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Looking into key bacterial proteins involved in gut dysbiosis

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Abstract

The gastrointestinal microbiota plays a pivotal role in health and has been linked to many diseases. With the rapid accumulation of pyrosequencing data of the bacterial composition, the causal-effect relationship between specific dysbiosis features and diseases is now being explored. The aim of this review is to describe the key functional bacterial proteins and antigens in the context of dysbiosis related-diseases. We subjectively classify the key functional proteins into two categories: Primary key proteins and secondary key proteins. The primary key proteins mainly act by themselves and include biofilm inhibitors, toxin degraders, oncogene degraders, adipose metabolism modulators, anti-inflammatory peptides, bacteriocins, host cell regulators, adhesion and invasion molecules, and intestinal barrier regulators. The secondary key proteins mainly act by eliciting host immune responses and include flagellin, outer membrane proteins, and other autoantibody-related antigens. Knowledge of key bacterial proteins is limited compared to the rich microbiome data. Understanding and focusing on these key proteins will pave the way for future mechanistic level cause-effect studies of gut dysbiosis and diseases.

Key Words: Gut microbiota; Pyrosequencing; Bacteria; Protein; Immune; Dysbiosis

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Core Tip: Revealing the causal-effect relationship between specific dysbiosis features and diseases requires understanding the roles of key bacterial proteins that are involved in dysbiosis. Some bacterial proteins may affect the microbiome by their inherent

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functions. Others shape the microbiome mainly by eliciting host immune responses. These key proteins warrant attention in future bioinformatic analyses and mechanistic studies.

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INTRODUCTION

The gastrointestinal microbiota is linked to numerous diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), colorectal cancer, cirrhosis, and many others. Thanks to the rapid decrease in the cost of pyrosequencing, the gut microbiota, often represented by the fecal bacteria composition, is now easy to profile by 16S rDNA sequencing and shotgun metagenomic sequencing. With the accumulation of known microbiome-disease correlations in many descriptive studies, the mechanisms of known dysbiosis features in the pathogenesis of related diseases have become a new frontier to be explored. Understanding these mechanisms is a prerequisite to developing the precise intervention methods targeting the gut microbiome. Thus, it is necessary to review the key microbial proteins involved in gut dysbiosis.

The gut microbiome produces numerous products for itself and the host. The collection of small molecules produced by the gut microbiota, termed the metabolome, represents promising targets for investigation and translation. The methodology and findings of studies of the gut metabolome have been reviewed elsewhere[1,2]. In addition, the gut microbiota produces exosomes, which have been reviewed by other excellent reviews[3]. The virome[4,5], parasitome[6], helminths, and protozoa-omics[6] are also recognized by omic-approaches but with less well documented mechanisms. In this review, we will focus on the key peptides, proteins, and antigens produced by bacteria and fungi in the context of dysbiosis and diseases.

To organize the review, we categorize the bacterial proteins into two groups: (1) The primary key proteins, whose action mainly depends on their inherent properties (Table 1); and (2) The secondary key proteins, whose action mainly depends on the host response to them (Figure 1, Table 2). This classification mainly depends on the current knowledge and is relative. Often, the bacteria-host interaction is bilateral. Thus, this classification is subjective and only helps navigate the mechanisms. For each group, we organize the key proteins according to their functions to assist in navigating this field rapidly.

PRIMARY KEY PROTEINS

Biofilm inhibitors

Biofilm formation is a process of extracellular synthesis by bacteria, and it has adverse effects on the immune response of the host[7], resulting in dysbiosis[8]. Bacteria are found in the intestinal mucosa of humans and clinical observations have revealed bacterial biofilms associated with mucosal colonization in patients with IBD[7]. Many infections also involve pathogens forming biofilms, including enterohemorrhagic *Escherichia coli* (EHEC)[9]. Probiotics have been documented to produce enzymes degrading biofilms of other species. *Escherichia coli* (*E. coli*) Nissle 1917 (EcN), a probiotic capable of alleviating inflammation, can produce its own biofilm and outcompete that of other intestinal pathogens[10]. Fang *et al*[11] found that DegP, a bifunctional (protease and chaperone) periplasmic protein secreted by EcN, contributes to the inhibition of EHEC biofilms by directly interacting with the EHEC cell surface while not affecting its own biofilm. Another probiotic, *Lactobacillus rhamnosus* GG (LGG), could also disrupt the biofilm formation of pathogenic *E. coli* and *Salmonella*[12]. This effect is mediated by its lectin like proteins, termed Llp1 (lectin-like protein 1) and Llp2[12]. Llp2, which is more active than Llp1, showed inhibitory

Table 1 Summary of primary key proteins

Classification	Name	Function	Ref.
Enzyme	DegP	Inhibiting EHEC biofilms.	[11]
Enzyme	Llp1, Llp2	Inhibiting biofilm formation of pathogen.	[12]
Enzyme	Protease of <i>S. boulardii</i>	Digesting both <i>C. difficile</i> toxin A and its receptor binding sites.	[15]
Enzyme	Lon protease	Degrading the oncogene c-MYC.	[19]
Secreted protein	P9	Inducing the secretion of GLP-1. Inducing the secretion of IL-6 in macrophages.	[21, 22]
Secreted protein	Peptide B7	Reducing CCR2 expression on all APCs from health people.	[25]
Secreted protein	MAM	Inhibiting the NF- κ B pathway and several cell immune responses. Inducing expression of TGF β .	[26-28]
Surface layer protein	MIMP	Inducing the secretion of anti-inflammatory cytokines and inhibiting inflammatory cytokines. Enhancing the intestinal barrier.	[29]
Enzyme	OGA	Hydrolysing O-GlcNAcylated NF- κ B-p65 and IKK β to inhibit NF- κ B signaling.	[30]
Bacteriocins	PediocinPA-1/AcHnisin Z	Reducing colonization of VRE <i>in vivo</i> .	[38]
	Microcin	limiting the expansion of pathogens.	[39, 40]
Bacteriocins	Enterocins	Inhibiting a wide spectrum of Gram-positive bacteria. Inhibiting the growth of cancer cells.	[42, 43]
Bacteriocins	Bacteriocin A, B	Degrading pathogenic biofilm and having antibacterial potential.	[36]
Bacteriocins	Nisin A	Changing the integrity of the cancer cell membrane.	[44]
Secreted protein	P8	Inducing host cell growth arrest at the G2 phase.	[46, 47]
Ribosomal proteins	HPRP-A1; HPRP-A2	Resisting infection. Arresting the cancer cells cycle at the G0/G1 phase and G2/M phase.	[48-53]
Innermembrane protein	Pre-FadA	Binding host epithelial cells.	[54]
Secreted protein	m-FadA	Inducing the invasion of host cells.	[54]
Outer membrane protein	Fap2	Leading to colonization of Fn. Facilitating tumor immunity evasion. Binding to and activating TIGIT. Inducing host lymphocyte apoptosis.	[55-57]
Secreted proteins	OMVs of Fn	Inducing the colonization of host epithelial cells.	[58-60]
Cell envelope-associated multiprotein systems	Sus-like systems	Inducing the colonization of host epithelial cells.	[64]
Pili	SpaCBA	Inducing the adhesion of mucus.	[66, 67]
Secreted proteins	EVs	Inducing the expression of the TJ protein-encoding genes and regulating the intestinal barrier. Inducing the expression of <i>PPARα</i> and <i>PPARγ</i> genes and <i>ANGPTL4</i> gene. Inhibiting blood lipase lipoproteins in the bloodstream.	[71, 72]
Secreted proteins	TcpC OMVs of EcN	Enhancing epithelial barrier.	[77-81]

EcN: *Escherichia coli* Nissle 1917; EVs: Extracellular vesicles; OMVs: Outer membrane vesicles.

activity against biofilm formation by various pathogens, including clinical *Salmonella* species and uropathogenic *E. coli* (UPEC) [12]. Thus, biofilm production and inhibition might represent key bacterial events in microbiome evolution, as well as promising targets to manage dysbiosis.

Toxin degraders

Probiotics may degrade pathogenic toxins and thus contribute to the homeostasis of gut microbiota. *Clostridium difficile* (*C. difficile*) mediates intestinal inflammation and mucosal damage by releasing two potent exotoxins, toxin A and toxin B [13], while the fungal probiotic *Saccharomyces boulardii* (*S. boulardii*) is known as the most efficient

Table 2 Summary of secondary key proteins

Classification	Name	Function	Ref.
Flagellin		Inducing the secretion of proinflammatory cytokines.	[87]
Flagellin		Recruiting flagellin specific CD4+ T-cells.	[85]
Flagellin		Inducing the secretion of flagellin antibodies.	[88,89]
Flagellin		Inducing the secretion of AMPs.	[90]
Flagellin		Inducing the secretion of human β -defensin 2.	[91]
Flagellin		Inducing the expression of lncRNA (HIF1A-AS2) and suppressing NF- κ B signaling pathway activation.	[92]
Outer membrane protein	OmpC, OmpW	Adhesion and invasion of the CD-associated <i>Escherichia coli</i> in intestinal epithelial cells. Cross-reactive bacterial proteins.	[95-97]
Outer membrane protein	FomA	Inducing upregulation of CD86, MHC II, and primary B cells. Inducing secretion of antigen-specific antibody IgA and IgG.	[99,100]
Bacterial division protein	FtsZ	Cross-reacting with TBB-5 and mediating the secretion of p-ANCA.	[102, 103]
Bacterial heat shock protein	GroEL	Cross-reacting with Hsp60 and inducing antibodies.	[110, 111]

p-ANCA: Perinuclear antineutrophil cytoplasmic antibody.

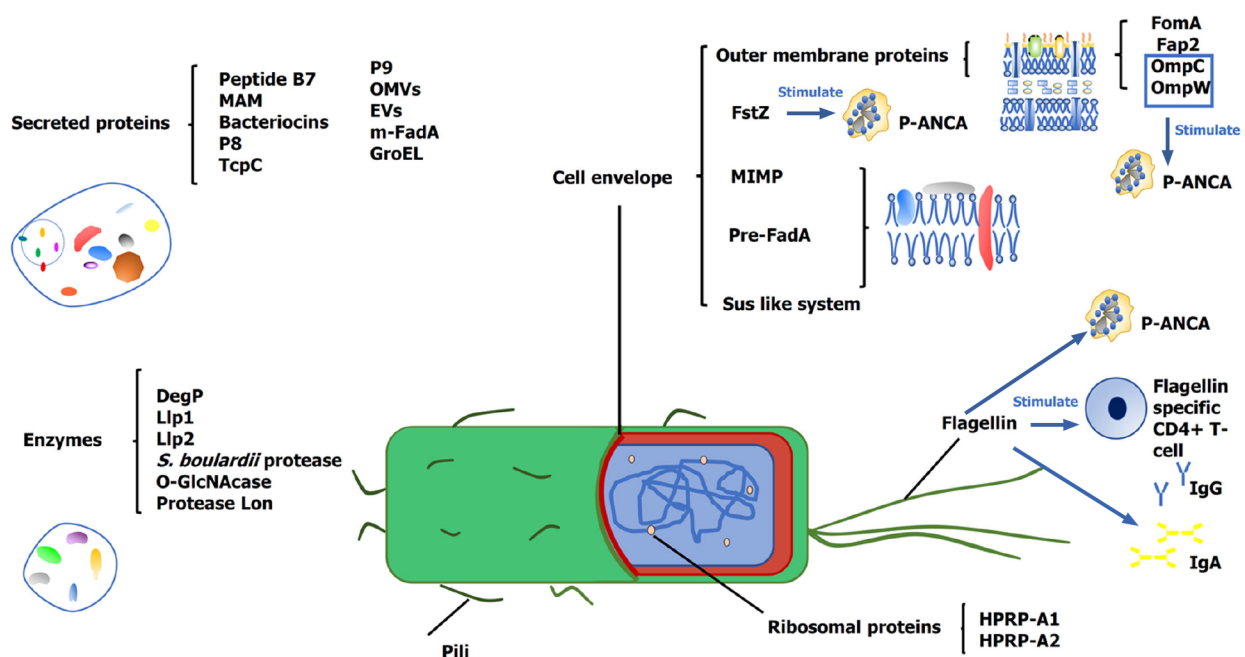


Figure 1 Summary of the location or form of key bio-active microbiota proteins. FtsZ and outer membrane proteins OmpC and OmpW were testified to stimulate perinuclear antineutrophil cytoplasmic antibody (p-ANCA). Flagellin was proved to stimulate p-ANCA, flagellin specific CD4+ T-cells, and flagellin associated IgG and IgA.

probiotic to prevent intestinal inflammation and mucosal damage associated with *C. difficile* infection[14]. The protective effect of *S. boulardii* is dependent on a 54 kDa protease, which digests both toxin A and its receptor binding sites[15]. Several human studies demonstrated that treatment with *S. boulardii* CNCM I-745 in dysbiosis leads to faster reestablishment of a healthy microbiome[16].

Oncogene degraders

Oncogene c-MYC is associated with oncogenic transcription in malignant tumor driven by chronic bacterial infections[17], and the up-regulated c-MYC also indicates a poor prognosis in some human cancers[18]. The Lon protease from UPEC shows potential for therapeutic targeting of c-MYC in cancers, the degradation of c-MYC is

dependent on both direct Lon protease cleavage and Hly-dependent activation of CK1 $\alpha 1$, and UPEC represses transcriptional MYC regulators to inhibit c-MYC expression [19]. In mice, the recombinant Lon (rLon) protease without major toxicity delayed tumor development and increased survival in MYC-dependent bladder and colon cancer models [19]. These results indicate that probiotics may block tumor proliferation by degrading the oncogene.

Adipose metabolism modulators

Akkermansia muciniphila (*A. muciniphila*), one of the gut microbiota, is connected with metabolic disorders, and it reduces the energy absorption under cold conditions in the intestine epithelium [20]. P9 is an 84 kDa protein, which is secreted by *A. muciniphila*. P9 increases the glucagon-like peptide-1 (GLP-1) secretion in a calcium-dependent manner and specifically promotes interscapular brown adipose tissue (iBAT) non-shivering thermogenesis in the gut hormone-releasing L cells and HFD mice [21]. The ligand–receptor capture (LRC)-TriCEPS technology shows that the P9 interacts with intercellular adhesion molecule 2 (ICAM-2), and ICAM-2 reduces the secretion of the P9-induced GLP-1 in a dose-dependent manner [21]. Moreover, P9 induced the secretion of interleukin-6 (IL-6) in macrophages [21], and IL-6 can stimulate GLP-1 secretion by intestinal L cells [22].

Anti-inflammatory peptides

The mucosal immune response plays an important role in IBD pathogenesis, and perturbations of the gut microbiota are a key element [23]. Probiotics can modulate the intestinal cytokine milieu to treat IBD [24] and other diseases. Peptide B7 from the probiotic *Bifidobacterium longum* decreases CCR2 expression on all antigen presenting cells from healthy controls but not from active IBD patients [25]. Although this bioactive peptide is useless for the treatment of active IBD patients, we cannot ignore its potential to prevent inflammation flares in the quiescent phase [25]. Another probiotic, *Faecalibacterium prausnitzii* (*F. prausnitzii*), one of the most abundant species in the human gut microbiota, possesses a 15 kDa protein with anti-inflammatory properties, termed a microbial anti-inflammatory molecule (MAM) [26]. The inflammatory suppressive role of MAMs from *F. prausnitzii* may be related to their effects on the inhibition of the NF- κ B pathway, several cell immune responses such as Th1, Th2, and Th17 cells, and the expression of TGF- β [27,28]. The micro integral membrane protein (MIMP) identified from *Lactobacillus plantarum* was found to decrease proinflammatory cytokines (IFN- γ , IL-17 and IL-23), increase anti-inflammatory cytokines (IL-4 and IL-10), and fortify the intestinal barrier in a dextran sulphate sodium induced colitis model [29]. Probiotics have been documented to produce enzymes hydrolyzing key proteins in the NF- κ B pathway [30]. O-GlcNAcase (OGA) is rich in *Bacteroidetes* and *Firmicutes*, the major probiotics distributed in the human gut, and reduced expression of bacterial OGA genes has been found in ulcerative colitis (UC) [30]. Bacterial OGAs are an advanced therapeutic strategy in UC that act by hydrolyzing O-GlcNAcylated NF- κ B-p65 and IKK β to inhibit NF- κ B signaling in both immune cells and intestinal epithelial cells [30].

Bacteriocins

Bacteriocins are ribosomally synthesized bactericidal or bacteriostatic peptides [31,32]. Bacteriocins from probiotics maintain the microbial population-level and community-level dynamics and inhibit other strains [33]. Bacteriocins are mainly divided into two classes: Posttranslationally modified class I and unmodified class II [34,35]. In a previous study, pediocin, enterocin-A, and enterocin-B were regarded as class II bacteriocins [31], and nisin belonged to class I bacteriocins [36,37]. Pediocin PA-1/AcH secreted by *Pediococcus acidilactici* (*P. acidilactici*) MM33 and nisin Z secreted by *Lactococcus lactis* (*L. lactis*) MM19, have been proven to reduce colonization of vancomycin-resistant enterococci (VRE) *in vivo* [38]. Microcin-producing EcN limits the expansion of competing *Enterobacteriaceae*, including commensal *E. coli*, adherent-invasive *E. coli*, and *Salmonella enterica* in the inflamed gut [39] by utilizing catecholate siderophores [40]. *Enterococcus faecium* produces two synergistic bacteriocins, enterocin-A (a pediocin-like bacteriocin) and enterocin-B. Although the inhibitory spectra of enterocins A and B have small differences, both enterocins from *Enterococcus faecium* T136 inhibit a wide spectrum of Gram-positive bacteria but not Gram-negative bacteria [41]. With a similar inhibitory spectrum, enterocin A has lower minimum inhibitory concentration (MIC) values than enterocin B [41].

Furthermore, the bactericidal effect is drastically increased when a mixture of the two bacteriocins is used [41]. The findings of a previous study suggested that the

heterodimer of bacteriocin A and B from *Enterococcus faecium* por1 had antibacterial, pathogenic biofilm degradation potential but did not result in haemolysis of human red blood cells[42]. A cancer cell growth inhibitory potential of enterocins has been demonstrated, and apoptotic makers were observed in enterocin treated cancer cells including HeLa, HT-29, and AGS cells[42]. The mechanism of their effects on cancer is that cancer cells have more microvilli on their surface, which allows the membrane of cancer cells to bind large quantities of bacteriocins[43]; thus, Nisin A from *L. lactis* changes the integrity of the cancer cell membrane and obstructs the rearrangement of phospholipids, resulting in increased ion permeability[44]. These bacteriocins enable probiotics to treat enterobacterial infections in the gut and even some cancers.

Host cell circle regulators

Some oral bacteria disseminate into the colon and alter the composition of the microbiota in the colon, resulting in intestinal dysbiosis and possibly leading to colorectal cancer (CRC)[8]. FadA from *Fusobacterium nucleatum* drives CRC proliferation through E-cadherin and increases the expression of transcription factors and inflammatory genes *via* activation of β -catenin signaling[45]. Some bacterial proteins provide new strategies to treat cancer. An 8 kDa protein called p8 was isolated from *Lactobacillus rhamnosus* (LR) KCTC 12202BP, which regulates the p53-p21-Cyclin B1/Cdk1 signaling pathway and causes cell growth arrest at the G2 phase in a dose-dependent manner[46]. Bacterial drug delivery systems are being applied to treat CRC. The p8 protein from *Pediococcus pentosaceus* SL4 (PP-p8) showed antiproliferative activity in a mouse CRC model[47]. Moreover, endogenous p8 expression was much more effective than exogenous recombinant- p8 expression. This makes gene therapy possible[47].

HPRP-A1 and its enantiomer HPRP-A2 are derived from ribosomal protein L1 (RpL1) of *Helicobacter pylori*[48]. These proteins can resist infection including fungi, bacteria, and parasites[49,50]. Moreover, they have anticancer potential, and both peptides lead to apoptosis *via* caspase-3-, caspase-8-, and caspase-9-dependent pathways and inhibit cancer cell growth by arresting the cell cycle at the G0/G1 phase and G2/M phase. HPRP-A1 and its enantiomer HPRP-A2 play an important role in the inhibition of gastrointestinal cancer[51-53].

Adhesion and invasion molecules

Fusobacterium nucleatum (Fn) is associated with CRC and promotes tumor formation. Fn is able to adhere to and invade intestinal endothelial cells by binding to adhesin FadA, a virulence factor from Fn[54]. FadA from *E. coli* enhances the connection between host epithelial cells and bacteria. FadA has two forms, anchored form (pre-FadA) and secreted form (mature FadA), thus the pre FadA-mFadA complex is regarded as a unique adhesin/invasin[54]. Fusobacterial lectin (Fap2) might mediate the binding of Fn to the host factor Gal-GalNAc in CRC, and Gal-GalNAc is highly expressed in human colorectal adenocarcinoma and metastases[55]. Other findings support that Fap2 of Fn not only leads to colonization but also facilitates tumor immunity evasion[55]. Fap2 directly binds to and activates TIGIT (an inhibitory receptor on human natural killer cells and different T cells), and the interaction between these two molecules inhibits the cytotoxicity of NK cells and the activities of cytotoxic T lymphocytes and T helper cells, increasing the immune evasion of tumor cells[56]. Fap2, as an apoptosis-inducing protein, also induces host lymphocyte apoptosis and destroys the host immune response, facilitating Fn survival[57]. Liu *et al* [58] identified outer membrane vesicles (OMVs) in Fn by LC/MS/MS analysis and identified several pathogenic proteins in OMVs, including FadA, Fap2, MORN2, YadA (Yersinia adhesin)-like protein, and autotransporter proteins[58]. The MORN2 domains of Fn may contribute to adhesion and active invasion[59]. Two YadA-like proteins exist in OMVs and outer membrane fractions, which reveal great adhesion ability[58]; therefore, YadA-like proteins are involved in resisting host immune defenses dependent on resisting serum killing activity and phagocytosis[60]. OMVs provide new insight into the research and development of vaccines against Fn[58].

Bacteroidetes is one of the most numerous Gram-negative bacteria in the mammalian gastrointestinal tract[61]. Cell envelope-associated multiprotein systems, namely, Sus (starch utilization system)-like systems[62], are abundant in *Bacteroides*. Polysaccharide utilization loci (PULs) in Sus-like systems are not only used to bind to and degrade dietary sugar[63], but they also encode a unique pathway, the *ccfA-E* genes, called commensal colonization factors (CCF systems) for species-specific saturable niche colonization[64]. Moreover, the CCF system is mediated by *B. fragilis* colonization during infection with *Citrobacter rodentium* and antibiotic treatment[64].

LGG has a very good mucus adhesive capacity compared to another *Lactobacillus strains*[65]. The LGG-specific SpaCBA pili are long and thin proteinaceous protrusions on bacterial surface, which involved in three pilin monomers: SpaA, SpaB, and SpaC [66]. The SpaCBA pili mediate adhesive capacity to mucus and contribute to biofilm formation[67]. Moreover, the SpaCBA pili may also regular immune response. The spaCBA knockout LGG had twofold increased IL-8 and some pro-inflammatory markers in Caco-2 cells compared to wild-type[67].

Intestinal barrier regulators

Under dysbiosis, increased permeability of the intestinal epithelium leads to low-grade inflammation and metabolic dysfunctions[68]. However, according to the leaky gut hypothesis, if only the *F. prausnitzii* is present as a probiotic, it will not be beneficial to the intestine health and dysbiosis-induced diseases but enter the bloodstream by passing through the gut barrier and may cause systemic consequences because of obesity and a high-fat diet (HFD)[69,70]. Moosavi *et al*[71] show that *F. prausnitzii*-derived extracellular vesicles (EVs) contain different proteins with a molecular weight of 11 to 245 kDa. Compared with *F. prausnitzii*, its EVs in the Caco-2 cell line significantly regulate the intestinal barrier permeability due to increasing the expression of the tight junction (TJ) protein encoding genes *ZO1* and *OCN*, as well as *PPARα* and *PPARγ* genes and their targeted gene *ANGPTL4* at the mRNA level[71]. TJ proteins connect the adjacent epithelial cells and block the paracellular space in order to obstruct pathogens[72]. *ANGPTL4* inhibits blood lipase lipoproteins in the bloodstream, which reduces the intake of free fatty acids and cholesterol into the tissues[73-76].

TcpC from EcN enhanced the intestinal barrier function by increasing the expression of the TJ proteins ZO-1, ZO-2, and claudin-14[77-79]. Moreover, the positive strains ECOR63 and ECOR57 increased the transepithelial electrical resistance (TER) in T-84 monolayers to strengthen the intestinal barrier[80]. In addition, OMVs and other soluble factors from these probiotic bacteria increase the upregulation of ZO-1 and claudin-14, but downregulation of claudin-2[81]. Raising claudin-2 levels lead to increased barrier permeability[82] and result in CD and UC[83,84]. OMVs and soluble factors, rather than TcpC, are able to strengthen the intestinal barrier[81].

SECONDARY KEY PROTEINS

Flagellin

Flagellin is a common conserved component of bacteria, and it induces both innate and specific immunity, showing a close relationship between dysbiosis and IBD[85], but flagellin of some probiotics has anti-inflammatory effects[86]. Flagellin is regarded as the major antigen in pathogenic bacteria. Flagellin binds with the pattern-recognition receptor Toll-like receptor 5 (TLR5), inducing the secretion of proinflammatory cytokines[87]. Compared with healthy controls, both Crohn's disease (CD) and UC patients have a relative increase in the proportion of flagellin specific CD4+ T-cells. Cook *et al*[85] found a positive correlation between the relative abundance of bacteria [*Escherichia/Shigella* and (*Ruminococcus*) *gnavus* group] in IBD patients and high concentrations of flagellin antibodies, including anti-Fla2 IgG and anti-Fla2 IgA[88]. Specifically, CBir1 flagellin has been associated with complicated CD, and enzyme-linked immunosorbent assays proved that anti-CBir1 IgG is independently associated with CD[89]. Flagellin may provide a clinically novel approach to prevent pathogen infections, including vancomycin-resistant *Enterococcus* (VRE). Intestinal epithelial cells and Paneth cells secrete the antimicrobial protein (AMP) RegIIIγ to kill microorganisms and directly respond to flagellin via the Toll-like receptor (TLR)-myeloid differentiation factor 88-mediated pathway[90]. Flagellin of EcN stimulates intestinal epithelial cells to produce human β-defensin 2 via three main MAP kinase pathways, including ERK1/2, JNK, and p38[91]. Bacterial flagellin also induces negative regulation of inflammation. *Roseburia intestinalis* (*R. intestinalis*), a dominant symbiotic microbiota in the intestine, suppresses inflammation by inducing Treg cells and upregulating anti-inflammatory cytokines. However, *R. intestinalis* is significantly reduced in CD patients[86]. Flagellin in *R. intestinalis* induces the expression of lncRNA (HIF1A-AS2) in a dose- and time-dependent manner via p38 STAT1 activation, and HIF1A-AS2 inhibits the expression of inflammatory genes by suppressing NF-κB signaling pathway activation[92].

Outer membrane proteins

Some evidence linking intestinal dysbiosis with autoimmune diseases has shown that they are both associated with increased inflammation[93,94]. Bacterial outer membrane proteins are more likely to trigger an immune response, and the perinuclear antineutrophil cytoplasmic antibody (p-ANCA) present in many autoimmune diseases cross-reacts with outer membrane proteins. P-ANCA autoantibody is associated with UC. A p-ANCA monoclonal antibody detects outer membrane porins OmpC and OmpW expressed by colonic bacteria *Bacteroides caccae* and *E. coli*[95,96]. A structural relationship of the cross-reactive bacterial proteins and the p-ANCA autoantigen has been observed in IBD[95,96]. OmpC also enhances the adhesion and invasion of the CD-associated *E. coli* strain LF82 in intestinal epithelial cells through the sigma (E) regulatory pathway[97]. *Fusobacterium nucleatum* (Fn) has been found to be increased in the microbiota of diarrhea dominant IBS. The FomA protein is a major outer membrane protein of Fn[98]. The FomA of Fn is an immune adjuvant, which is a Toll-like receptor 2 (TLR2) agonist that induces upregulation of CD86 and MHC II in mice and primary B cells *in vitro* and antigen-specific antibody IgA and IgG secretion *in vivo* [99]. These characteristics enhance inflammation in the small intestine epithelium in both cell and mouse experiments[99]. Fn causes microbial dysbiosis, exacerbates visceral hypersensitivity in a colonization-independent manner, and induces the specific IgA agonist FomA[100]. Moreover, FomA has been proven to be an antigen that stimulates the secretion of symptom-associated antibodies[100].

Other autoantibody-related antigens

Primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) are frequently associated with chronic IBD, including UC and CD[101]. The immune reaction in PSCs is mediated by autoantibodies, including pANCA, that recognize both β -tubulin isotype 5 (TBB-5) and the bacterial antigen cell division protein FtsZ[102]. Human TBB-5 and FtsZ share a high degree of structural homology in evolutionarily conserved epitopes[103]. Moreover, B cells respond directly to microbial constituents in PSCs and AIH[104].

Helicobacter hepaticus (Hh) can induce intestinal inflammation in DC-LMP1/CD40 mice[105]. These immunodeficient mice lost intestinal CD103+ DCs and IL-10+ Helios-induced Tregs (iTregs) but had increased IL17+ IFN γ + Th17/Th1 cells and pathogenic IFN γ + Th1 cells[106,107]. They developed fetal colitis similar to human IBD, because CD40-CD40L interactions are connected with the pathogenesis of IBD [108,109]. A 60 kDa Hh-protein, GroEL, as the main antigen recognized by antibodies in an iTreg-free setting, triggers fatal colitis[110]. The bacterial GroEL and human heat shock protein 60 (Hsp60) share a high similarity and molecular mimicry[111,112], hence the antibodies cross-react with Hsp60 and GroEL, which contribute to IBD and autoimmune diseases[110].

CONCLUSION

Understanding the key bacterial proteins is significant to both the diagnosis and management of dysbiosis related diseases. For the incendiary proteins involved in autoimmune diseases and tumors, the presence of the specific marker in the microbiota or its specific antibodies might indicate the prognosis of diseases. The therapeutic value of targeting these markers would also be tempting. Knowing the key elements of microbiota could provide much more specific target than generally modulating the microbiota, which is super-high dimensional in taxonomy.

The current mainstream microbiome manipulation approaches are intensively investigated, including supplement of probiotics and prebiotics, and fecal microbiota transplantation (FMT). However, the probiotics should be strain-defined to gain standardized safety, dose, and effect; the adverse events associated with FMT have been found recently. The transplanted probiotics met indigenous microbiome-mediated mucosal colonization resistance in mice and even a specific colonization resistance in a person-, strain-, and region- dependent manner in humans[113]. Our recent mathematical model studies also suggested intriguing behavior of microbiome in response to probiotic supplement[114]. For FMT, the risk of unknown infections is still inevitable even after rigorous tests on the donors. The specific microbial proteins are easier to be cloned, purified, tested, optimized, and standardized, which is crucial for the pharmacology. Furthermore, the natural beneficial bacterial proteins can be artificially engineered and optimized to maximum their mechanism. This review summarizes the pathogenic and therapeutic mechanisms of some bioactive microbial

proteins. This field is cutting edge, and there is a need for further studies to explore the role of the key gut microbial proteins in dysbiosis associated diseases.

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