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REVIEW

The Oral Microbiota and Its Implications for Inflammatory Bowel Disease: A Literature Review

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Abstract: Background: Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD) and ulcerative colitis (UC) and represents a heterogeneous spectrum of chronic intestinal inflammation with no exclusive etiology. Emerging evidence underscores that IBD arises from complex interactions between host factors and microbial communities. The disruption of microbial homeostasis facilitates the colonization and invasion of opportunistic pathogens within the gut, precipitating an exaggerated host immune response and driving disease progression. While extensive research has elucidated the role of the gut microbiota in IBD pathogenesis, the contribution of the oral microbiota to this process is garnering increasing attention. Oral microbes can translocate to the intestine via the swallowing of saliva, and harmful oral bacteria and proinflammatory immune cells from the oral mucosa may migrate to the gut, eliciting immune activation. This review explores the emerging role of the oral microbiota in IBD pathogenesis and synthesizes recent advancements in understanding the intricate relationship between oral microbial communities and IBD.

Keywords: oral-gut axis, microbial translocation, dysbiosis, impaired intestinal barrier function

Introduction

Inflammatory bowel disease, including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disorder of the gastrointestinal tract characterized by persistent, relapsing inflammation and mucosal ulceration.[1] Clinically, IBD manifests as severe diarrhea, weight loss, and debilitating abdominal pain,[2] leading to substantial morbidity and a profound decrease in quality of life.[3] While IBD has a high prevalence in developed countries (>0.3%), its incidence is rising rapidly in newly industrialized countries.[4] By 2025, the global burden of IBD is projected to affect up to 30 million individuals.[5] Current research underscores that IBD arises from complex multifactorial etiologies, including genetic predispositions, environmental triggers, dysregulation of the systemic immune response and alterations in the gut microbiota.[6–8]

Advances in "omic" technologies have enabled a comprehensive analysis of the genetic and metabolic profiles of these microbial communities.[9] IBD progression is increasingly linked to the disruption of host–microbial symbiosis and significant alterations in the composition of the gut microbiota.[10,11] The gut microbiota plays a pivotal role in the pathogenesis of IBD, influencing its initiation, progression, and exacerbation.[12] This microbial ecosystem is remarkably diverse, encompassing approximately 1000 different bacterial species and over 15,000 distinct strains.[13] While the stomach and small intestine contain a relatively small bacterial population, the colon harbors approximately 10^{12} microorganisms per gram of content.[14]

The human gut microbiota is composed of five predominant phyla of bacteria: *Firmicutes* (60 to 80%), which includes the classes *Clostridia, Bacilli* and *Negativicutes; Bacteroidetes* (20 to 40%), including *Flavobacteria, Bacteroidia, Sphingobacteria* and *Cytophagia; Verrucomicrobia; Actinobacteria; Proteobacteria* to a lesser extent; and one Archaea phylum, *Euryarchaeota*.[15] Previous studies[16] have shown that the microbiota varies significantly across different age groups. Even within the same age group, significant differences have been observed

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between the gut microbiota and the oral microbiota. *Bifidobacterium* is the most abundant genus in the intestines of newborns. Studies have reported that viable *Bifidobacteria* are present in neonatal oral fluid (OF) and that OF at birth is a possible transmission route of *Bifidobacteria* to the infant gut.[17] The transmission of subgingival plaque bacteria to the gut is more prevalent in elderly individuals than in adults.[18] Furthermore, certain bacterial taxa, including *Bilophila, Desulfovibrio*, and *Campylobacter*, which have been identified as predictors or indicators of diseases such as gastroenteritis and bacteremia, are more frequently shared between fecal and subgingival plaque or tongue-coating microbiota in elderly individuals than in younger adults.[18–20] Compared with healthy individuals, IBD patients exhibit significant dysbiosis, decreased bacterial diversity, and unstable bacterial communities in the inflamed intestinal mucosa, with bacterial translocation and ectopic growth occurring in some cases.[21,22] Some researchers have employed gut microbiota-based predictive models to distinguish IBD and confirmed that patients with different types of IBD exhibit variations in bacterial abundance[23] (Figure 1). For example, reductions in *Firmicutes* and certain clusters of *Clostridium*, an increase in *Enterobacteriaceae*, and changes in the relative abundances of *Bacteroides, Bifidobacterium*, and *Lactobacillus* have been identified.

The oral microbiota, in addition to its function in initial digestion, is crucial for maintaining oral and systemic health.[24] The oral microbiota is defined as the collective genome of microorganisms residing in the oral cavity. It is the second-largest microbiota after the gut and has been shown to be highly susceptible to environmental influences.[25] Adults produce ≥ 1000 mL of saliva daily, of which approximately 600 mL is swallowed, containing up to 10^9 bacteria/mL. Thus, the oral microbiota serves as an important reservoir for the gut microbiota, playing a significant role in maintaining the internal stability of the gut microbial ecosystem. Therefore, the hypothesis that certain oral bacteria may induce various diseases by disrupting the gut microbiota is reasonable.[26] Iwauchi et al observed a high degree of

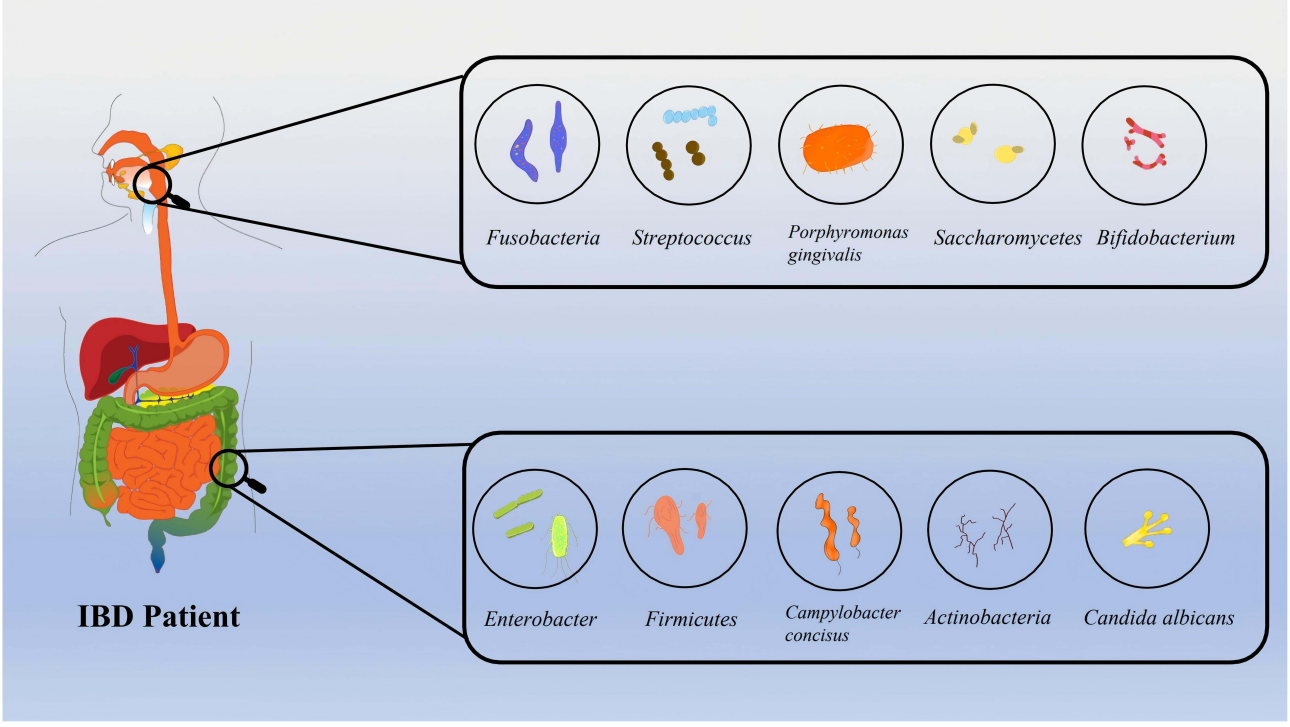

Figure 1 Differences in Oral and Intestinal Microbiota Among Patients with IBD. Compared to healthy individuals, patients with IBD exhibit significant alterations in both oral and gut microbiota. In the oral cavity of IBD patients, alongside beneficial bacteria such as Bifidobacterium and Saccharomycetes, pathogenic species are notably enriched. For example, Fusobacteria, a key contributor to periodontitis, can trigger aberrant immune-inflammatory responses through ectopic colonization of the gut. Similarly, Porphyromonas gingivalis, a major periodontal pathogen, plays a pivotal role in the induction or exacerbation of IBD. Additionally, Streptococcus is detected at higher levels in the saliva of CD patients compared to healthy controls. Within the gut microbiota of IBD patients, Enterobacteriaceae, including Escherichia coli and Klebsiella pneumoniae, are prominent and can initiate a cascade of immune responses following the disruption of microbial homeostasis. Fungal dysbiosis is also evident, with Candida albicans detected at a strikingly high prevalence of 97.1%.

similarity between the oral and fecal microbiota and confirmed the translocation of oral bacteria to the gut using metagenomic sequencing analysis.[27]

Due to the existence of the oral–gut axis, the considerable distance between the beginning and end of the digestive tract, and chemical barriers such as gastric acid and bile,[28] the oral and gut microbiomes are well separated.[29] However, an impairment of the oral–gut barrier can allow for translocation and communication between these organs,[30] enabling commensal bacteria to become chronic inflammatory stimuli in adjacent tissues.[31] As the function of the oral–gut barrier decreases, microbial translocation from the oral cavity becomes more common.[32] Seedorf et al[33] reported that oral-derived bacteria, including those from the phyla *Actinobacteria, Firmicutes, Bacteroidetes*, and *Proteobacteria*, can overcome the physical barriers of the host and persist in the sterile distal gut.

Crucially, microbial composition is modulated by dietary factors—fruit and fiber intake reduce inflammation while enhancing beneficial taxa like Bifidobacterium[34–36]—and medicinal components (eg, curcumin, omega-3) that bidirectionally regulate this axis through anti-inflammatory and barrier-repair mechanisms.[37–41] However, an impairment of the oral–gut barrier can allow for translocation and communication between these organs,[30] enabling commensal bacteria to become chronic inflammatory stimuli in adjacent tissues.[31] Notably, probiotics competitively inhibit pathogen translocation along this axis,[42] while omega-3 resolves systemic inflammation to improve both oral and gut health.[43,44] As the function of the oral–gut barrier decreases, microbial translocation from the oral cavity becomes more common.[32] Such translocation dynamics are further influenced by nutraceuticals; for instance, curcumin metabolites generated by gut microbiota ameliorate intestinal inflammation despite originating from oral-targeted interventions.[40,41] Seedorf et al[33] reported that oral-derived bacteria, including those from the phyla Actinobacteria, Firmicutes, Bacteroidetes, and Proteobacteria, can overcome the physical barriers of the host and persist in the sterile distal gut. Human cohort studies reveal that specific oral pathobionts exhibit differential gut colonization efficiency. For instance, *Klebsiella pneumoniae* translocated to the gut in 11.3% of IBD patients.[45] Murine models quantify translocation rates through fluorescently labeled oral bacteria, demonstrating that 18.5%±3.2% of orally administered *Fusobacterium nucleatum* stably colonizes the colon within 72 hours.[46] Researchers have confirmed that typical oral-resident species can be detected within the digestive tract of patients with gastrointestinal diseases.[47] Oral microbial translocation also occurs in healthy individuals,[48] implying that if gastrointestinal homeostasis is compromised, the oral microbiota may become opportunistic pathogens.[28]

The salivary microbiota of IBD patients differs from that of healthy individuals,[49] with lower biodiversity and more severe dysbiosis.[50] Various oral manifestations, such as recurrent aphthous stomatitis, oral ulcers, xerostomia, periodontitis, and gingivitis, are frequently observed in IBD patients, indicating an association between the oral microbiota and these manifestations.[51] Given that IBD is currently incurable and tends to lead to lifelong relapses,[52] monitoring and managing this disease are highly important.[53] Investigating the differences in the oral microbiota between IBD patients and healthy individuals, as well as the impact of the disease stage on the microbiota, can provide a more effective and convenient means of detecting disease progression. This approach provides new insights and evidence for disease monitoring and treatment in IBD patients.

With in-depth research into the mechanisms of IBD, a variety of advanced technologies and biologic agents have been developed for its treatment.[54] Gazzaniga et al[55] described methods for developing microfluidic organ-on-a-chip models of the small and large intestine lined with epithelial cells isolated from duodenal, jejunal, ileal, or colonic organoids derived from wild-type or transgenic mice. These models are used to identify specific bacterial strains that regulate the host's response to pathogens and to study the cellular and molecular basis of host-microbe interactions. Thomas et al[56] performed longitudinal gut biopsies in IBD patients and integrated single-cell RNA sequencing with spatial transcriptomics to construct a cellular atlas of anti-TNF response. This multimodal technology platform provides a critical tool for precision assessment of therapeutic efficacy.

Oral Microbiota

Oral Microbial Composition

The microbial ecology of the oral cavity is highly complex, representing a rich biological environment with unique ecological niches that provide distinct habitats for microbial colonization. The oral cavity or mouth has several distinct

microbial habitats, such as the teeth, gingival sulcus, attached gingiva, tongue, cheek, lip, hard palate, and soft palate.[57–59] Contiguous to the oral cavity are the tonsils, pharynx, esophagus, eustachian tubes, middle ear, trachea, lungs, nasal passages, and sinuses.[60]

We define the human oral microbiome as the collection of all microorganisms found on or within the human oral cavity and its contiguous extensions (terminating at the distal esophagus).[61] The normal microbiome is composed of bacteria, fungi, viruses, archaea, and protozoa.[62] Accumulating evidence links oral bacteria to numerous systemic diseases, such as cardiovascular diseases,[63] metabolic disorders,[64] gastrointestinal cancers,[65] pneumonia,[66] and Alzheimer's disease.[67]

The Human Oral Microbiome Database comprises approximately 774 prokaryotic species. These species belong to 185 genera and 12 phyla, of which approximately 58% are formally named, 16% are unnamed but cultivated, and 26% of the species are known only as uncultivated phylotypes.[68] The 12 phyla include *Firmicutes, Fusobacteria, Proteobacteria, Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Spirochaetes, SR1, Synergistetes, Saccharibacteria* (TM7) and *Gracilibacteria* (GN02).[69] The phyla *Firmicutes, Fusobacteria, Proteobacteria, Actinobacteria, Bacteroidetes*, and *Spirochaetes* account for 96% of the total oral bacteria,[70] with *Firmicutes* being the most abundant, followed by *Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes*, and *Fusobacteri*a.[71] Within the phylum *Firmicutes*, the genus *Streptococcus* (19.2%) is the most abundant, followed by *Veillonella* (8.6%).[72]

Despite similarities in the distribution of the oral microbiota across different populations, the diversity of the oral microbiota is both individual-specific and site-specific.[73] At the genus level, a conserved core oral microbiota exists in healthy individuals. The microbes in our oral cavity engage in symbiotic relationships based on a mutual benefit. These commensal populations do not cause harm and maintain a check on pathogenic species by preventing their adhesion to mucosal surfaces.[74] Bacteria become pathogenic and cause infections and diseases only once they breach the commensal barrier.[75]

The differences in oral microbiota between the two subtypes of IBD are also worth exploring, but related studies are scarce. One study found that the abundance of the *Firmicutes* and *Proteobacteria phyla* in the gut microbiota of UC patients was significantly increased, while the abundance of the Bacteroidetes phylum was significantly reduced.[76] Another study found that *Escherichia coli* and *Ruminococcus* were more abundant in CD patients, while *Faecalibacterium, Blautia, Bifidobacterium*, and *Roseburia* were more abundant in UC patients.[77]

Functions of the Oral Microbiota

The oral microbiome usually exists in the form of a biofilm. It plays a crucial role in maintaining oral homeostasis, protecting the oral cavity, and preventing disease development. Identifying the microbiome and its common interactions with neighboring organisms is crucial for understanding the mechanisms underlying key players in oral health and disease.[78] First, the oral microbiota effectively prevents pathogen colonization by occupying ecological niches and competing with pathogenic bacteria. The renewal of the oral mucosa, the actions of mastication and swallowing, and lysozyme in saliva constitute physiological barriers in the oral cavity, limiting the bacterial quantity and diversity and thereby helping to maintain the balance of the oral microecosystem.[79] Second, the oral microbiota is involved in the initial digestion of food and nutrient absorption, producing metabolites such as short-chain fatty acids (SCFAs). The oral microbiota can utilize amino acids within the body for protein synthesis or catabolism,[80] generating bioactive metabolites that act as virulence factors and participate in biological processes such as inflammation and immune responses.[81–83] Finally, the oral microbiota interacts with the host immune system to modulate immune responses. It not only stimulates the maturation and activation of immune cells but also engages pattern recognition receptors in microbial responses, thereby influencing the structure and function of host epithelial cells.[84] Metabolites generated from the fermentation of amino acids by the oral microbiota can exert cytotoxic effects and induce tissue inflammation.[85] With the development of metabolomics, monitoring and analyzing the oral microbiota have gradually been adopted as novel diagnostic approaches, providing new strategies for identifying disease mechanisms and biomarkers related to the diagnosis and prognosis. However, most current studies are limited to correlational conclusions and lack direct causal evidence. The clinical value of the oral microbiota warrants further discussion.

The Association Between the Oral Microbiota and IBD

The Potential Role of the Oral Microbiota in the Onset and Progression of IBD

In healthy individuals, the oral microbiome is considered in dynamic equilibrium, as it fluctuates in response to both endogenous and exogenous factors.[86] Factors such as diet, nutrition, lifestyle, and socioeconomic status can influence the stability of the oral microbiota,[75,87] thereby potentially promoting the development of certain diseases. IBD is a global condition that is particularly prevalent in developed countries. With economic development, the incidence in developing countries is also increasing annually. In China, the incidence is approximately 3.44 per 100,000 individuals.[88] The relationship between the oral microbiota and its changes and IBD is currently a research hotspot,[89] with studies indicating that the oral microbiota plays a significant role in the progression of IBD.[90]

Said et al analyzed the composition of the salivary microbiota of 35 IBD patients using 16S rRNA sequencing and compared it with that of 24 healthy controls. They concluded that, compared with healthy controls, the diversity of the salivary microbiota in IBD patients did not show significant changes, but marked differences in relative abundance were observed.[91] Specifically, the relative abundance of *Bacteroidetes* was strongly influenced by *Prevotella*, whereas that of *Proteobacteria* was significantly affected by *Haemophilus* and *Neisseria*. Xun et al reported that the ratio of *Firmicutes* to *Bacteroidetes* was increased in IBD patients, indicating that in the oral cavity of IBD patients, the abundance of *Firmicutes* increased, whereas that of *Bacteroidetes* decreased.[92] Some researchers have found that inflammatory markers in the saliva of IBD patients also undergo significant changes. Elevated levels of IgA and interleukin (IL)-1β, as well as reduced lysozyme levels, have been reported.[93] Certain specific oral microbial taxa are detected at relatively high rates in oral samples from IBD patients. For example, the detection rate of *Campylobacter* in the saliva of UC patients is 100%, and that in CD patients is 85%, whereas it is only 75% in healthy populations.[94]

Common Bacteria and IBD

Fusobacterium nucleatum

Fusobacteria are gram-negative anaerobic bacilli with species-specific reservoirs in the human mouth, gastrointestinal tract and other tissues and are associated with oral inflammatory diseases.[95] *Fusobacterium nucleatum* (*F. nucleatum*) is invasive and proinflammatory in human oral epithelial cells, inducing the secretion of proinflammatory chemokines.[96] However, *F. nucleatum* is not a predominant colonizer of the human gut and rarely establishes itself in a healthy intestinal environment. In contrast, it has a significant competitive advantage within the tumor microenvironment of colorectal cancer.[97] Compared with unaffected adjacent colonic tissue, colorectal tumors and colorectal adenocarcinomas are highly enriched with *F. nucleatum*. Amber et al[98] applied quantitative PCR and detected an increased abundance of *F. nucleatum* in the intestinal mucosa of patients with colonic adenomas. Similarly, several studies have reported that, compared with healthy individuals, the abundance of *F. nucleatum* in the intestines of colorectal cancer patients is increased.[99,100] Liu et al[101] discovered that in the colonic tissues of mice treated with dextran sulfate sodium (DSS) and *F. nucleatum*, the protein expression levels of Zonula occludens-1 (ZO-1) and Occludin were decreased, whereas the phosphorylation of myosin light chain (MLC), which is responsible for remodeling tight junction proteins, was increased. *F. nucleatum* not only downregulated the levels of the TJ proteins ZO-1 and Occludin but also affected the distribution of junction proteins. *F. nucleatum* can affect intercellular junction proteins in the intestinal barrier, promoting the disruption of intestinal barrier function and exacerbating intestinal inflammation. Some researchers[102,103] have reported that, compared with nonadenoma controls, colorectal adenomas enriched with *F. nucleatum* exhibit overactivation of the NF-κB pathway and increased expression of inflammatory cytokines such as IL-6, IL-12, IL-17, and TNF-α. Researchers have hypothesized that during the chronic inflammatory phase of IBD, *F. nucleatum* may exacerbate colorectal cell damage and compromise the integrity of the intestinal epithelial barrier by inducing the release of inflammatory mediators. Additionally, *F. nucleatum* may interact with noninvasive, proinflammatory bacterial species, facilitating their translocation across the epithelium and thereby accelerating disease progression.

Porphyromonas gingivalis

Porphyromonas gingivalis, a major pathogen of periodontal disease, may play a significant role in the induction or exacerbation of IBD.[104] It can produce a variety of virulence factors, such as lipopolysaccharide (LPS), gingipains

(gingival proteinases), peptidyl-arginine deiminase of *Porphyromonas gingivalis* (PPAD), fimbriae, and capsules.[105] Studies have orally administered bacteria to mice to simulate periodontal disease and found that serum IL-17 levels were significantly elevated in experimental groups. Mice orally administered *P. gingivalis* exhibited dysbiosis and disruption of the gut microbiota.[106] *P. gingivalis* can induce abnormal inflammatory and autoimmune responses in the host by secreting PPAD, which increases protein citrullination. This mechanism may contribute to the pathogenesis of various inflammatory conditions, including periodontal disease and potentially systemic diseases.[107,108] PPAD from *P. gingivalis* catalyzes the same citrullination reaction as mammalian peptidyl-arginine deiminase (PAD), thereby significantly altering protein conformations and functions.[109] PAD can modify and transform host proteins by catalyzing and converting peptidyl-arginine to peptidyl-citrulline—a process known as citrullination.[110] Immunohistochemistry showed that PAD staining was strong in the intestinal lamina propria cells of mice with DSS-induced acute colitis and patients with UC, confirming that citrullination can promote inflammation.[111] The balance between Th17 and Treg cells plays a crucial role in the progression of IBD.[112,113] *P. gingivalis* ultrasonicates induce the apoptosis of $CD4^+$ T cells and upregulate the expression of the Th17-related transcription factor RoRγt and the production of the proinflammatory cytokines IL-17 and IL-6. *P. gingivalis* ultrasonicates downregulate the expression of the essential Treg transcription factor Foxp3 and the production of the anti-inflammatory cytokines TGF-β and IL-10 through the Toll-like receptor 4 (TLR4) pathway.[114] In summary, *P. gingivalis* can induce intestinal inflammation through its virulence factors. However, the specific mechanisms by which periodontitis exacerbates the progression of IBD remain to be further investigated.

Enterobacteriaceae

Enterobacteriaceae bacteria are typically considered gut bacteria rather than exclusive to the oral cavity. A study[45] has shown that *Enterobacteriaceae* residing in saliva can induce pathogenic immune responses when ectopically colonized in the gut. Members of the *Enterobacteriaceae* family, particularly the genus *Klebsiella*, have been identified as potent Th1 inducers in the gut. These bacteria can elicit severe intestinal inflammation when colonizing hosts genetically predisposed to IBD. *Klebsiella pneumoniae* (*K. pneumoniae*) is a gram-negative rod-shaped bacterium that is commonly found in the normal flora of the human oral cavity, skin, and gut.[115] Owing to its strong resistance to external environments and its propensity for antibiotic resistance, it is recognized as a significant pathogen for hospital-acquired infections.[116] Young et al[117] developed a mouse model of oral infection with *K. pneumoniae* and showed for the first time that this pathogen can stably colonize the gastrointestinal tract of immunocompetent mice without disrupting the host microbiota. Zhang et al[118] isolated a strain of *K. pneumoniae*, designated KLPJ, from the colon tissues of patients with UC. Their study indicated that KLPJ is capable of inducing colitis and exacerbating DSS-mediated colitis. The mechanism underlying KLPJ-mediated colitis involves the caspase-11-mediated release of mature IL-18 from intestinal epithelial cells. This release of IL-18 plays a pivotal role in the induction of IFN-γ production, which subsequently enhances the activity of natural killer (NK) cells and promotes T-cell proliferation. Concurrently, research has shown that the *K. pneumoniae* strain KP-2H7 activates TLR4 on intestinal dendritic cells,[102] prompting intestinal epithelial cells to secrete IL-8 and thereby increasing inflammation.[119]

Campylobacter concisus (*C. concisus*) is an emerging *Campylobacter* species that is prevalent in the human oral microbiota.[120] The bacterium is a gram-negative, motile, curved or spiral-shaped rod capable of damaging epithelial barrier functions and invading intestinal cells in vitro.[41] PCR detection has revealed that the prevalence of *C. concisus* in the saliva of UC patients is 100%, that in CD patients is 85%, and that in healthy controls is only 75%.[41] Man et al[121] used PCR technology to detect the enrichment of *Campylobacter* in fecal samples from pediatric patients with CD. A study revealed a relatively high prevalence of the *Campylobacter* genus, specifically *C. concisus* and *C. ureolyticus*, in biopsy samples from adults with UC, suggesting that these species of bacteria may be involved in the chronic inflammation characteristic of UC.[122] Man et al[123] found that infection with *C. concisus* significantly increased intestinal epithelial permeability in Caco-2 cells. Caco-2 cells are a widely used human colorectal adenocarcinoma cell line that forms a tight intestinal barrier, mimicking the human intestinal epithelium.[124] They are commonly employed to study drug absorption, toxicity, and the effects of pathogens on intestinal cells.[125] *C. concisus* also induced the movement of the tight junction proteins ZO-1 and Occludin from the cell membrane into the cytosol. These rearrangements of tight

junction proteins led to a significant increase in barrier permeability, highlighting the potential of *C. concisus* to disrupt intestinal barrier integrity.

Some *C. concisus* strains, particularly those isolated from patients with IBD, have been shown to upregulate the surface expression of LPS receptors, including TLR4 and myeloid differentiation factor 2, in HT-29 cells.[126] Previous studies have shown that *C. concisus* can stimulate the production of the proinflammatory cytokine IL-8 in intestinal cell lines.[127] Additionally, *C. concisus* upregulates the expression of the adhesion molecule CD11b on neutrophils exposed to the bacteria and further stimulates the oxidative burst response of neutrophils in a dose-dependent manner.[128] Currently, two virulence factors produced by *C. concisus* have been implicated in intestinal diseases. One of these toxins is the zonula occludens toxin (Zot), which targets intestinal epithelial tight junctions and may increase the pathogenicity of the bacterium. The Zot genes in *Campylobacter* species are encoded by prophages and are divided into two clusters, which encode $Zot_{CampyType\_1}$ and $Zot_{CampyType\_}2$.[129] The two types of Zot toxins share similarities, yet their overall sequence identities vary greatly, particularly at the C-terminus.[130] Mahendran et al discovered that $Zot_{CampyType\_1}$ inflicted prolonged damage on Caco-2 monolayers. The persistent detrimental impact of *C. concisus* Zot is attributable, at least in part, to the induction of apoptosis and the secretion of proinflammatory cytokines, including TNF-α and IL-8, by intestinal epithelial cells.[131] Moreover, *C. concisus* Zot upregulates the expression of TLR3, the proinflammatory cytokines IL-6 and IL-8, and the chemokine CXCL16.[132] These findings suggest that *C. concisus* not only exacerbates disease progression by increasing receptor expression in infected cells but also increases intestinal epithelial permeability and inflammation through the production of virulence factors.

Streptococcus mutans

Streptococcus mutans (*S. mutans*) is the most abundant genus in the mouth, and as a member of this genus, *S. mutans* plays a central role in the development of caries.[133] Studies have shown that *S. mutans* can enter the bloodstream or adhere to various sites along the circulatory pathway, even during routine daily activities, leading to inflammatory responses and tissue damage.[134] In CD patients, the detection rate of *S. mutans* was significantly higher in saliva than in the control samples. This finding suggests that oral pathogens may contribute to systemic inflammatory processes in CD patients.[135] Certain strains of *S. mutans* can adhere to or invade hepatocytes, potentially activating them. This activation occurs because both cultured hepatocytes and liver tissues produce IFN-γ when stimulated by bacteria. However, the IFN-γ production mediated by *S. mutans* may trigger the inflammatory cascade, leading to the generation of many other inflammatory molecules. These molecules, including IFN-γ, may eventually reach the colon, exacerbating colitis-related inflammation.[136]

Candida albicans

Candida albicans (*C. albicans*) is a gram-positive, oval-shaped yeast that commonly resides in the oral cavity, upper respiratory tract, gastrointestinal tract, and vagina of healthy individuals.[137] It typically exists in low numbers and does not cause disease in healthy hosts. In individuals with weakened immunity, such as premature infants, elderly individuals, and those with compromised immune systems, *C. albicans* can become an opportunistic pathogen.[138] Multiple studies have shown that fungal dysbiosis can lead to the development and exacerbation of gastrointestinal diseases.[139,140] Studies[141] have shown that IBD patients exhibit fungal dysbiosis in the gut, with a detection rate of *C. albicans* as high as 97.1%, which is significantly higher than that in healthy individuals and patients with irritable bowel syndrome (IBS). In contrast to *C. albicans*, the abundance of *Saccharomyces* spp., including *Saccharomyces cerevisiae*, is reduced in the feces of IBD patients, with their abundance decreasing in individuals with active inflammation.[142] These findings suggest an association between *Candida albicans* and the development of intestinal inflammation.

Kyla et al[143] used the DSS-induced colitis model to test the role of filamentation during disease using vehicle (no *C. albicans*), wild-type *C. albicans*, yeast-locked *C. albicans* (TetOn-NRG1) and hyphal-locked *C. albicans* (TetOff-NRG1). These findings suggest that IgA-targeted hyphal cells and the Als1 adhesin exacerbate colitis. One finding[144] suggested that candidalysin is a key virulence determinant that fuels proinflammatory immunity by *C. albicans* in the gut and that strains with high damage capacity promote intestinal inflammation through IL-1β-dependent mechanisms. In previous studies, Zwolinska-Wcislo et al[145] showed that in a rat model of UC infected with *C. albicans*, the healing

process was significantly delayed compared with that in UC rats not infected with *C. albicans*. In infected rats, the colonic blood flow (CBF), IL-1β, and TNF-α levels were reduced, whereas the myeloperoxidase (MPO) content was increased. After a period of fluconazole treatment, the changes in these inflammatory markers significantly reversed, suggesting that antifungal therapy may be beneficial for the repair of colonic damage in UC patients during *C. albicans* infection.

These findings further support the notion that the oral microbiota, whether commensal or pathogenic, can disseminate to the gut and promote IBD pathogenesis through dysbiosis. (Table 1).

Potential Mechanisms by Which the Oral Microbiota Affects IBD

The specific pathogenesis of IBD has not yet been fully elucidated. Currently recognized risk factors include intestinal dysbiosis and an impairment of the intestinal immune barrier. Research on the key role of microbes in the pathogenesis of IBD has gradually emerged and has been proven to be significantly correlated.[146] Changes in the composition and function of the microbiota seem to exist before the clinical flare-up of ulcerative colitis in some patients, which may exacerbate intestinal inflammation.[147] Inflammation of the oral mucosa can promote the proliferation of *Enterobacteriaceae* bacteria, such as *Klebsiella* and *Enterobacter*, and the ectopic intestinal colonization of these bacteria plays a crucial role in the deterioration of intestinal inflammation.[46] The possible mechanisms by which the oral microbiota affects IBD include the aspects described below (Figure 2).

Disruption of the Intestinal Barrier

Some scholars[148] propose that the impact of the oral microbiota on IBD is "multistage in development". This hypothesis suggests that the process includes several stages: first, increased abundance and virulence of oral disease-associated bacteria and a reduction in intestinal colonization resistance; second, translocation of these bacteria to the intestine; and third, colonization of the intestine by these oral disease-associated bacteria and exacerbation of disease in individuals with IBD. Impaired epithelial barrier function is considered a key feature of IBD.[149] The intestinal epithelial barrier, which consists mainly of the mucus layer, intestinal epithelial cells, and tight junction proteins, serves as both a physical barrier and a biological barrier to protect the intestinal tissue from bacterial invasion.[150] Impaired epithelial barriers can lead to increased intestinal permeability, the systemic dissemination of gut pathogens, and activation of aberrant immune

Table 1 Key Studies Investigating the Role of Oral Microbiota in Inflammatory Bowel Disease

Study	Study Type	Sample Size/Model	Key Findings
Liu, H. et al (2020) *Journal of digestive diseases*[101]	Human & Animal	91 IBD patients	*F. nucleatum* was significantly enriched in the feces of patients with IBD and its abundance correlated with disease activity. *F. nucleatum* damaged intestinal barrier by regulating the expression and distribution of tight junction proteins zonula occludens-1 and occludin.
Sato, K. et al (2017) *Scientific reports*[106]	Animal (Mouse)		Mice fed *P. gingivalis* exhibited dysbiosis and disruption of the gut microbiota with concomitant elevation of serum endotoxin and inflammatory markers.
Zhang, L. et al (2010) *Journal of clinical microbiology*[94]	Human	18 IBD patients, 59 HC	C. concisus is part of the normal human oral microflora.the prevalence of C. concisus in the saliva of UC patients is 100%, that in CD patients is 85%, and that in healthy controls is only 75%
Szymanska, S. (2014) *PloS one*[135]	Human	150 IBD patients, 75 HC	Compared with the control group, IBD patients had higher counts of *S. mutans* in their saliva
Zwolinska-Wcislo, M. et al (2009) *Journal of physiology and pharmacology*[145]	Human & Animal	89 IBD patients, 12 HC	The rats with ulcerative colitis induced by TNBS infected with *C. albicans* exhibited a delay in the healing of these ulcerations. Significant *C. albicans* colonization of the colon is more common in patients with long-term UC.

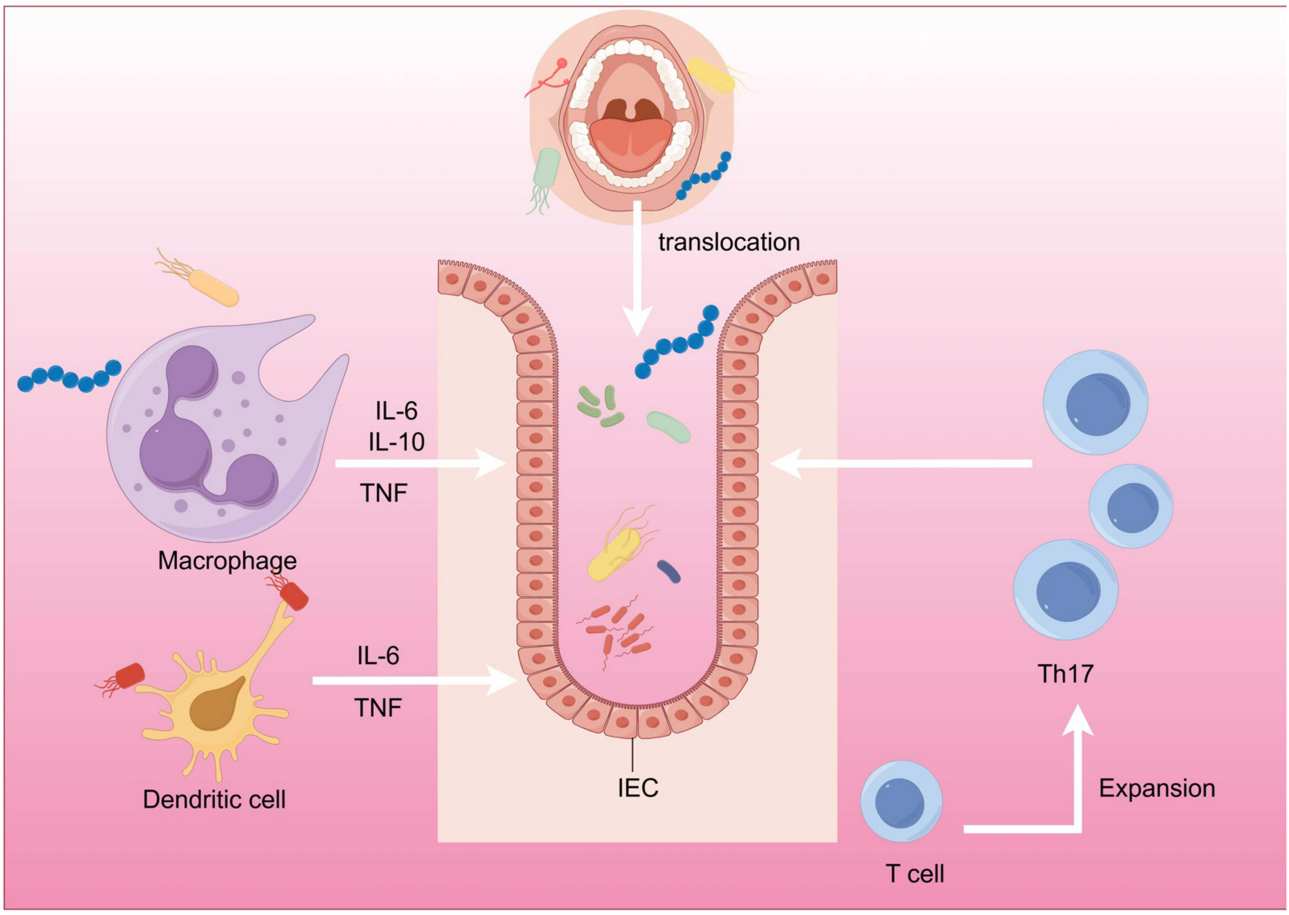

Figure 2 Possible mechanisms of oral microbes affecting IBD. The increased virulence of oral bacteria, coupled with the reduced resilience of intestinal epithelial cells (IECs), facilitates the translocation of oral microbiota to the gut. These bacteria directly impair IEC integrity through robust adhesive and invasive mechanisms. Moreover, specific bacterial species can alter T-cell differentiation, disrupting the balance between Th17 and regulatory T (Treg) cells, thereby exacerbating intestinal inflammation. Additionally, they induce the production of both pro-inflammatory cytokines (eg, IL-6) and anti-inflammatory cytokines (eg, IL-10), modulating the dynamics of intestinal inflammatory responses.

responses. All of these factors are key contributors to IBD. The mucus layer, which is rich in Mucin 2 (MUC2), is secreted by goblet cells and forms a biological barrier that protects the intestine from invasion by commensal and pathogenic bacteria.[151] Prolonged bacterial stimuli are known to induce neutrophil recruitment in the lamina propria and inhibit the secretion of MUC2 by goblet cells, thus leading to a decrease in MUC2 levels and an increase in the vulnerability of the intestinal mucosal barrier during active mucosal inflammation.[152,153] P-glycoprotein (P-gp) plays a critical role in the protection of the intestinal epithelium by mediating the efflux of drugs/xenobiotics from the intestinal mucosa into the gut lumen. Certain bacteria, such as those from the phyla *Proteobacteria* and *Firmicutes*, can regulate the expression of P-gp, thereby influencing the activity of intestinal inflammation.[154] *F. nucleatum* not only directly invades the intestinal mucosa but also accelerates the UC process through its derived extracellular vesicles (EVs).[155] These EVs can promote the upregulation of proinflammatory cytokines (eg, IL-1β, IL-6, and TNF-α), downregulate the expression of the anti-inflammatory cytokine IL-10 and tight junction proteins, and disrupt epithelial barrier function in intestinal epithelial cells. In experimental models, Fn-EVs significantly exacerbate colitis severity, an effect mediated by the downregulation of miR-574-5p and the activation of autophagy via the miR-574-5p/CARD3 axis.[156] *Fusobacterium nucleatum* exosomes (Fn-Exos) induce DNA damage via the miR-129-2-3p/TIMELESS axis, subsequently activating the ATM/ATR/p53 pathway, which ultimately promotes cellular senescence and colonic inflammation.[157] One pathotype of *Campylobacter*, AToCC, can encode Zot, increasing intestinal epithelial permeability.[116,118] Kojima et al[158] discovered that specific strains of *Streptococcus sanguinis*, such as TW289 and ATCC10556, exhibit strong adhesion and

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invasiveness to gastrointestinal epithelial cells, significantly exacerbating colitis in mice. Additionally, *K. pneumoniae* can colonize the gut and invade the intestinal mucosa, thereby disrupting the intestinal barrier.

Impacts on Host Immune and Inflammatory Responses

Th17 cells promote tissue inflammation, whereas Treg cells (differentiated from $CD4^+$ T cells) suppress autoimmunity in IBD patients. Some studies suggest that a Treg cell deficiency may be a core component of IBD pathogenesis.[159,160] An imbalance between Th17 and Treg cells, which differentiate from $CD4^+$ T cells, contributes to IBD. Certain gut microbiota can shift the Th17/Treg balance toward Treg cells by releasing polysaccharide A (PSA). Research has shown that *Klebsiella* isolated from the saliva of IBD patients colonizes the intestine ectopically to elicit colitis development,[103] and *Klebsiella*-reactive Th17 cells may migrate to the gut to exacerbate intestinal inflammation.[132] *Porphyromonas gingivalis* in the oral cavity of mice can translocate to the gut and induce Th17 cell production.[161] *Bacteroides fragilis* upregulates Foxp3 expression and promotes Treg cell differentiation. *Clostridium* clusters IV and XIV also induce Foxp3 expression and Treg cell differentiation.[162] The virulence factors of *F. nucleatum* inhibit T-cell function, and its outer membrane proteins Fap2 and RadD induce lymphocyte death.[163] Additionally, *F. nucleatum* promotes the expression of proinflammatory cytokines such as IL-6 and TNF-α, leading to Th17 cell differentiation. It also increases STAT3 phosphorylation and activates the STAT3 signaling pathway.[84,90] IL-10 is a key anti-inflammatory cytokine that is essential for establishing immune tolerance to the initial microbiota. Research has identified high-titer neutralizing anti-IL-10 antibodies in infants with severe colitis, findings that align with mouse studies and highlight the potential of anti-IL-10 antibodies to induce or exacerbate colitis in vivo.[164] Maharshak et al[165] developed an IL-10-deficient mouse model in which the development and progression of intestinal inflammation were associated with an increase in *Escherichia coli* abundance.

Microbe–Host Interactions

Microbes produce a vast array of bioactive metabolites that affect the human body. Metabolic disorders are associated with alterations in the composition and function of the gut microbiota. Specific categories of microbiota-derived metabolites, particularly bile acids, SCFAs, branched-chain amino acids, trimethylamine N-oxide, tryptophan, and indole derivatives, are implicated in the pathogenesis of metabolic disorders.[166]

SCFAs promote the induction and expansion of regulatory T cells and macrophages in the gut,[167] thereby inhibiting inflammation induced by pathogens.[168] Acetate (C2), propionate (C3), and butyrate (C4), which are products of microbial fermentation, are associated with a variety of physiological functions.[169] C3 promotes the cytoplasmic acidification of *Salmonella* and disrupts the intracellular pH homeostasis of the pathogen, thereby restricting its proliferation.[170] C4 activates the transcription factor hypoxia-inducible factor-1 (HIF-1) in intestinal epithelial cells, thereby protecting the gut barrier from damage caused by *Clostridium difficile* toxins.[171] Compared with healthy controls, IBD patients have lower levels of SCFAs in their feces. In UC patients, decreased concentrations of C2 and C3 have been observed, although C4 levels are not significantly reduced.[172] Patients with IBD who are in remission have higher levels of C4 than those with a severe, active disease.[173] In general, microbial dysbiosis in patients with CD and UC is associated with a reduction in the abundance of bacteria that produce SCFAs. Ectopic colonization of the oral microbiota can lead to gut dysbiosis, affecting SCFA production.

Tryptophan metabolism is also closely linked to IBD. Tryptophan (Trp), an essential amino acid that is crucial for brain function, is the precursor of serotonin (5-HT). Certain bacterial strains can promote the production of Trp in the body, which may help maintain normal gut motility.[174] The oral microbiome plays a crucial role in the breakdown and utilization of nutrients, and its composition can influence metabolic pathways, including those involved in Trp metabolism.[175] Bacterial catabolism of Trp produces many metabolites, several of which can modulate aspects of the host immune response. These metabolites influence the differentiation of regulatory $CD4^+$ T cells (Tregs), the maintenance of intestinal intraepithelial lymphocytes (IELs), and the activation of natural killer T (NKT) cells.[176,177] Studies have shown that host-produced Trp metabolites, such as kynurenine (Kyn), and microbially produced Trp metabolites, such as indole (IND) and indole-3-propionate (IPA), can regulate intestinal barrier function by modulating the gut epithelium via IL-10 receptor (IL-10R) expression.[178] Specifically, these metabolites activate the aryl hydrocarbon

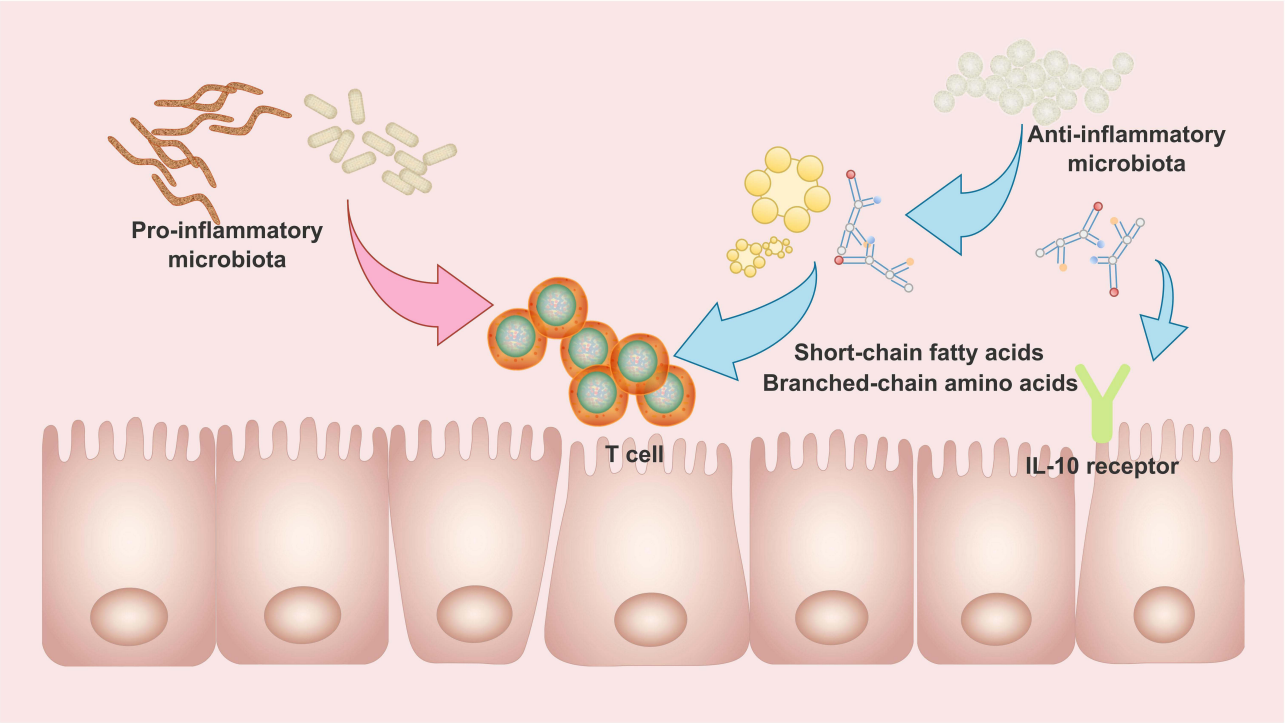

Figure 3 Interactions between Microbiota and Host Gut Cells. Some anti-inflammatory microbiota can produce metabolites such as short-chain fatty acids and branched-chain amino acids. These metabolites enhance the intestinal barrier and alleviate intestinal inflammation through pathways like regulating T cells and binding to intestinal cell receptors. In contrast, some pro-inflammatory microbiota can exacerbate intestinal inflammation by regulating T cells.

receptor (AhR) in the gut epithelium, which in turn stimulates the Wnt/β-catenin signaling pathway to increase intestinal barrier integrity.[179] Scott et al[180] discovered that Trp metabolites originating from the gut microbiota can enhance intestinal epithelial barrier function following exposure to inflammatory stimuli, including proinflammatory cytokines and DSS-induced colitis. Imbalances in Trp metabolism may reduce the availability of 5-HT in the gut, thereby affecting gut motility and exacerbating gastrointestinal disease symptoms.[181]

Conclusions

The oral microbiota may play crucial roles in the pathogenesis, progression, and treatment of IBD. Dysbiosis of the oral microbiota can influence IBD through mechanisms such as immune modulation and inflammation. Future research into the interactions between the oral microbiota and IBD may provide new strategies for early diagnosis, disease management, and treatment. For better management of IBD, clinicians should prioritize patients' oral health through regular oral examinations and improved oral hygiene to reduce the accumulation of pathogenic bacteria. In addition to traditional pharmacological treatments, modulating the microbiota to restore the balance of the oral and gut microbiota may offer more personalized and comprehensive treatment options for IBD patients.

Abbreviations

IBD, Inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; *F. nucleatum, Fusobacterium nucleatum; C. concisus, Campylobacter concisus; K. pneumoniae, Klebsiella pneumoniae; C. albicans, Candida albicans; S. mutans, Streptococcus mutans*; HC, healthy control.

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Figure 2 was printed by Figdraw. Figure 3 utilized diagrams.net (formerly known as draw.io, developed by JGraph Ltd., official website: https://app.diagrams.net/) to create all flowcharts and architecture diagrams. And Figure 3 was partly generated using Biovisart (https://biovisart.com.cn).

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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