantly to immune modulation? How do bacteriophage proteins influence bacterial protein expression and host interactions? The multi-kingdom nature of the gut ecosystem likely involves protein-mediated interactions we have yet to appreciate.

Evolutionary questions also remain. How have microbial proteins coevolved with host immune systems? Do certain bacterial proteins families show signature of selection for immunomodulatory properties? How rapidly do bacterial protein sequence and structure of evolve in response to host immune pressure? Addressing these questions could illuminate the ancient partnership between microbiota and host.

7.3. Integration with Multi-Omics Approaches

Future progress will require integration of protein-level data with other omics layers like genomics, transcriptomics, metabolomics and host immunophenotype [137]. While genomics reveals potential, what proteins could theoretically be proved, proteomics reveals reality of what proteins are actually present. Transcriptomics bridges these, showing what proteins are being synthesized, though with imperfect correlation to final protein abundance.

Metabolomics complements proteomics by revealing the functional consequences of enzymatic protein activities. Integration protein data expression with metabolite profiles can illuminate which proteins are functionally active and what metabolic transformations they catalyze [138]. Such integration helps distinguish proteins that are merely present from those actively shaping the biochemical environment.

Host transcriptomic and immunophenotyping data contextualize microbial protein effects. Correlating microbial protein expression with host gene transcription, immune cell populations, cytokine levels and antibody response levels which microbial proteins associate with particular host states [139]. Machine learning approaches can identify complex multivariate patterns across these data layers that would be impossible to discern through univariate analyses. Temporal multi-omics profiling captures dynamic changes in microbiota-host interactions. Following microbial protein expression, metabolite production and host responses over time during interventions or disease progression levels causal and time-dependent interactions [140]. Such longitudinal designs are essential for distinguishing drivers from passengers in complex microbiota-associated phenotypes.

7.4. Regulatory and Clinical Translation Challenge

Translating protein-based microbiome therapeutics to clinical practice faces regulatory challenges. Purified microbial proteins may be regulated as biologics, requiring extensive safety and efficacy testing. Engineered probiotics face even more stringent oversight due to genetic modification concerns. Developing regulatory frameworks that appropriately balance innovation with safety is essential for advancing this field [141].

Manufacturing and quality control challenges also exist. Producing microbial proteins at scale with consistent quality or culturing engineered probiotics under GMP conditions while maintaining genetic stability, requires significant investment and expertise. Developing efficient production platforms and robust quality assurance methods will be necessary for commercial viability.

Intellectual property considerations influence development incentives. Naturally occurring microbial proteins may be difficult to patent, potentially limiting industry investment despite

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therapeutic promise. Engineered or novel formulations may be more protectable, potentially skewing development toward modified rather than natural products. Balancing open science with commercial incentives remain an ongoing challenge in microbiome research.

8. Conclusion

The protein biochemistry of gut microbes and probiotics represents a rich and underexplored dimensions of host-microbe interactions with profound implications for immunity, health and disease. While metabolites have dominated microbiome research discourse, proteins serve as equally important and in many cases more specific and potent mediators of microbiota-host communication. Recent advances, particularly in understanding bacterial extracellular vesicles and their protein cargo, has revealed previously unappreciated mechanisms by which microbiota influence not only gut immunity but also systemic and even neurological health [142,143]

This review has synthesized current understandings of protein-mediated mechanisms underlying gut microbiota and probiotic effects on host immunity. We have explored how surface-associated proteins, secreted factors, peptides and extracellular vesicle cargo engage pattern recognition receptors, modulate epithelial barrier function, shape immune cell differentiation and influence host-pathogen interaction. Emerging technologies for personalized probiotic selection based on individual microbiome protein profiles and host immunogenetics promise to revolutionize therapeutic approaches [119].

From a translational perspective, protein-focused research opens exciting therapeutic avenues. Purified probiotic proteins, protein-enriched bacterial lysates, engineered probiotics with enhanced protein functions and small molecules targeting pathogen proteins all represent potential next-generation therapeutics [123,144] Bacterial extracellular vesicles loaded with therapeutic protein cargo represent a particularly promising platform, with applications ranging from gut health to cancer immunotherapy and neurological disorders [143,145,146]. As our mechanistic understanding deepens and technical capabilities advance, the protein dimension of microbiome research will likely yield novel diagnostic and therapeutic tools that complement and extend traditional probiotic approaches. Ultimately, a comprehensive understanding of gut microbiota-host interactions requires embracing complexity where recognizing that bacteria communicate with hosts through diverse molecular languages including small molecules, proteins, nucleic acids and lipids, all operating within intricate ecological network. By illuminating the protein dimension of this communication, we gain critical insights into mechanisms underlying microbiota effects on health and disease, paving the way for more sophisticated, mechanistically grounded approaches to microbiome-based medicine.

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Abbreviations

The following abbreviations are used in this manuscript:

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AMP	Antimicrobial Peptide
DC	Dendritic Cell
EGFR	Epidermal Growth Factor Receptor
EPS	Extracellular Polymeric Substance
EV	Extracellular Vesicle
GALT	Gut-Associated Lymphoid Tissue
HDAC	Histone Deacetylate
HSP	Histone Shock Protein
IBD	Inflammatory Bowel Disease
IgA	Immunoglobulin A
IL	Interleukin
MAPK	Mitogen-Activated Protein Kinase
MAM	Microbial Anti-Inflammatory Molecule
MUC2	Mucin 2
NF-κB	Nuclear Factor Kappa B
NOD	Nucleotide-Binding Oligomerization Domain
PAMP	Pathogen-Associated Molecular Patterns
PRR	Pattern Recognition Receptor
PTM	Post-Translational Modification
SCFA	Short-Chain Fatty Acid
TGF-β	Transforming Growth Factor Beta
TLR	Toll-Like Receptor
TNF-α	Tumor Necrosis Factor Alpha
Treg	Regulatory T cells
T3SS	Type III Secretion Systems

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