Review

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Modulation of the Intestinal Barrier by Oral Bacteria in Inflammatory Bowel Disease

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Beyond the established oral-gut axis links in inflammatory bowel disease (IBD), this review provides an in-depth mechanistic analysis of how specific oral pathobionts disrupt the five intestinal barriers, microbial, chemical, physical, immune, and vascular, driving disease pathogenesis through distinct yet synergistic mechanisms. We synthesize evidence that key pathogens (e.g., *Fusobacterium nucleatum* (*Fn*), *Porphyromonas gingivalis* (*Pg*)) orchestrate multistep pathogenesis: ectopic translocation followed by targeted barrier disruption, *Fn* degrading tight junctions, *Pg* eroding mucus via gingipains, and *Klebsiella* spp. hijacking T helper 1 cells (Th1) immunity. This pathogen-centric taxonomy reveals pathophysiological sequences: mucosal invasion by *Fn* precedes microbiota dysbiosis, while *Pg* virulence factors directly compromise vascular integrity, decoupling translocation routes from barrier-specific outcomes. Notably, we characterize how barrier-specific damage generates therapeutic targets: mucus restoration counters *Pg* enzymatic degradation, toll-like receptor 4 (TLR4) blockade inhibits Klebsiella-driven inflammation, and Fusobacterium adhesin A (FadA) inhibition prevents *Fn* endothelial invasion, transitioning from associative findings to mechanism-based interventions. By integrating spatially resolved mechanisms across barrier layers, this work establishes a conceptual framework: oral pathogens act as "barrier disruptors" whose targeted neutralization may improve the IBD disease trajectory. This mechanistic framework positions oral barrier disruption as a druggable axis in IBD, offering actionable biomarkers and microbiota-directed therapeutic strategies.

Keywords: inflammatory bowel disease; oral microbiota; intestinal barrier; pathogenesis; barrier dysbiosis; gut microbiota

Introduction

Inflammatory bowel disease (IBD) refers to chronic inflammatory disorders of the gastrointestinal tract, primarily encompassing Crohn's disease (CD) and Ulcerative colitis (UC). These conditions are characterized by relapsing and remitting courses, with symptoms that flare and subside cyclically. Globally, the incidence and prevalence of IBD are increasing. Studies identify North America as having the highest IBD rates, with UC incidence at 19.2 per 100,000 (prevalence 505 per 100,000) and CD incidence at 20.2 per 100,000 (prevalence 322 per 100,000) [1,2]. Since 1990, IBD has become increasingly prevalent in developing countries. In Hong Kong, southern China, the incidence of IBD has risen from 1.0 to 3.1 per 100,000. India currently reports the highest IBD incidence in the Asia-Pacific region, at 9.31 per 100,000 [1,2]. Consequently, IBD has emerged as a global health challenge, causing both intestinal and extraintestinal symptoms. Although the precise etiology of IBD remains unclear, the condition is thought to result from complex interactions between genetic factors and environmental triggers [3,4]. IBD leads to chronic intestinal inflammation and epithelial damage, primarily driven by dysregulation in the host-microorganism interface [5]. One proposed initiating factor in IBD is the disruption of the intestinal barrier, which permits luminal pathogens to invade the mucosa and initiate inflammatory responses [6]. The intestinal barrier comprises five functionally distinct yet interrelated components that collectively maintain intestinal homeostasis: the microbial, chemical, physical, immune, and vascular barriers (Fig. 1) [7].

The human oral cavity, as the initial entry point of the gastrointestinal tract, harbors a diverse and abundant microbiota. More than 700 microbial species colonize various oral niches, making the oral microbiota second only to

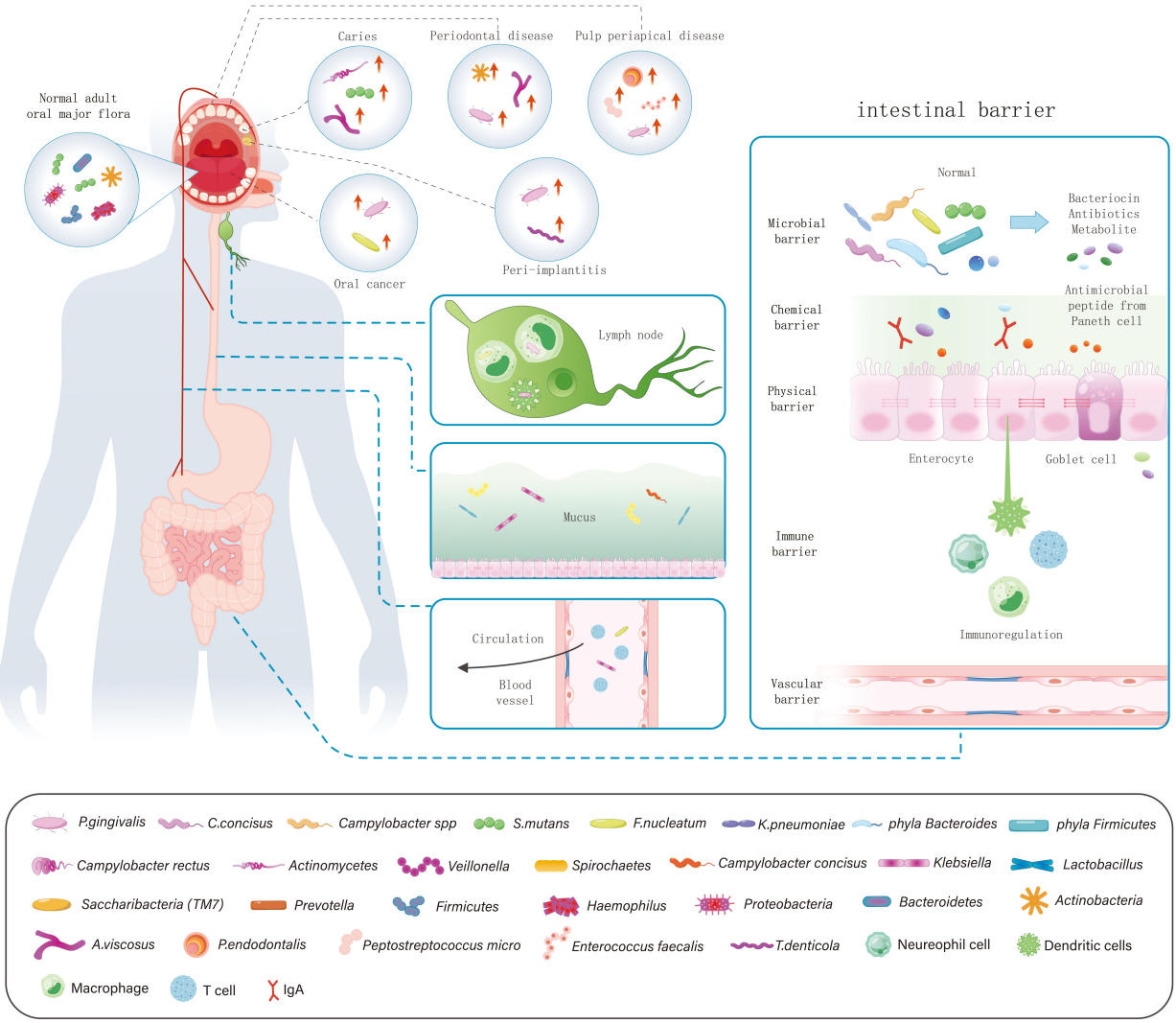

Fig. 1. Three-stage model of ectopic colonization in inflammatory bowel disease (IBD) and the five components of the intestinal barrier. The gastrointestinal tract is a continuous, mucosa-lined tube extending from the mouth to the anus. Oral dysbiosis contributes to pathological processes within the oral cavity, including dental caries and periodontitis (left panel). Altered oral microbiota profiles may further influence IBD through a proposed multistage model. The first stage involves an increased abundance and virulence of oral bacteria. In the second stage, oral-associated bacteria may translocate to the intestine via the circulatory system, lymphatic route, or gastrointestinal tract. In the third stage, oral bacteria well-adapted to inflammatory environments colonize the disrupted intestinal milieu, interacting with host epithelial and immune components to exacerbate inflammation. The intestinal barrier comprises five components (right panel): microbial, chemical, physical, immune, and vascular layers, which collectively maintain intestinal homeostasis. Illustration was created using BioRender (https://www.biorender.com/). *TM7*, *Saccharibacteria*; IgA, Immunoglobulin A.

the gut in terms of microbial diversity [8,9]. The predominant bacterial phyla in healthy oral cavities are *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*, whereas *Fusobacteria*, *Saccharibacteria* (*TM7*), and *Spirochaetes* occur in lower abundance [10]. While microbial composition varies across oral sites, keystone pathogens such as *Streptococcus mutans* (*Sm*), *Porphyromonas gingivalis* (*Pg*), and *Fusobacterium nucleatum* (*Fn*) have been implicated in both oral and systemic diseases [11–13].

Recent advances in microbiome research have uncovered associations between oral microorganisms and systemic diseases, including IBD [14], cancer [15], cardiovascular disease [16], Alzheimer's disease [17], diabetes [18], and rheumatoid arthritis [19]. Emerging evidence suggests that ectopic colonization by oral bacteria may contribute to IBD pathogenesis, and murine models of colitis have demonstrated that perturbations in oral microbiota can disrupt intestinal barrier integrity [3,20]. Therefore, the

aim of this review was to elucidate the mechanistic pathways through which oral bacteria contribute to intestinal barrier dysfunction. A deeper understanding of these mechanisms may aid in improving IBD diagnosis and therapy. Given that non-bacterial oral species in IBD remain underexplored, this review focuses primarily on the bacterial components of the oral microbiota.

Oral Microbiota Is Closely Related to IBD

Characteristics of Oral Microbiota in IBD

Although dysbiosis of oral microbiota has been implicated in IBD, the mechanistic interplay remains poorly characterized. Said *et al*. [21] utilized 16S rRNA sequencing to investigate the taxonomic profiles of salivary microbiota in a cohort comprising 35 IBD patients and 24 healthy controls (HCs). Their results revealed a significant increase in Bacteroidetes and a notable reduction in *Proteobacteria* within the salivary microbial communities of IBD patients. At the genus level, taxonomically resolved analysis further revealed significant enrichment of *Prevotella* and *Veillonella* in the IBD cohort. Conversely, *Streptococcus* and *Haemophilus* exhibited lower prevalence in the IBD group compared to HCs. Qi *et al*. [14] further identified a distinct imbalance in the oral microbiota of IBD patients, characterized by elevated abundances of *TM7*, *Absconditabacteria* (*SR1*), *Leptotrichia*, and *Prevotella*, bacteria known for their ability to form oral biofilms. Additionally, Qi *et al*. [14] documented elevated levels of IBD-associated inflammatory cytokines, which were positively correlated with *TM7* and *SR1*.

Furthermore, UC and CD exhibit distinct salivary microbiota profiles. Analysis of salivary bacterial DNA from 25 HCs, 13 CD patients, and 54 UC patients revealed increased abundances of *Streptococcus* and *Enterobacteriaceae* in UC patients, with decreased levels of *Lachnospiraceae* and *Prevotella*. In contrast, CD patients demonstrated increased *Veillonella* and decreased *Neisseria* and *Haemophilus* [14]. These differences extend beyond salivary flora to include subgingival plaques. For example, a cohort study found elevated levels of *Capnocytophaga, Rothia*, and *TM7* in pediatric CD patients compared to matched HCs [22,23].

The composition, structure, and functional role of oral microbiota in IBD patients are markedly distinct from those of healthy individuals. These microbial alterations may serve as potential biomarkers for the early diagnosis and treatment of IBD [22]. However, the precise distinctions between UC- and CD-associated oral microbiota remain unclear, and further investigation is warranted [24].

Oral Bacteria Contribute to IBD Development

The oral microbiome plays a critical role in systemic health, extending beyond localized dental pathologies. Colonization by oral microbiota and their metabolites may contribute to dysregulated mucosal immune activation [25]. For instance, the oral microbiota in Alzheimer's disease patients shows distinct compositional shifts, including increased abundances of *Moraxella*, *Leptotrichia*, and *Sphaerochaeta*. Patients with type I diabetes exhibit elevated levels of the phyla *Actinobacteria* and *Firmicutes*, while symptomatic atherosclerosis is associated with enrichment of *Anaeroglobus*. Additionally, oral dysbiosis can trigger the production of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), which activate systemic innate immune responses [13]. These immune and inflammatory responses are considered central mechanisms linking oral dysbiosis to systemic diseases [26].

Oral microbiota can translocate to systemic organs, including the brain. For instance, *Pg* has been identified in postmortem brain tissues of Alzheimer's disease patients [27]. Similarly, oral bacteria have been detected within atherosclerotic plaques in individuals with cardiovascular disease [16]. Translocation of oral microbes to the gastrointestinal tract occurs more frequently due to the anatomical and physiological continuity between the oral cavity and the gut, and specific oral bacteria are capable of colonizing and proliferating in the pancreas and gastrointestinal tract [20].

However, the causal relationship between oral bacterial imbalances and IBD remains to be fully elucidated. Causality-focused study has demonstrated that specific oral bacteria contribute to IBD progression [28]. Viable *Campylobacter concisus* (*Cc*) and *Fusobacterium nucleatum* (*Fn*) can migrate to the gut, where they colonize the mucosal niches, an event associated with IBD [29,30]. Advances in sequencing technologies have clarified the correlation between increased levels of oral-associated bacteria (OB) in the gut and IBD. This was initially documented in treatment-naïve pediatric patients with CD, who exhibited elevated levels of OB, including *Fn*, *Haemophilus parainfluenzae*, and *Veillonella parvula*, in both mucosa and stool samples. This longitudinal study also revealed an association between severe UC and persistent colonization by oral-derived taxa such as *Veillonella dispar*, *V. parvula*, *H. parainfluenzae*, and *Campylobacter* spp. [31]. Earlier investigations revealed higher abundances of *Prevotella* spp., *Streptococcus* spp., *Veillonella* spp., and *Fusobacterium* spp. in colonic biopsies from IBD patients compared to non-inflamed tissues from the same individuals [32]. Furthermore, several studies have linked IBD with increased intestinal levels of *Klebsiella pneumoniae* [33–35]. Consequently, the detection of oral-derived bacteria in gut samples may serve as a promising diagnostic tool and support the development of rapid, point-of-care testing for IBD.

Periodontitis may also elevate the risk of developing IBD [22,36]. Research suggests that individuals with active periodontal disease and concurrent IBD exhibit more severe periodontitis and greater oral biofilm abundance [22]. Cross-disorder genome-wide association studies (GWAS) have identified shared etiopathogenetic mechanisms be-

tween these conditions, including inflammasome-mediated inflammation [37,38]. A recent study found that individuals with periodontitis had a higher risk of developing UC compared to HCs [39]. Moreover, during the initial stages of IBD, salivary dysbiosis is associated with both localized and systemic inflammation [21,40,41]. Notably, *Prevotella* spp. upregulate virulence-associated gene expression during periodontitis [42], potentially exacerbating both local and systemic inflammatory responses. While epidemiological studies support an association between periodontitis and IBD, establishing causality requires prospective, multicenter cohort studies with rigorous adjustment for confounding variables, including periodontal pathogen burden (e.g., *Pg*), host immunogenetic profiles, and socioenvironmental covariates (e.g., diet, urbanization). These studies should incorporate mediation analysis to elucidate the mechanisms underlying the oral-gut axis in IBD pathogenesis.

Mechanistic Role of Pathogenic Oral Bacteria in IBD Development

In addition to identifying significant imbalances in the oral microbiota of individuals with IBD, numerous studies have proposed plausible mechanisms by which oral bacteria trigger host responses that contribute to IBD pathogenesis. For example, Read *et al*. [43] outlined a three-stage mechanistic framework describing the ectopic colonization of oral pathobionts (e.g., *Klebsiella* spp.) in the intestinal niche during IBD progression, alongside associated pathophysiological consequences. This model comprises three operational stages: initially, the abundance and virulence of oral disease-associated bacteria increase, coinciding with reduced resistance to intestinal colonization. Subsequently, these bacteria translocate to the gut, and finally, colonization by pathogenic oral bacteria exacerbates IBD severity (Fig. 1).

The first stage entails the formation and proliferation of pathogenic bacteria within the oral cavity. In the periodontitis-colitis model, intestinal colonization by oral bacteria is contingent upon preexisting periodontitis, highlighting the significance of oral dysbiosis in promoting bacterial translocation [20]. Metagenomic linkage analyses have revealed identical microbial strains co-colonizing the oral cavity and intestine, providing direct evidence of intersite transfer [20]. This observation supports the hypothesis that oral microbes can migrate across anatomical boundaries, potentially influencing systemic health. Clarifying the mechanisms of this translocation is essential for developing microbiota-targeted interventions [44]. However, definitive evidence of direct translocation remains elusive. High-resolution metagenomic and metatranscriptomic profiling of paired oral and intestinal samples from extensive IBD cohorts is required to demonstrate the presence and proliferation of identical bacterial strains in both sites in patients with IBD.

The second stage encompasses the ectopic colonization of the gut by oral pathobionts. Although the precise translocation routes remain mechanistically unresolved and are likely taxa-specific, several mechanisms have been proposed. Bacteremia, defined as the presence of bacteria in the bloodstream, is frequently associated with periodontitis and may result from biofilm contact with ulcerated oral tissues [45]. In murine models, administration of *Pg* led to elevated blood endotoxin levels [46]. Moreover, intravenous administration of *Sm* exacerbated colitis in mice, although this effect was not observed when *Sm* was delivered via the gastrointestinal route [47]. Alternatively, oral bacteria may reach the gut through ingestion and survive transit through the gastrointestinal tract [48]. A compromised gastric barrier may thus facilitate intestinal colonization by oral bacteria. Aside from gastric acidity and the colonization resistance mediated by commensal gut microbiota, the precise mechanisms by which oral bacteria overcome chemical barriers (e.g., bile, gastric acid) and physical barriers remain undetermined and require further investigation [49].

In the third stage, pathogenic oral bacteria thrive under the inflamed intestinal conditions characteristic of IBD, gaining a selective advantage that may further exacerbate inflammation and accelerate IBD progression (Fig. 1). Elevated levels of three key oral bacteria (*Fn*, *Klebsiella* spp., and *Cc*) have been detected in the intestines of patients with IBD [50]. Despite their taxonomic differences, these bacteria exhibit shared pathological behaviors, including disruption of the intestinal barrier and activation of host inflammatory pathways [51,52]. These microbes engage with the gut-associated immune system and contribute to IBD pathogenesis. Within the innate immune system, *Klebsiella* spp. has been shown to activate Interleukin-1β (IL-1β) signaling in intestinal mononuclear phagocytes, aggravating colitis in murine models [20]. These microbes also modulate adaptive immune responses, further fueling chronic intestinal inflammation [53] (Fig. 1).

Mechanistically, the pathophysiological influence of these bacteria can be attributed to three main processes: induction of gut microbiota dysbiosis, exacerbation of intestinal barrier disruption, and modulation of host immune responses. This review examines how oral bacteria impact the intestinal barrier in IBD, focusing on key species, including *Fn*, *Pg*, *Sm*, *Cc*, and *Klebsiella* spp., that have been implicated in IBD onset and progression.

Pathogenetic Mechanisms of Oral Bacteria in the Intestinal Barrier in IBD

The intestinal barrier, which functions to absorb nutrients while protecting the host from external invasion, comprises five distinct layers: the microbial, chemical, physical, immune, and gut vascular barriers [54] (Fig. 2).

In this section, we examine the effects of oral bacteria on each of these intestinal barrier layers. Anatomically,

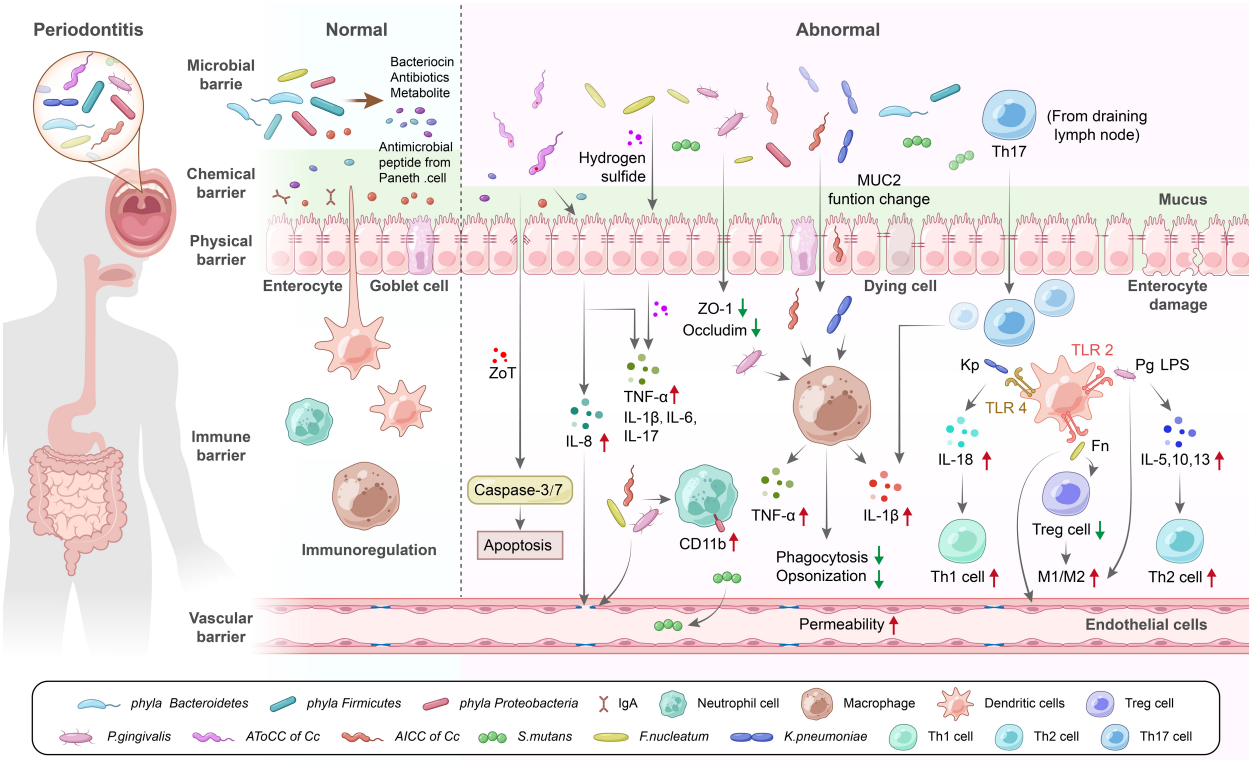

Fig. 2. Specific oral bacteria play pathogenic roles in the onset of IBD. Healthy intestines primarily employ three strategies to limit colonization by exogenous pathogens, including ingested oral bacteria. (1) The indigenous gut microbiota secretes bacteriocins, antibiotics, and metabolites while competing for nutrients and ecological niches. (2) Microbe-associated molecular patterns are recognized by host receptors. (3) Both innate and adaptive immune responses are activated for microbial control. Under pathological conditions, ectopic colonization by oral bacteria can promote IBD onset through various mechanisms: (1) Disruption of the gut microbial barrier: *Fn* aggravates ulcerative colitis (UC) by inducing dysbiosis, decreasing *Bifidobacterium* and *Faecalibacterium*. *Pg* alters gut microbial composition, leading to a reduction in *Firmicutes*. (2) Disruption of the gut chemical barrier: *Fn* depletes mucin from goblet cells, compromising the mucus gel layer and causing luminal obstruction. *Pg* produces proteases that degrade the inner protective mucus layer by cleaving the MUC2 C-terminal domain. (3) Disruption of the gut physical barrier: *Fn* reduces ZO-1 and occludin levels in the colon. *Pg* decreases TJ integrity and suppresses ZO-1 and occluding expression in intestinal tissues, thereby compromising intestinal permeability. Additionally, *AToCC* interferes with tight junction processes. (4) Disruption of the gut immune barrier: *Pg* secretes gingipains that selectively inactivate pro-inflammatory cytokines released by activated dendritic cells. *Pg* and *Kp* migrate to the gut, induce pro-inflammatory cytokines (TNF-α, IL-1β), and increase the M1/M2 macrophage ratio. *Pg* and *Cc* activate neutrophils by upregulating CD11b and enhancing the oxidative burst response, stimulating innate immunity. *Pg* LPS induces a Th2-skewed response, whereas *Kp* promotes a Th1-biased response. *Pg* and *Fn* increase the Th17/Treg ratio by suppressing Treg cells. (5) Disruption of the gut vascular barrier: *Fn* disrupts VE-cadherin-mediated endothelial junctions, enhancing permeability and allowing bacterial translocation. *Pg* impairs vascular relaxation and endothelial integrity. *Sm* aggravates colitis by invading the bloodstream rather than crossing from the luminal side of the gastrointestinal tract. Illustration was created using BioRender (https://www.biorender.com/).

the mouth and intestine are continuous and interconnected along the gastrointestinal tract, providing a direct physiological pathway for the migration of oral microbiota to the gut. Chemically, the passage of saliva and ingested food from the oral cavity to the intestines is facilitated by intermediary organs such as the esophagus and stomach. Beyond anatomical and chemical connectivity, a microbial continuum may also exist between the oral and intestinal ecosystems.

Gut Microbial Barrier

The gut microbial barrier, the first line of defense in the intestinal system, comprises a diverse consortium of microorganisms. The dominant phyla, *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*, account for approximately 99% of the gut microbial population [55–57]. Together, the oral and gut microbiota represent the two largest microbial ecosystems in the human body. Notably, the gut microbiota plays a critical role in host growth, immune modulation, and various physiological processes [28].

Gut microbial barriers, along with associated microecosystems, restrict the translocation of microbial products into the bloodstream. However, an imbalance within the intestinal microbiota contributes significantly to the onset and progression of IBD. Recently, increasing attention has been directed toward the oral–gut microbial axis, which regulates how oral-associated bacteria (OB) colonize the intestine and contribute to the pathogenesis of IBD [28]. According to a multistage model proposed by Read *et al*. [43], the progression involves: (1) an increase in the abundance and virulence of OB and reduced resistance to intestinal colonization; (2) successful traversal of the gastrointestinal tract by OB, overcoming physiological factors such as saliva, gastric acid, bile, and intestinal secretions; (3) establishment of OB colonies in the gut, leading to exacerbation of IBD symptoms. Recent evidence suggests that OB and their metabolic products can structurally alter the gut barrier and impair various host functions.

A study by Cai *et al*. [39] reported that OB may inhibit the growth of dominant intestinal flora, resulting in harmful consequences. Furthermore, a clinical study identified *Fusobacteria*, from phylum to genus level, as potential microbial markers in patients with irritable bowel syndrome [58]. While clinical studies provide correlational insights, they often fail to establish mechanistic roles for OB in disease pathogenesis. Conversely, *in vivo* experimental models offer causal evidence. For example, *Fn* has been shown to aggravate UC by inducing gut microbial dysbiosis, marked by a reduction in beneficial bacteria such as *Bifidobacterium* and *Faecalibacterium*, and an increase in opportunistic pathogens like *Escherichia* and *Shigella* [59] (Table 1, Ref. [30,33,46,58–86]).

Administration of *Pg*, a Gram-negative oral anaerobe implicated in the pathogenesis of periodontitis, induces significant shifts in gut microbiota composition. These changes are characterized by an increase in *Bacteroidetes*, and a decrease in *Firmicutes*, and elevated serum endotoxin levels [62,63]. *Pg*, along with other oral microbiota, can colonize the gastrointestinal tract and modulate gut microbial communities. In germ-free mice cohoused with human salivary microbiota, *Pg* has been shown to significantly reduce the relative abundances of *Intestinimonas* and *Lachnospiraceae* in the colon [60]. Moreover, 16S rRNA sequencing analyses demonstrated that oral administration of *Pg* alters the composition of gut microbiota, with increased abundances of *Bacteroides* and *Staphylococcus* spp. and a concomitant reduction in *Lactobacillus* spp. [61,87].

Oral-associated bacteria (OB) can suppress the propagation of intestinal pathogens and reduce gut microbial diversity, as corroborated *in vivo* by transplantation of oral microbiota into animal models. For example, oral gavage of *Fn* in rats exacerbates visceral hypersensitivity and diminishes the diversity of intestinal microbiota [58]. Another study reported that *Pg* administration reduces both gut bacterial and fungal alpha diversity in the gut, partly through expansion of IL-9^{+}CD4^{+} T cells [62]. These findings underscore the need for multicenter, large-scale clinical studies to better define IBD-specific dysbiosis patterns and to assess the efficacy of targeted microbial transplantation or supplementation strategies.

In summary, oral pathobionts such as *Fn* establish "pathogen-permissive niches" by competitively inhibiting resident commensal bacteria through the secretion of antimicrobial peptides and metabolite disruption, such as depletion of short-chain fatty acids (e.g., butyrate). This ecological imbalance initiates a self-perpetuating cycle of dysbiosis, wherein reduced colonization resistance further promotes oral bacterial overgrowth. These insights support the development of therapeutic strategies, including strain-specific antagonists targeting key virulence factors (e.g., FadA adhesin nanobodies) and the use of probiotic consortia with oral-pathogen inhibitory capacity [14,28].

Gut Chemical Barrier

The gut chemical barrier, serving as the second line of defense, consists primarily of mucus, digestive secretions, bile acids, and antimicrobial peptides such as secretory Immunoglobulin A (IgA). These substances create a biochemical shield that prevents microbial adhesion to and invasion of the intestinal epithelium [7,88–90]. Structurally, the chemical barrier is organized into two layers: the inner layer, which adheres tightly to the epithelium and remains sterile, and the outer, more voluminous layer, which provides a niche for commensal bacteria. The establishment and maintenance of this barrier depend on the synergistic functions of Paneth cells, goblet cells, and components of the mucosal immune system [89].

When the mucus layer is compromised, the intestinal epithelium becomes more vulnerable to bacterial infiltration, thereby worsening inflammation in IBD. *Fusobacterium nucleatum* (*Fn*) has been shown to deplete mucin produced by goblet cells, leading to breaches in the mucus gel layer and the formation of intraluminal plugs; however, the expression levels of goblet markers such as Trefoil Factor 3 (TFF-3) and Resistin-Like Molecule Beta (RELM-β) remained largely unchanged [66]. In a previous study, mice treated with *Fn* exhibited disrupted colonic architecture, characterized by mucus layer depletion and immune cell infiltration, whereas vehicle-treated controls maintained normal colonic morphology [64]. *Fn* activates the endoplasmic reticulum stress (ERS) pathway and damages the mucosal barrier both *in vivo* and *in vitro* by targeting Caspase Recruitment Domain Family Member 3 (CARD3). This implicates *Fn* in modulating the molecular interplay between CARD3 and ERS, contributing to CD pathogenesis (Table 1) [65].

Pg produces a range of virulence factors that contribute to its pathogenicity, including lipopolysaccharides (LPS), capsular polysaccharides, fimbriae, and gingipains. Among these, gingipains (Arg-gingipain A (Rgp) A, Rgp

Table 1. Roles of oral-derived bacterial species in intestinal barrier impairment during IBD progression.

Barrier type	Species and model (mice/cell)	Specimen and detection method	Effects	References
Microbial barrier				
Fn	DSS mice	Fecal, 16S rRNA	Decrease: The diversity of intestinal microbiota	[58]
	DSS mice	16S rRNA	Increase: Escherichia-Shigella (opportunistic pathogens)	[59]
			Decrease: *Bifidobacterium*, *Faecalibacterium*	
Pg	GF or humanized microbiota mice	Intestinal biopsy, 16S rRNA	Decrease: *Intestinimonas*, *Lachnospiracae*	[60]
	mice	Fecal, 16S rRNA	Increase: *Bacteroides*, *Staphylococcus*	[61]
			Decrease: *Lactobacillus* spp.	
	mice	Intestinal biopsy, 16S rRNA	Decrease: Both gut bacterial and fungal α-diversity	[62]
	mice	Intestinal biopsy, 16S rRNA	Increase: The proportion of *phylum Bacteroidetes*	[63]
			Decrease: The proportion of *phylum Firmicutes*	
Chemical barrier				
Fn	mice, HT29 cells	Intestinal biopsy	Mucus layer depletion	[64]
	DSS mice, IECs	Intestinal biopsy	Gut mucosal barrier damage	[65]
	mice, Caco-2, T cells	-	Breaches in mucus gel layer, mucus plug formation in the lumen	[66]
Pg	CHO-K1 cells	-	Mucus-detaching protease production in the gut	[67]
	DSS mice	-	Mucus detachment	[46]
Physical barrier				
Fn	DSS mice	Intestinal biopsy	IECs apoptosis; Damage TJ proteins	[59]
	DSS mice	-	Invasion of Caco-2 cells	[30]
	DSS mice, Caco-2 cells	Intestinal biopsy	Epithelial integrity damage and increased permeability via ZO-1 and occludin	[68]
Pg	DSS mice	Intestinal biopsy	Partial amelioration of IEC damage in DSS colitis mice	[69]
	mice, organoids	Intestinal biopsy, 16S rRNA	Downregulate gene expression of TJP-1 and occludin	[63]
	DSS mice, IECs	Intestinal biopsy	Disrupt the colonic epithelial barrier by decreasing the expression of TJ proteins.	[70]
			Pg-specific epithelial barrier disruption	
Cc	Co-cultured HT-29	-	Reduce the expression of TJ proteins occludin and tricellulin	[71]
Klebsiella	TNBS mice	Intestinal biopsy	Reduce Claudin-1, ZO-1, and occludin	[72]
Immune barrier				
Fn	DSS mice, Caco-2 cells	-	Induce Th1/Th17 differentiations, $CD4^+$ T cell proliferation, increase secretion of TNF-α, IFN-γ, IL-1β, IL-6	[68]
	Humanized microbiota mice, HT-29	Intestinal biopsy	Promote pro-inflammatory cytokines (TNF, IL-6, IFN-γ, and MCP-1)	[64]
	Caco-2 cells	-	Autophagic flux impairment, promoting pro-inflammatory responses	[73]
	IECs, immune cells	-	Neutralizing TLR2/4 decreases Fn-mediated cytokine release	[74]

Table 1. Continued.

Barrier type	Species and model (mice/cell)	Specimen and detection method	Effects	References
Pg	DSS mice, T cells	-	Directly upregulate the Th17/Treg ratio	[75]
	mice	-	Increase M1/M2 macrophage ratio; decrease Th17	[61]
	mice	-	Increase $CD4^+$ T cells	[62]
	PBMCs	PBMCs	Increase IL-17, activate T cell, NF-κB-induced intestinal inflammation	[76]
	mice, neutrophils	-	Activate TLR2-Mal-PI3K signaling	[77]
	CRC cells	-	Activate MAPK/ERK signaling pathway	[78]
Klebsiella	GF mice	Intestinal biopsy, 16S rRNA	Upregulate TH cells, DCs and IEC; stimulate IL-18 secretion	[33]
	TNBS mice	Intestinal biopsy	Increase COX-2, IL-1β, IL-6, TNF-α, NF-κB activation, and lipid peroxidation	[72]
	DSS/IL-$10^{-/-}$ mice	Intestinal biopsy	Activate IL-1β and Th17 cells of oral origin	[79]
Cc	Co-cultured HT-29, THP-1	-	Activate TNF-α, IL-1β, IL-6 (from THP-1 cells)	[71]
Gut vascular barrier				
Fn	HUVECs	-	Increase endothelial permeability	[80]
	HUVECs	-	Increase vascular permeability	[81]
Pg	mice	-	Impaired vascular relaxation via vascular BH4/nNOS/NRF2 pathways	[82]
	HMEC-1	-	Increased vascular permeability via proteolytic cleavage of adhesins	[83]
	Zebrafish, HMEC-1	-	Degrades PECAM-1 and VE-cadherin *in vitro*; mediates vascular damage *in vivo*	[84]
	mice, HUVEC	-	Impairs endothelial integrity	[85]
Sm	mice	Intestinal biopsy	Increase disease activity index (DAI); decrease in survival rate	[86]

Fn, *Fusobacterium nucleatum*; *Pg*, *Porphyromonas gingivalis*; DSS, dextran sulfate sodium; GF, germ-free; IEC, intestinal epithelial cell; TLR, toll-like receptor; CHO-K1, Chinese Hamster Ovary K1; TJ, tight junction; ZO-1, zonula occludens-1; *Cc*, *Campylobacter concisus*; HT-29, Human Colorectal Adenocarcinoma Cell Line HT-29; TNBS, 2,4,6-trinitrobenzene sulfonic acid; $CD4^+$, Cluster of Differentiation 4^+; Th1/Th17, T helper 1 cells/T helper 17 cells; TJP-1, tight junction protein-1; TNF-α, tumor necrosis factor-α; IFN, Interferon; IL, Interleukin; MCP, Monocyte Chemoattractant Protein; M1/M2, classically/alternatively activated macrophages; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells; TLR2-Mal-PI3K, toll-like receptor 2-MyD88 adaptor-like-Phosphoinositide 3-Kinase; TH, T helper cells; DCs, dendritic cells; COX-2, Cyclooxygenase-2; PBMC, Peripheral Blood Mononuclear Cells; CRC, colorectal cancer; THP-1, Human Monocytic Leukemia Cell Line; HUVEC, Human Umbilical Vein Endothelial Cells; PECAM-1, Platelet Endothelial Cell Adhesion Molecule-1; VE-cadherin, vascular endothelial cadherin; *Sm*, *Streptococcus mutans*.

B, and Lys-gingipain (Kgp)) are considered the key mediators of *Pg* pathogenicity [91]. *Pg* generates specific proteases, notably Rgp B, which degrades the inner protective mucus layer by cleaving the C-terminal region of mucin 2 (MUC2), thereby disrupting the gut chemical barrier [67]. Importantly, *Pg* can also impair the chemical barrier integrity without directly colonizing the gut. In dextran sulfate sodium (DSS)-induced colitis models, the mucus layer becomes unstable and is more susceptible to detachment by gingipains, leading to worsened intestinal inflammation [46]. *Pg* ingestion also promotes lactate accumulation via bacterial glycolysis while suppressing host synthesis of antimicrobial metabolites such as succinate and n-butyrate [61].

In vitro study suggests the *Cc* may evade toll-like receptor (TLR) 5 recognition, thereby avoiding the stimulation of mucus secretion and crypt flushing responses [52]. Additionally, *Campylobacter jejuni* infection significantly reduced colonic mucin-2 mRNA in IL-10$^{-/-}$ mice by day six post-infection [92].

Oral-associated bacteria (OB) exert dual destructive effects on the gut chemical barrier: direct proteolysis of MUC2 and induction of ERS in goblet cells. These mechanisms synergistically impair mucosal regeneration and alter sulfide metabolism, a critical yet overlooked aspect of IBD pathophysiology. Future research should focus on the development of intestinal organoid models to quantify pathogen penetration kinetics and engineering mucin-mimetic biomaterials for targeted barrier repair.

Gut Physical Barrier

The intestinal physical barrier, the third line of defense, comprises a single layer of tightly connected epithelial cells supported by the lamina propria and muscularis mucosae [89,93,94]. A key component of this barrier is the tight junction (TJ) complex, which includes proteins such as zonula occludens-1 (ZO-1), ZO-2, and occludin that seal intercellular spaces and regulate paracellular permeability [95]. The integrity of the gut physical barrier largely depends on the structural and functional integrity of these TJ proteins [95].

In a murine colitis model induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS), *Fn* reduced the expression of TJ-associated proteins claudin-1, ZO-1, and occludin in the colon [72,93]. In both Caco-2 cells and a DSS-induced colitis mouse model, *Fn* exacerbated IBD symptoms by compromising epithelial integrity and increasing intestinal permeability through modulation of TJ proteins ZO-1 and occludin [68]. Similarly, another DSS-induced mouse model showed that oral administration of *Pg* reduced TJ protein expression and impaired the intestinal barrier, accompanied by significant shifts in the gut microbial composition, characterized by increased *Clostridiaceae* abundance [70]. *Pg* also suppresses ZO-1 and occludin expression in intestinal tissues, thereby compromising epithelial barrier function [63]. However, the effect of *Pg* on intestinal epithelial cells appears inconsistent; one study reported that *Pg*-derived LPS partially ameliorated DSS-induced colitis in mice by attenuating intestinal epithelial cell (IEC) damage [69].

An *in vitro* study showed that the *Fn*-type strain ATCC 25586T, which is invasive in cultured oral epithelial cells, also penetrates Caco-2 cells [30]. Another *in vitro* study indicated that *Pg*-specific gingipains may disrupt the physical barrier by altering IEC permeability [70]. *Cc* impairs the tricellular tight junctions (tTJs) in Human Colorectal Adenocarcinoma Cell Line HT-29 (HT-29) colonic epithelial cells by stimulating underlying immune cells. These activated immune cells release pro-inflammatory cytokines (TNF, IL-1β, and IL-6), which subsequently increase antigen permeability [71]. *Cc* infection correlates with the depletion of tricellulin, a tTJ-specific protein, further compromising epithelial barrier integrity [71].

In conclusion, OB may compromise the intestinal physical barrier by downregulating TJ protein expression and disrupting epithelial permeability (Table 1).

Gut Immune Barrier

The intestinal immune barrier plays a crucial role in maintaining mucosal and systemic immune homeostasis. It is composed of immune cells, including macrophages, dendritic cells, and lymphocytes, primarily residing in the lamina propria and mesenteric lymph nodes [86,96]. Ectopic colonization by specific oral bacteria (*Fn*, *Pg*, *Sm*, *Cc*, *Kp*) may initiate a cascade of events that exacerbate chronic intestinal inflammation. These bacteria can excessively stimulate the secretion of inflammatory cytokines, disrupt host immunity, evade immune surveillance, and contribute to gut microbiota dysbiosis [33,63,97] (Table 1).

Fn stimulates CD4$^+$ T cell proliferation and Th1/Th17 polarization via Signal Transducer and Activator of Transcription 3 (STAT3)-dependent signaling. This amplifies the release of multiple cytokines, including TNF-α, IFN-γ, IL-1β, IL-6, and IL-17 [68,98]. Evidence suggests that *Fn* promotes colorectal carcinoma progression by recruiting myeloid-derived suppressor cells, which exert dual immunosuppressive effects, attenuating T-cell proliferation and simultaneously inducing caspase-dependent apoptotic signaling [68]. In TNBS-induced colitis mouse models, *Fn* is implicated in various inflammatory processes in the gut. For example, *Fn* increases the Treg population by activating TLR2/TLR4 receptors in TLR2$^{-/-}$ and TLR4$^{-/-}$ mice, leading to intestinal inflammation [99]. Moreover, *Fn* proteins $>$50 kDa enhance immune cell infiltration and upregulate mucosal transcription of IFN-γ, classical pro-inflammatory cytokines (TNF, IL-6), and MCP-1 in murine models [64]. Sun *et al.* [74] reported that neutralizing antibodies against TLR2 and TLR4 reduce *Fn*-mediated cytokine and chemokine production in human periodontal ligament cells, suggesting that *Fn* may drive gut inflamma-

tion via TLR2 and TLR4 signaling in IECs and immune cells. *Fn* may also impair autophagic flux and increase pro-inflammatory cytokine levels via reactive oxygen species in Caco-2 cells [73]. These findings implicate *Fn* as a pathobiont orchestrating dual-axis mucosal disruption: gut inflammation and immune dysregulation.

A recent study revealed that *Pg* activates TLR4-dependent signaling in $CD4^+$ T cells, inducing dysregulated Th17/Treg lineage-specific transcription factors and effector cytokines, thereby increasing the Th17/Treg ratio and promoting intestinal inflammation. This implies that pathogenic *Pg* can directly alter the Th17/Treg balance via distinct TLR pathways [75]. *Pg* LPS has the potential to trigger Th- and T-cell responses, marked by elevated IL-5, IL-10, and IL-13, along with a reduced IFN-γ level. These findings support the inclination of *Pg* LPS to drive a semi-T helper 1 cells (Th2)-like immune response [100]. *Pg* also upregulates the classically/alternatively activated (M1/M2) macrophage balance, reduces Th17 cell frequency, and lowers fecal IgA levels, thus promoting chronic inflammation in murine models [61]. Another *in vivo* study demonstrated that *Pg* indirectly induces intestinal inflammation by enhancing gut immune barrier function through increased $CD4^+$ T cell infiltration and IL-9 production [62]. In patients with gingivitis and periodontitis, *Pg* outer membrane proteins stimulate blood mononuclear cells to express IL-17, activate T cells, and contribute to intestinal inflammation *in vitro* [14]. One study showed that *Pg* differentially modulates two TLR2 pathways in neutrophils: Myeloid Differentiation Primary Response 88 (MyD88), a key component of the protective TLR2-MyD88 pathway, is degraded via proteasomal activity, thereby favoring activation of the Toll-Like Receptor 2-MyD88 adaptor-like-Phosphoinositide 3-Kinase pathway (TLR2-Mal-PI3K pathway) and promoting dysbiotic inflammation *in vivo* [77]. Additionally, *Pg* enhances inflammation in human colorectal cancer cells by activating the mitogen-activated protein kinases (MAPK)/Extracellular Signal-Regulated Kinase (ERK) signaling pathway [78].

Klebsiella (*Kp*), the predominant colonizer, promotes Th1 cell induction and activates dendritic cells and IECs in the intestine via the TLR4 signaling; *Kp* also triggers intestinal IL-18 secretion [33]. These are pivotal processes in IBD pathogenesis. Periodontitis increases *Kp* abundance, which induces colitis by enhancing inflammasome-mediated IL-1β secretion from lamina propria macrophages [79]. *Kp* derived from the salivary microbiota of CD patients, activates dendritic cells via the TLR4 signaling pathway, leading to IL-18 release, TH1 cell recruitment, and subsequent colitis development [33]. *Kp* also upregulates COX-2 and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), activates NF-κB, and promotes lipid peroxidation in the colon [72]. In co-culture experiments, *Cc* infection of HT-29/B6 Glucocorticoid Receptor/Mineralocorticoid Receptor (HT-29/B6-GR/MR) colonic epithelial monolayers with M1-like THP-1 macrophages leads to immune cell activation after 48 hours, causing the release of TNF, IL-1β and IL-6, which subsequently impair the integrity of TJ [71]. The zonula occludens toxin produced by *Cc* activates intestinal epithelial cells and macrophages, inducing the release of pro-inflammatory cytokines and amplifying macrophage responses to other gut microbes. *Cc* also activates neutrophils by upregulating the adhesion molecule CD11b and enhancing oxidative burst activity [101], further worsening intestinal inflammation similar to colitis [81].

The ectopic colonization by OB may also indirectly disrupt the gut immune system. Oral pathobiont-reactive Th17 cells acquire gut-homing properties and migrate to inflamed intestinal sites. There, Th17 cells respond to translocated OB (*Fn*, *Pg*, *Sm*), contributing to the initiation and progression of colitis [20].

Consequently, OB increases the M1/M2 macrophage ratio, expands the Th17 population, and depletes Tregs. Furthermore, OB interferes with immune cells and IECs by activating diverse signaling pathways, including TLR2/TLR4, NF-κB, STAT3, MAPK, and autophagy. OB also induces "trained immunity" via epigenetic reprogramming, establishing an inflammatory memory that extends beyond the initial infection. These insights support the exploration of programmable "synthetic immune niches" using engineered hydrogels loaded with cytokine-sensing nanobodies or CRISPRa modules to reset epigenetic memory for future IBD therapies.

Gut Vascular Barrier

The gut vascular barrier (GVB) is a network of blood vessels that regulates the transport of gut-derived substances to other organs, such as the brain and liver [27,102]. The GVB shares certain similarities with the blood-brain barrier. However, it is comparatively less restrictive and allows the passage of molecules up to 4 kDa in size [103]. Larger molecules (>4 kDa) and microbes that bypass the mucosal and epithelial barriers are typically retained in the lamina propria (LP), unless the GVB is compromised and its permeability altered [104] (Table 1).

Fusobacterium nucleatum (*Fn*) binds to vascular endothelial cells through the interaction between vascular endothelial cadherin (VE-cadherin) and its surface adhesin FadA. This binding disrupts VE-cadherin-mediated intercellular junctions, thereby increasing permeability and allowing bacterial translocation through paracellular gaps [80]. Moreover, *Fn* infection downregulates CD31 expression in vascular endothelial cells, further compromising cell-cell adhesion and increasing vascular leakage [105, 106].

One Study suggested that *Pg* infection may impair vascular relaxation and endothelial integrity by altering the vascular Tetrahydrobiopterin/Neuronal Nitric Oxide Synthase/Nuclear Factor Erythroid 2-Related Factor 2 pathways (BH4/nNOS/NRF2) pathways [82]. *Pg* also dis-

rupts TLR-NF-κB signaling in endothelial cells, leading to decreased cell proliferation, increased mesenchymal transition, and apoptosis in both *in vivo* and *in vitro* models [85]. Outer membrane vesicles (OMVs) derived from *Pg* not only enhance vascular permeability but also promote a pathogenic phenotype by degrading endothelial cell-cell adhesins, such as Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1), through gingipain activity [83]. Farrugia *et al*. [84] demonstrated that *Pg* degrades PECAM-1 and VE-cadherin, contributing to vascular damage in zebrafish and HMEC-1 cells. Moreover, the administration of *Pg* elevates serum endotoxin (LPS) levels and facilitates bacterial DNA translocation to the liver in infected mice, suggesting that systemic inflammatory responses may result from modifications of the GVB [46,63]. Administration of *Streptococcus mutans* strain *Bacteroides fragilis* strain TW295 (TW295) aggravated colitis in DSS-treated mice and reduced survival rates by invading the bloodstream rather than remaining confined to the mucosal lumen of the gastrointestinal tract [97].

Collectively, these findings suggest that OB may contribute to increased vascular permeability and GBV disruption in the gut. However, further investigations are required to validate these OB-mediated effects.

Conclusion

This review synthesizes evidence that the oral microbiota, especially pathobionts such as (e.g., *Fn*, *Pg*), contribute to IBD pathogenesis through a proposed multistage model. OB target the disruption of multiple intestinal barrier systems. Microbial Barrier: OB induce dysbiosis by suppressing beneficial commensals and enriching opportunistic pathogens, thereby disrupting the ecological balance of the gut. Chemical Barrier: OB degrade the protective mucus layer and impair antimicrobial peptide function, weakening the chemical defense of the gut. Physical Barrier: OB compromise epithelial integrity by downregulating TJ proteins and increasing paracellular permeability, which facilitates luminal antigen entry. Immune Barrier: OB trigger dysregulated immune responses, promoting Th1 and Th17 differentiation, increasing M1/M2 macrophage ratios, inhibiting Tregs, and activating inflammatory signaling pathways, ultimately sustaining chronic inflammation. GVB: OB disrupt endothelial cell junctions, enhancing vascular permeability and potentially allowing systemic dissemination of bacteria or inflammatory mediators.

Collectively, these barrier disruptions, orchestrated by translocated oral pathobionts, initiate and perpetuate chronic intestinal inflammation characteristic of IBD. Future studies should aim to definitively establish strain-level identity between oral and gut microbiota in IBD patients, elucidate the predominant translocation pathways of specific taxa, and clarify the host immune and metabolic responses modulated by key oral pathobionts within the gut microenvironment. Translational research should also focus on developing non-invasive diagnostic biomarkers based on oral microbial profiles or circulating oral pathogen components. Therapeutically, targeting ectopically colonizing oral pathobionts or reinforcing intestinal barrier function presents a promising frontier. Targeting the oral-gut axis may ultimately offer more precise approaches to IBD prognosis and management.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

Conceptualization, XL; Methodology, YJ and XC; Data Curation, YJ, HL; Formal Analysis, XL, KC, YJ; Investigation, YJ, HL; Visualization, XC, ZL; Validation, XC, ZL. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Figs. 1 and 2 were created using BioRender. The authors have no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

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