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REVIEW

New Insights into the Role of Oral Microbiota Dysbiosis in the Pathogenesis of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a group of chronic intestinal inflammatory disorders with a prolonged duration characterized by recurrent relapse and remission. The exact etiology of IBD remains poorly understood despite the identification of relevant risk factors, including individual genetic susceptibility, environmental triggers, and disruption of immune homeostasis. Dysbiosis of the gut microbiota is believed to exacerbate the progression of IBD. Recently, increasing evidence has also linked oral microbiota dysbiosis with the development of IBD. On the one hand, IBD patients show significantly unbalanced composition and function of the oral microbiota known as dysbiosis. On the other, overabundances of oral commensal bacteria with opportunistic pathogenicity have been found in the gut microbiota of IBD patients. Herein, we review the current information on the causative factors of IBD, especially recent evidence of IBD-associated oral microbiota dysbiosis, which has seldom been covered in the previous literature review, highlighting the pathogenic mechanisms of specific oral bacteria in the development of IBD. Ectopic colonization of several oral bacteria, including a subset of *Porphyromonas gingivalis*, *Streptococcus mutans*, *Fusobacterium nucleatum*, *Campylobacter concisus*, and *Klebsiella pneumoniae*, may lead to destruction of the intestinal epithelial barrier, excessive secretion of inflammatory cytokines, disruption of the host immune system, and dysbiosis of gut microbiota, consequently aggravating chronic intestinal inflammation. Studying oral microbiota dysbiosis may open future horizons for understanding IBD pathogenesis and provide novel biomarkers for IBD. This review also presents the current treatment and new perspectives for IBD treatment.

Keywords Inflammatory bowel diseases · Risk factors · Oral microbiota dysbiosis · Ectopic colonization · Intestinal epithelial barrier · Microbial-based treatment strategies

Abbreviations

APC	Antigen-presenting cell
CBP	Collagen-binding protein
Cc	*Campylobacter concisus*
CCK	Cholecystokinin
CD	Crohn's disease
CDI	*Clostridioides difficile* infection
CPS	Capsular polysaccharide
Cr	*Campylobacter rectus*
Cu	*Campylobacter ureolyticus*
EEN	Exclusive enteral nutrition
EIMs	Extra-intestinal manifestations
EPS	Extracellular polymeric substances
FMT	Fecal microbiota transplant
Fn	*Fusobacterium nucleatum*
GI	Gastrointestinal
HCs	Healthy controls
IBD	Inflammatory bowel disease
IC	Indeterminate colitis
IECs	Intestinal epithelial cells
IL	Interleukin
Kp	*Klebsiella pneumoniae*
LPS	Lipopolysaccharides
MACs	Microbiota-accessible carbohydrates
MAMP	Microbe-associated molecular pattern
Pg	*Porphyromonas gingivalis*
PN	Parenteral nutrition
PRR	Pattern recognition receptor
SCD	Specific carbohydrate diet
SCFAs	Short-chain fatty acids

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S-ECC	Severe early childhood caries
Sm	*Streptococcus mutans*
TLR	Toll-like receptors
TNF-α	Tumor necrosis factor alpha
UC	Ulcerative colitis
WSD	Westernized diet
Zot	Zonula occludens toxin

Introduction

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC), are inflammatory disorders of the gastrointestinal (GI) tract with a chronic relapsing-remitting course [1]. The incidence and prevalence have been gradually rising in Africa, Asia, and South America since the 1990s [2], but vary widely from developed to developing countries, with the rates increasing over the last two to three generations in the developed countries while only for one generation in most of the developing countries [3]. The etiology of IBD remains unclear; it may be based upon a complex interaction among genetic predisposition, environmental factors, dysbiosis of gut microbiota, and deficiency in the intestinal immune system (Fig. 1).

More than 200 susceptibility loci have been found to be associated with the pathophysiology of IBD [4]. These loci point to an interplay between the immune system and microbiota in IBD. For CD, disease-related genes have been discovered mostly in innate immunity, defective processing of intracellular bacteria including *NOD2/CARD15* [5], unfolded protein response (UPR)-associated genes such as *XBP1* [6], and autophagy-associated genes such as *ATG16L1* [7], *IRGM* [8], and *LRRK2* [9]. For UC, the focus has been laid largely upon the intestinal mucus barrier function [10]. Deficiencies in *ECM1* [11], *CDH1* [12], *HNF4a*, and *LAMB1* [13] all have adverse effects on the epithelial defense function. Interleukin (IL)-23R, *IL12B*, *STAT3*, *JAK2*, and TYK2, which are included in the adaptive immunity of interleukin-23 signaling and T-helper 17 cells, together with IL-10 in interleukin-10 signaling, appear to be implicated in both CD and UC [14].

The rising incidence of IBD highlights the role of environmental triggers. Recognized environmental factors, such as smoking [15], diet [16], breastfeeding [17], gastrointestinal infections [18], stress [19], and drugs such as antibiotics [20], oral contraceptive agents (OCPs) [21], and nonsteroidal anti-inflammatory agents (NSAIDs) [22], all play important roles in the development of IBD. Specifically, smoking increases the risk of CD and reduces the risk of UC [23]. These environmental factors change the composition and metabolites of gut microbiota, mainly characterized by decreased diversity and disturbed immunoregulatory properties, resembling those confirmed in systemic inflammatory conditions like rheumatoid arthritis, osteoarthritis, and spondylarthritis [24].

Specifically, among the various environmental factors, diet highly influences the gut microbial composition and

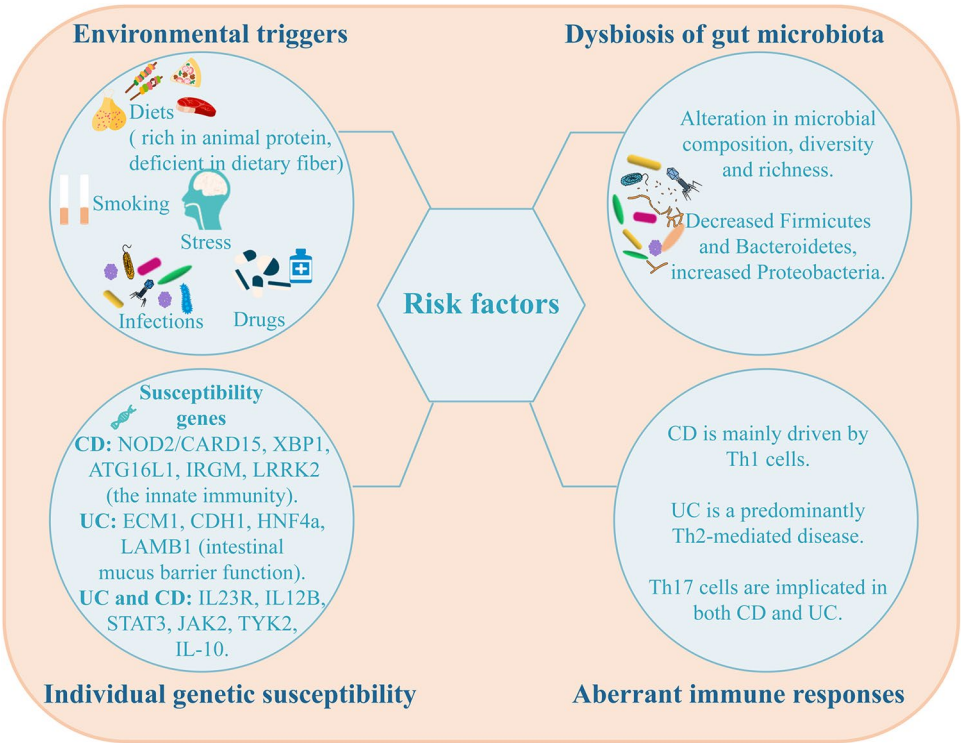

Fig. 1 Risk factors of inflammatory bowel disease (IBD). IBD may arise from a complex interplay among environmental triggers, individual genetic susceptibility, dysbiosis of gut microbiota, and aberrant immune responses

immune system, playing the major role in the onset and progression of IBD (Fig. 2). The western diet (WSD) pattern, characterized by high fat and sugar intake, has been suggested as a risk factor for IBD [25]. Components of the WSD tend to reduce gut microbiome diversity, promote pro-inflammatory microbiota, reduce the production of short-chain fatty acids (SCFAs), and disrupt the mucosal barrier. SCFAs, the major products of fiber fermentation, play important roles in intestinal homeostasis and host immune function. Bacteria involved in fiber degradation including *Prevotella* and *Treponema*, which are significantly decreased. Furthermore, WSD promotes the expansion and activity of bacteria associated with colonic mucus degradation, resulting in barrier dysfunction [26].

The H_2S toxin hypothesis put forward that the primary determinants of H_2S production associated with dietary sulfur and an abundance of sulfate-reducing bacteria (SRB) account for the pathogenesis of UC. An animal-based diet leads to higher dietary sulfur. Excessive H_2S induces oxidative stress, energy starvation, and colonocyte death and disrupts the gut barrier function [27]. Decreased consumption of dietary fiber also increases the risk of IBD. Metabolizing the fiber from fruits into SCFAs by intestinal microbiota inhibits NF-κB and the transcription of proinflammatory mediators. Moreover, the aryl hydrocarbon receptor (AhR) mediates the effects of fiber and plays vital roles in protecting against environmental antigens [28]. Consumption of highly processed and refined foods and of additives such as emulsifiers, preservatives, and artificial sweeteners can negatively affect gut microbiota. Dietary emulsifiers promote colitis by facilitating higher expression of mucolytic bacteria including *Akkermansia muciniphila* and *Ruminococcus gnavus* [29]. Furthermore, when studying CD-like ileitis model mice, artificial sweeteners increase the abundance of Proteobacteria and the infiltration of bacteria into the ileal lamina propria [30]. Moreover, dietary phosphate can also promote intestinal inflammation through the activation of NF-κB in macrophages [31].

Both innate and adaptive immune systems are important for maintaining host health. Macrophages and dendritic cells (DCs) are essential for innate and adaptive immune responses. The adaptive immune system reveals distinct responses to different pathogens, and the selective activation of a particular subset of DCs may induce specific immune responses, including Th1, Th2, and Th17 responses, to extracellular bacteria. CD is mainly driven by Th1 cells, whereas UC is a predominantly Th2-mediated disease [32, 33]. Th17 cells are implicated in playing a pathogenic role in both CD and UC [34, 35]. The cross talk between antigen-presenting cells (APC) and Th cells is also impaired under inordinate conditions, which greatly influence the homeostasis of the immune system. To conclude, ectopic colonization of oral

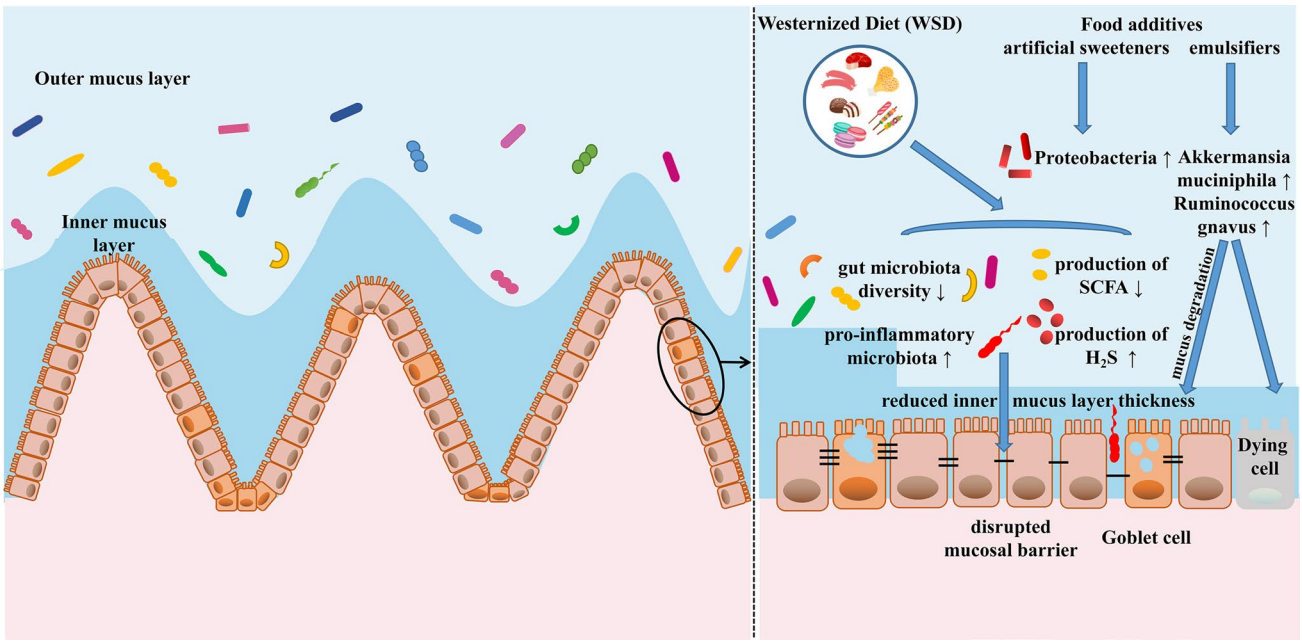

Fig. 2 Diet-mediated gut microbiota dysbiosis in the development of IBD. Components of the western diet (WSD) tend to reduce gut microbiota diversity, promote pro-inflammatory microbiota, reduce the production of short-chain fatty acids (SCFAs), increase H_2S production promoting colonocyte death, increase mucus penetrability, and disrupt the intestinal mucosal barrier. Food additives also negatively affect gut microbiota. Dietary emulsifiers promote colitis by facilitating higher expression of mucolytic bacteria including *Akkermansia muciniphila* and *Ruminococcus gnavus*. Artificial sweeteners increase the abundance of Proteobacteria and the infiltration of bacteria into the ileal lamina propria

bacteria can disrupt the ecological balance among the oral microbiota, host, and immune system. Disturbed activation of APC and differentiation of Th cells may both lead to intestinal inflammation.

Apart from genetic predisposition, environmental triggers, and the relevant gut microbiota dysbiosis mentioned above, growing evidence indicates that the oral microbiota play a significant role in the pathogenesis of IBD. The oral microbiota contribute significantly to bowel health and disease. On the one hand, IBD patients show distinct oral microbiota dysbiosis. Diverse bacterial species have been associated specifically or non-specifically with IBD. On the other, overabundances of oral commensal bacteria with opportunistic pathogenicity have been found in the gut microbiota of IBD patients. The interaction between dislocated oral bacteria and immune responses in IBD has received increasing attention and provided insights into the ongoing explorations in this field. The link between oral-gut microbiota and intestinal inflammation has been established in mice with colitis, and attracting more attention in human studies now, a deeper understanding of oral bacteria-induced intestinal inflammation might help in treating IBD.

Oral Microbiota in Healthy Conditions

The human oral cavity is colonized by over 700 types of microorganisms including bacteria, archaea, fungi, and viruses, among which bacteria are the predominant constituent [36]. The Human Oral Microbiome Database (HOMD) (www.homd.org) aims to provide comprehensive information on the approximately 700 prokaryote species existing in the human oral cavity, which are closely related to human health and disease based on a curated 16S rRNA gene-based provisional naming scheme [37].

Compared with other body habitats, the microbial community of the oral cavity is unique and site-specific. The mucosa, anaerobic pockets, supragingival plaque, subgingival plaque, and saliva harbor unique microbiota [38]. Nasidze et al. studied the composition of the oral microbiota in the saliva samples of 120 healthy individuals from 12 countries worldwide; their results confirmed individual specificities with few geographic specificities among these subjects [39]. Firmicutes, Proteobacteria, Bacteroidetes, and Actinobacteria showed the highest abundance, while Fusobacteria, TM7, spirochaetes, OD2, and Synergistes were comparatively fewer in the oral microbiota of healthy adults. In addition, oral communities also showed interpersonal variation despite these similarities, embodied in the dominant bacteria, with some mainly dominated by *Streptococcus*, while others were dominated by *Prevotella*, *Neisseria*, *Haemophilus*, or *Veillonella* [40]. The abundance of microbiota differs remarkably among the dental plaque, saliva, and mucosa, with the highest in the dental plaque and lowest in the oral mucosa [41]. The oral microbiota undergoes physiological changes with age and during the replacement of dentition. The dominant bacteria in the deciduous dentition period are Firmicutes and Proteobacteria, including a large amount of *Streptococcus*, *Acinetobacter* and *Moraxella*, but in the mixed dentition and permanent dentition period they are Firmicutes and Bacteroidetes. *Veillonellaceae*, spirochetes, and TM7 increase in abundance with age [42].

In addition to bacteria, oral fungi, archaea, and viruses also greatly contribute to the diversity and ecological stability of the human oral community. Archaea belong to non-bacterial prokaryotes and have a more limited number of species than bacteria, the majority of which are methanogens [43]. Nguyen et al. reported *Methanobrevibacter*, *Methanobacterium*, *Methanosarcina*, *Methanosphaera*, and *Thermoplasmatales* in the oral cavity [44]. Fungi are relatively rare, constituting < 0.1% of the oral microbiota. Fungi are hard to isolate and culture with the existing methods, leading to very little progress in this field. Ghannoum et al. examined the profile of the oral fungal microbiota among 20 healthy individuals and reported that > 75 genera of fungi harbored in the healthy oral cavity, among which the most abundant was *Candida*, followed by *Cladosporium*, *Aureobasidium*, and *Aspergillus* [45]. Further analysis indicated that the most common *Candida* species was *C. albicans* [46].

The healthy human oral cavity contains eukaryotic viruses and bacteriophages [47], and the latter make up the majority of the oral virome. *Herpesviridae*, *Papillomaviridae*, and *Anelloviridae* are the most common eukaryotic viruses, and most of these infections are asymptomatic in healthy individuals [48].

The oral microbiota make important contributions to maintaining both oral and systemic states. Interactions among the complex communities inhabiting the oral cavity as well as their interactions with the host all contribute vitally to the status of the oral and general health. Disturbances of the oral microbiota are associated with not only oral diseases but also systemic infections and inflammation. Subsequent evidence has linked the oral microbiota with numerous systemic diseases [49].

Studies Show IBD-Associated Oral Microbial Patterns

Approximately one third of IBD patients are characterized by the existence of extraintestinal manifestations (EIMs), including pathological changes in the mouth, eyes, skin, and joints [50]. CD lesions may occur in the entire digestive tract, from mouth to the anus. The oral manifestations of CD may be reflected in the changes in the oral mucosa and the tooth and tooth-supporting structures, such as papillomatosis

of the oral mucosa, vesicular eruptions, pyostomatis vegetans, gingival hyperplasia, dental caries, and periodontitis, which are associated with oral microbiota dysbiosis [51]. Dental caries are common in preschool-aged children and can occur at any age, characterized by destruction of the tooth tissues [52]. In children with severe early childhood caries (S-ECC), *Sm*, *Granulicatella elegans*, *Veillonella spp.*, *Bifidobacteriaceae spp.*, *Actinomyces*, *Leptotrichia*, and *Prevotella* showed higher abundance in the plaque of children with S-ECC compared to caries-free children [53]. The relative abundance of *Streptococcus*, *Actinomycetes*, *Veillonella*, *Lactobacillus*, and *Propionibacterium* was also higher in the plaque of caries-active adults [54]. IBD patients showed higher prevalence of dental caries than HCs. Specifically, CD patients who had undergone restrictive surgery had a higher DMF score and more *Lactobacilli* and *Sm* in the saliva compared to HCs [55].

Periodontal diseases, including gingivitis and periodontitis, are biofilm-induced bacterial infections of the tooth-supporting structures including the gingiva, periodontal ligament, and alveolar bone [56]. Gingivitis is the early stage, and periodontitis is a more advanced stage of periodontal diseases, which mainly result from dysbiosis of the oral microbiota; if left untreated, they can eventually lead to tooth loss and systemic inflammation [57]. In a study of the salivary and subgingival microbiota, Bacteriodetes, Actinobacteria, and Spirochaetes were more abundant in HCs than in periodontitis, while *Porphyromonas*, *Tannerella*, *Prevotella*, and *Filifactors* were more abundant in chronic periodontitis. IBD patients have an increased prevalence and moderate severity of periodontitis [58]. The colonization of periodontal pathogens, in particular *Campylobacter rectus* (*Cr*), might account for the periodontal manifestation of CD [59].

Besides abundance changes in dental caries- and periodontitis-associated oral pathogens, IBD patients also showed significant changes in the composition, structure, and function of the oral microbiota (Table 1). Studies comparing patients of IBD with healthy matched controls showed dysbiotic bacterial signatures within the oral microbiota related to intestinal inflammation.

Docktor et al. found a significant decrease in the overall microbial diversity of pediatric CD based on swab samples taken from the tongue. Fusobacteria and Firmicutes were

Table 1 Oral microbiota dysbiosis (composition changes and functional disturbances) in inflammatory bowel disease

Disease	Sampling location	Subjects	Oral microorganisms with increased relative abundance	Oral microorganisms with decreased relative abundance	Functional disturbances in IBD	Region	References
Pediatric IBD	Tongue and buccal mucosal brushings	CD ($n=40$); UC ($n=31$); HCs ($n=43$)	Spirochaetes Synergistetes Bacteroidetes	Fusobacteria Firmicutes	–	Boston, MA	[60]
Pediatric CD	Subgingival plaque samples	Discovery cohort: CD ($n=35$); HCs ($n=43$) Validation cohort: CD ($n=43$); HCs ($n=31$)	TM7 *Capnocytophaga* *Rothia*	–	–	Philadelphia, PA	[61]
Adult IBD	Saliva	CD ($n=21$); UC ($n=14$); HCs ($n=24$)	Bacteroidetes *Prevotella* *Veillonella*	Proteobacteria *Streptococcus* *Haemophilus*	–	Okinawa, Japan	[62]
Adult IBD	Saliva	CD ($n=13$); UC ($n=54$); HCs ($n=25$)	*Streptococcaceae* and *Enterobacteriaceae* in UC; *Veillonellaceae* in CD	*Lachnospiraceae* and *[Prevotella]* in UC; *Neisseriaceae* in CD	Basic metabolic processes↓; Genetic information processes↓; Oxidative stress and virulence↑	Beijing, China	[63]
Adult IBD	Saliva	CD ($n=12$); UC ($n=10$); HC ($n=8$)	Saccharibacteria (TM7) Absconditabacteria (SR1) *Prevotella* *Bulleidia* *Leptotrichia* *Atopobium*	*Streptococcus* *Rothia*	Carbohydrate metabolism↑; Protein processing in the endoplasmic reticulum↑; Genetic information processing↓	Nanjing, Jiangsu, China	[64]

CD Crohn's disease, *HCs* healthy controls, *IBD* inflammatory bowel disease, *UC* ulcerative colitis

significantly reduced in CD, whereas Spirochaetes, Synergistetes, and Bacteroidetes were increased in UC wcompared with HCs [60].

Kelsen et al. studied subgingival samples from pediatric CD patients and described a significant increase in the proportions of TM7, *Capnocytophaga* and *Rothia* at week 0. Interestingly, differences between the subgingival microbiota of CD and HCs observed at baseline were not detected following effective treatment for CD at week 8 [61].

Said et al. found that the salivary microbiota in adult IBD was significantly different from that of HCs, characterized by increased Bacteroidetes, *Prevotella*, and *Veillonella*, with decreased Proteobacteria, *Streptococcus*, and *Haemophilus* in IBD patients. They also confirmed that dysbiosis of the salivary microbiota is related to inflammatory responses in IBD, reflected in a strong correlation between IL-1β levels and the relative abundance of *Prevotella* [62].

Zhe Xun et al. revealed enrichment of *Streptococcaceae* and *Enterobacteriaceae* in UC, and *Veillonellaceae* in CD, while depletion of *Lachnospiraceae* and [*Prevotella*] in UC and *Neisseriaceae* in CD. Other than changes in the composition, functional disturbances were also observed in IBD salivary microbiota, including a loss of genetic information processes and an increase in the biosynthesis and transport of substances relating to oxidative stress and virulence [63].

Our study published recently in *Genomics* investigated Chinese adult patients with UC or CD and assessed the dynamic changes in oral microbiota compared with HCs. Our results suggested that Saccharibacteria (TM7), Absconditabacteria (SR1), *Leptotrichia*, *Prevotella*, *Bulleidia*, and *Atopobium*, some of which are oral biofilm-forming bacteria, were significantly increased in the salivary microbiota of IBD patients. Moreover, TM7 and SR1 showed a positive correlation to inflammatory cytokines associated with IBD, indicating alterations in oral microbiota are related to altered inflammatory immune responses in IBD. In addition, upregulation of carbohydrate metabolism and protein processing in the endoplasmic reticulum, but downregulation of genetic information processing, have also been demonstrated when studying functional variations of oral microbiota in IBD [64].

Oral Bacteria Take Part in the Pathogenesis of IBD: Higher Abundance with Pathogenic Roles

Whether dysbiosis observed in IBD is a cause or an outcome of the disease remains controversial. However, fundamental studies carried out in specific pathogen- and germ-free mice have confirmed several pathogenic oral bacteria participating in disease progression.

Microbes of oral origin have been found in diseases at various non-oral sites, including digestive system conditions such as IBD [65], liver cirrhosis [66], and colon cancer [67]. The saliva contains many oral-resident bacteria. A specific group of oral bacteria may finally colonize the intestine by withstanding the effects of saliva, gastric acid, bile acid, and intestinal juice. This review outlines the pathogenetic mechanisms of oral microbiota in IBD, mainly oral bacteria, including *Pg*, *Sm*, *Fn*, *Cc*, *Cr*, *Campylobacter ureolyticus* (*Cu*), and *Klebsiella* on the initiation and progression of IBD. Table 2 summarizes the oral microbiota associated with IBD, which showed a high diversity in the sub-gingival microbial samples [59], saliva [55, 68], fecal [69], or mucosa biopsy samples [70–73] of IBD patients. All these bacteria are original residents in the oral cavity, and a subset has pathogenic potentials. Once colonizing the extra-oral sites, these bacteria may become pathogens, especially in immune-compromised individuals, leading to disturbed gut microbiota and consistent intestinal inflammation.

Mechanistic Insights into the Pathogenic Oral Bacteria in the Development of IBD

Besides discovering the great oral microbiota dysbiosis in IBD, many published reports have provided plausible mechanisms by which oral bacteria cause the host responses to induce IBD. The mechanistic roles of five bacteria are discussed in turn and summarized in Fig. 3.

Microorganisms play important roles in both the maintenance of epithelial homeostasis and protection against potential pathogens. Ingested oral bacteria with saliva poorly colonize the healthy intestine as intestinal commensal bacteria may restrict the colonization of exogenous pathogens. The intestinal indigenous microbiota, predominantly probiotics, secrete bacteriocin, antibiotics, and metabolon and compete for nutrition and space to antagonize exogenous pathogens [74]. The formation of the microbe-associated molecular pattern (MAMP) through the intestinal microbiota also contributes enormously to the restriction of exogenous pathogens. The host immune system recognizes bacteria-specific antigens through the pattern recognition receptor (PRR) and activates downstream immune cascade responses [75]. In addition, stimulation of innate immunity, including the intestinal epithelial barrier, and regulation of adaptive immunity play an important role in pathogen restriction of the intestine. Once the restriction ability of commensal gut microbiota is weak, oral pathogenic bacteria can migrate and colonize the gut.

The intestinal epithelial barrier, which is mainly composed of the mucus layer, intestinal epithelial cells (IECs), and tight junction, is both a physical and a biological barrier protecting the intestinal lumen against a diversity of

Table 2 Detection rate of pathogenic oral bacteria in inflammatory bowel disease

Oral microbiota	Disease	Specimen	Detection rate in IBD	Detection rate in HCs	P	Region	Detection method	References
Oral bacteria with higher relative abundance in the oral cavity of IBD patients compared to healthy controls								
Campylobacter concisus	UC	Saliva	100% (5/5)	75% (44/59)	< 0.05	Sydney	PCR	Zhang et al. [68]
	CD		85% (11/13)		< 0.05			
Campylobacter rectus	CD	Sub-gingival microbial samples	94.6% (139/147)	–	–	Aachen, Germany	Dot-blot hybridization	Stein et al. [59]
Porphyromonas gingivalis	Adult CD	Sub-gingival microbial samples	62.6% (92/147)	–	–	Aachen, Germany	Dot-blot hybridization	Stein et al. [59]
Streptococcus mutans	CD	Saliva	1.5 (Arbitrary unit)	0.9 (Arbitrary unit)	0.016	Huddinge, Sweden	Dentocult-SM Orion Diagnostica	Sara et al. [55]
Oral bacteria with higher relative abundance in the intestine of IBD patients compared to healthy controls								
Campylobacter concisus	Pediatric CD	Intestinal biopsy specimens	51.5% (17/33)	2% (1/52)	< 0.001	Sydney, Australia	PCR	Zhang et al. [73]
Campylobacter concisus	Pediatric CD	Fecal	65% (35/54)	33% (11/33)	0.008	Sydney, Australia	PCR	Man et al. [69]
Campylobacter concisus	Adult UC	Biopsy samples	33.3% (23/69)	10.8% (7/65)	0.0019	Aberdeen, United Kingdom	PCR	Mukhopadhya et al. [70]
Campylobacter ureolyticus	UC	Biopsy samples	21.7% (15/69)	3.1% (2/65)	0.0013	Aberdeen, United Kingdom	PCR	Mukhopadhya et al. [70]
Fusobacterium nucleatum	Adult UC	Biopsy samples	50.0% (11/22)	17.6% (6/34)	0.02	Guelph, Ontario, Canada	PCR	Strausset al. [71]
Klebsiella	UC	Biopsy samples	31.0% (9/29)	–	–	Stuttgart, Germany	PCR	Höring et al. [72]
	CD		21.4% (3/14)	–	–			

IBD inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *HCs* healthy controls, *PCR* polymerase chain reaction

microbiota under normal circumstances. The mucus covering the intestinal epithelium mainly consists of densely O-glycosylated MUC2 mucin secreted by goblet cells and serves as the first line of defense against pathogenic microorganisms. The glycosylated MUC2 mucin can form two layers. The inner sterile layer attaches to the epithelium, and the outer layer with an expanded volume is colonized by bacteria. It is confirmed that the inner mucus layer is primarily lacking in bacteria [76]. Defects in the mucus will increase exposure of the epithelium to bacteria, trigger inflammatory responses, and exacerbate inflammation in IBD [77]. Damage to the mucus layer is a critical cause of IBD, structural weakening of which is an early event in the pathogenesis of UC [78].

The best-described mechanisms of the oral microbiota in IBD occurrence are destruction of the intestinal epithelial barrier, excessive secretion of inflammatory cytokines, disruption of the host immune system, and induction of immune escape.

Pg

Pg is a widely identified keystone pathogen for periodontal diseases, which can migrate from mouth to the intestine in mice, inducing gut microbiota dysbiosis with increased Bacteroidetes and decreased Firmicutes, weakening intestinal barrier function through downregulation of the gene expressions of tjp-1 and occludin [79].

Gingipains secreted by *Pg* can help it escape the innate immune responses and selectively inactivate pro-inflammatory factors released by activated DCs. Abdi et al. compared a mutant strain of *Pg* (W50) lacking in immune modification with the standard strain obtained from the American Type Culture Collection (W50-ATCC) and found that the former achieved significantly enhanced immune suppression, suggesting that different genotypes of *Pg* have distinct pathogenic mechanisms [80].

Abnormal immune responses can be induced by microbiota dysbiosis, along with effects of metabolites. Ectopic

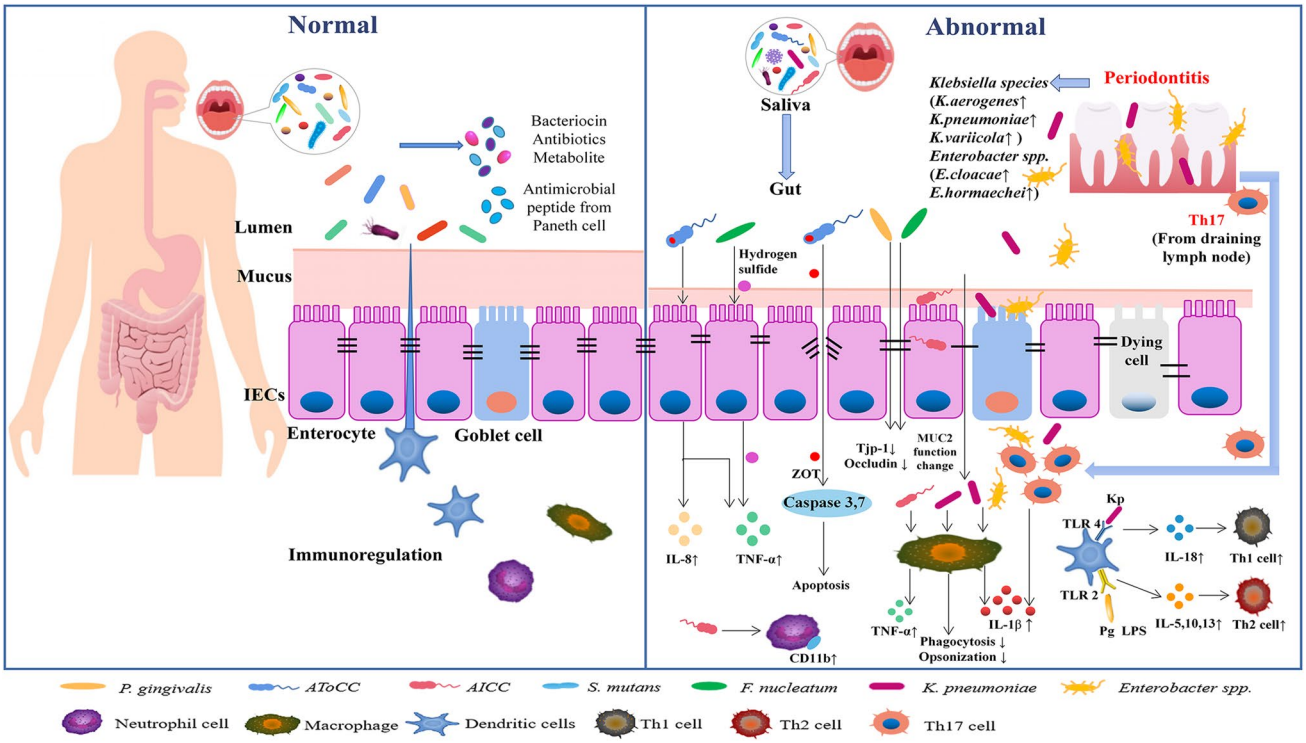

Fig. 3 Pathogenic roles of specific oral bacteria in the pathogenesis of IBD. Healthy intestines restrict colonization of exogenous pathogens including ingested oral bacteria mainly in three ways. (1) The intestinal indigenous microbiota can secrete bacteriocin, antibiotics, and metabolites and compete for nutrition and space. (2) A microbe-associated molecular pattern (MAMP) is formed. (3) Innate immunity and regulation of adaptive immunity are stimulated. In aberrant conditions, ectopic colonization of oral bacteria can induce the development of IBD via several mechanisms: (1) Destruction of the intestinal epithelial barrier: *P. gingivalis* can downregulate the expressions of tjp-1 and occludin, *AToCC* can break the processes related to tight junctions, and *F. nucleatum* can stimulate the function change of MUC2. (2) Secretion of inflammatory cytokines: *F. nucleatum* can induce the pro-inflammatory cytokine TNF-α. Hydrogen sulfide produced by *F. nucleatum* inhibits the effective use of anti-inflammatory butyrate in colon cells. (3) Disruption of the host immune system and induction of immune escape: *P. gingivalis* can secrete gingipains and selectively inactive pro-inflammatory factors released by activated DCs; *C. concisus* can stimulate neutrophil cells by upregulating the neutrophil adherence molecule CD11b and oxidative burst response, leading to the activation of the innate immune system; *P. gingivalis* LPS can induce a stronger Th2 response while *K. pneumoniae* a stronger Th1 response. (4) Specific *Klebsiella spp.* and *Enterobacter spp.* could migrate to the gut, activate the inflammasome in colonic mononuclear phagocytes, and trigger intestinal inflammation. (5) Oral pathobiont-reactive Th17 cells could translocate from the mouth to the inflamed gut, activated by translocated oral pathobionts, and induce colitis

colonization of the oral microbiota and its metabolites may also cause immoderate mucosal immune activation. The colonization of the oral microbiota in the intestine is followed by the induction of different mucosal CD4 + T-cell subsets. Pulendran et al. claimed that *Pg* lipopolysaccharides (LPS) can induce Th- and T-cell responses characterized by significantly higher levels of IL-5, IL-10, and IL-13 but a lower level of IFN-γ, confirming that *Pg* LPS predisposes immune responses toward a semi-TH2-like rather than TH1-type response [81].

Sm

Sm is the identified pathogen of dental caries. *Sm* strains are classified into serotypes *c*, *e*, *f*, and *k*, with serotype *c* accounting for > 70%, serotype *e* approximately 20% and serotypes *f* and *k* < 5%, respectively, in the oral cavity of healthy individuals [82]. Some serotype *k* or *f Sm* strains expressing the collagen-binding protein (CBP) can cause hemorrhagic stroke because of their abilities to bind the collagen and resist phagocytosis [83]. Kojima et al. reported that specific strains isolated from UC patients had different serotypes from that of the standard strain, MT8148. Administration of a serotype *k* strain TW295 from UC patients, rather than standard MT8148, can increase the disease activity index and aggravate colitis in mice. Localization of TW295 and upregulated expression of interferon-γ were also observed in hepatocytes. TW295 was present less in the colon and small intestine than in the liver, indicating that the interaction of specific *Sm* with hepatocytes is crucial in the development of colitis [84].

Fn

Fusobacterium is a group of gram-negative anaerobes principally colonizing the oral cavity, but can also inhabit the intestine. *Fn* is known as a pathogen in both humans and animals [85]. The mechanistic role of *Fn* has been relatively well explored. *Fn* infection can stimulate proinflammatory cytokine TNF-α both in vitro (in LS 174 T-cells) and in vivo (in rat colonic cells) [86]. Large amounts of hydrogen sulfide produced by *Fn* serve as a highly toxic end product of cysteine metabolism, inhibiting the effective use of butyrate in colon cells and resulting in chronic intestinal inflammation [87].

Some studies have confirmed that colonization and invasion of *Fn* may promote the progression of intestinal inflammation by affecting MUC2 mucin production. Compared with minimally invasive strains isolated from the healthy gut mucosa of control subjects, highly invasive *Fn* isolates from the lesions of CD patients displayed significantly enhanced expressions of MUC2 and tumor necrosis factor alpha (TNF-α).

It has been proven that *Fn* can promote the progression of colorectal carcinoma by recruiting myeloid-derived suppressor cells capable of inhibiting the proliferation and inducing the apoptosis of T-cells [88]. It is therefore hypothesized that *Fn* can stimulate colonic neoplasia by downregulating adaptive immunity mediated by anti-tumor T-cells, resulting in resistance to anti-tumor immune response and facilitating the pathogenesis of colorectal carcinoma. Virulence factors derived from *Fn* have been shown to inhibit the activity of T-cells, and the outer membrane proteins Fap2 and RadD of *Fn* can induce cell death in human lymphocytes [89].

Cc

Cc can be classified into at least two different pathotypes based on their virulence mechanisms, adherent toxigenic *Cc* (*AToCC*) and adherent invasive *Cc* (*AICC*) [90]. *AToCC* strains possess a zonula occludens toxin (zot). The zot gene encodes a toxin that can increase intestinal permeability, with polymorphisms in different *Cc* strains. It can upregulate PAR2 expression and break the processes related to tight junctions and cytoskeletal remodeling and is detectable in 30% of oral Cc strains. *Cc* ZOT808T polymorphism has been associated with active IBD [91]. Zot of *Cc* can stimulate intestinal epithelial cells and macrophages to release pro-inflammatory cytokines and enhance the responses of macrophages to other enteric bacteria [92].

The AICC strains of *Cc* can survive intracellularly within epithelial cells by autophagy. Sørensen demonstrated the ability of the oral reference strain *Cc* ATCC33237 to stimulate neutrophil cells by upregulating the neutrophil adherence molecule CD11b and oxidative burst response, resulting in the activation of the innate immune system [93]. In another study investigating the effects of different *Cc* strains on the expressions of Toll-like receptors (TLR) and their co-receptor, the myeloid differentiation factor in intestinal epithelial cells, Ismail found that *Cc* strains from both the oral cavity and intestine upregulated the expressions of TLR4 and MD-2 in HT-29 cells [94].

Kp and *Klebsiella* spp.

Studies have demonstrated the ability of *Kp* to invade colonic epithelial cells in mice. Several experiments have been carried out to clarify how *Kp* penetrates the intestinal barrier. Hsu found that *Kp* could translocate across the intestinal epithelium through Rho GTPase- and phosphatidylinositol 3-kinase/Akt-dependent cell invasion, but failed to observe the distribution of the tight junction protein ZO-1 or occludin [95].

The capsule has an extracellular polysaccharide structure. *Kp* characteristically produces a large amount of capsular polysaccharide (CPS) covering the bacterial surface. CPS as an acidic polysaccharide synthesized via the Wzy-dependent polymerization pathway [96], protects bacteria from toxic serum factors, and resists the opsonization and phagocytosis of macrophages, DCs, neutrophils, and epithelial cells [97]. A study published in *Science* shows that ectopic colonization of oral-derived bacteria can drive differentiation of T-cells into TH1 cells and induce intestinal inflammation in mice. In this study, Atarashi et al. reported that *Klebsiella* strains, especially *Kp-2H7* isolated from the salivary microbiota of two CD patients, activated DCs and epithelial cells through the Toll-like receptor 4 (TLR4) signaling pathway, stimulated secretion of IL-18, elicited recruitment and activation of TH1 cells, and consequently led to intestinal inflammation [98].

Enterobacter spp.

Besides the five specific bacteria mentioned above, a recent study published in *Cell* has demonstrated that periodontitis leads to the enrichment of *Klebsiella* (*Klebsiella aerogenes*, *Klebsiella pneumoniae*, *Klebsiella variicola*) and *Enterobacter* spp. (*Enterobacter cloacae*, *Enterobacter hormaechei*) in the oral cavity and exacerbated gut inflammation in vivo. On the one hand, amassed oral pathobionts during periodontitis could migrate to and colonize the colitic gut, enhance IL-1β production, and activate the inflammasome in colonic mononuclear phagocytes. On the other, oral pathobiont-reactive Th17 cells resulting from periodontitis in the oral cavity could also translocate from the oral mucosa-draining lymph nodes to the inflamed gut. Once arriving in the gut, oral-derived Th17 cells can be activated by translocated oral pathobionts and induce colitis. Hence, oral inflammation

such as periodontitis exacerbates gut inflammation by supplying the gut with both colitogenic pathobionts and pathogenic T-cells [99].

To conclude, oral bacteria-mediated destruction of the intestinal epithelial barrier may increase intestinal permeability and mucosal degradation, leading to the impairment of intestinal resistance to pathogens and intestinal inflammation. Ectopic colonization of oral bacteria disrupts the ecological balance among the oral microbiota, host, and immune system, leading to continuous intestinal inflammation.

Current Treatment and Microbiome-Based Strategies for IBD

Treatment for IBD aims at inducing and maintaining long-term deep remission and avoiding complications of active disease. The treatment strategies for IBD are challenging in view of its relapsing–remitting course, and most current treatment strategies aiming to suppress the immune system tamp down symptoms rather than eradicate causes, with considerable incomplete efficacy and significant side effects. Consequently, more attention should be given to the modification of oral and gut microbiota when treating IBD, and prospective treatment must carefully balanced both the oral and gut microbiota (Fig. 4).

A non-specific anti-inflammation strategy, including the combined application of amino salicylic acid drugs, glucocorticoids, and immunosuppressants, is the traditional treatment of IBD. However, these strategies showed considerable substantial adverse events, high recurrence rates, and poor efficacy after long-term use. Biological agents are increasingly used in moderate to severe IBD with ineffective traditional treatment [100]. Despite the efficacy of the anti-TNF drugs, one-third of patients show no response to them. Patients responding or not responding to TNF-α inhibitor therapy showed significant differences in the gut microbial composition, characterizing by increased *Bifidobacterium*, *Lachnospira*, *Lachnospiraceae*, *Collinsella*, *Eggerthella*, and *Roseburia* taxa and reduced *Phascolarctobacterium* in CD patients with treatment success. *Bifidobacterium* can metabolize oligosaccharides and serve as a probiotic in IBD. *Lachnospiraceae* and *Roseburia* participate in the production of SCFAs providing nutrition for intestinal epithelial cells and inducing regulatory T-cells [101]. To conclude, the composition of gut microbiota correlates with the response to anti-TNF drugs, and modifying the gut microbiota may promote the response to biological drugs. Other biological agents, such as interleukin inhibitors, integrin inhibitors, JAK inhibitors, and antisense oligonucleotides, play different roles in the pathogenesis of IBD [100]. However, these agents mostly focus on immunosuppression rather than on modification of the gut microbiota. Hence, safer and more effective biological agents and investigation of their potential to modify gut microbiota need more attention; more studies are needed in this regard.

Fecal microbiota transplantation (FMT) refers to transplantation of the infusion of feces covering gut microbiota from healthy donors to the gastrointestinal tract of a recipient patient to treat disease associated with gut microbiota dysbiosis. Several clinical trials of FMT have demonstrated efficacy in UC patients [102–104]. Previous randomized clinical trials showed different responses due to variation in fecal donors, routes (enema or nasoduodenal), and frequency of transplantation administration. Multi-center, double-blind, randomized, placebo-controlled trials are needed to further investigate the effectiveness of FMT.

Dietary interventions for IBD can generally be divided into kinds of elimination diets, inclusion of prebiotics, inclusion of anti-inflammatory mediators, and exclusion of

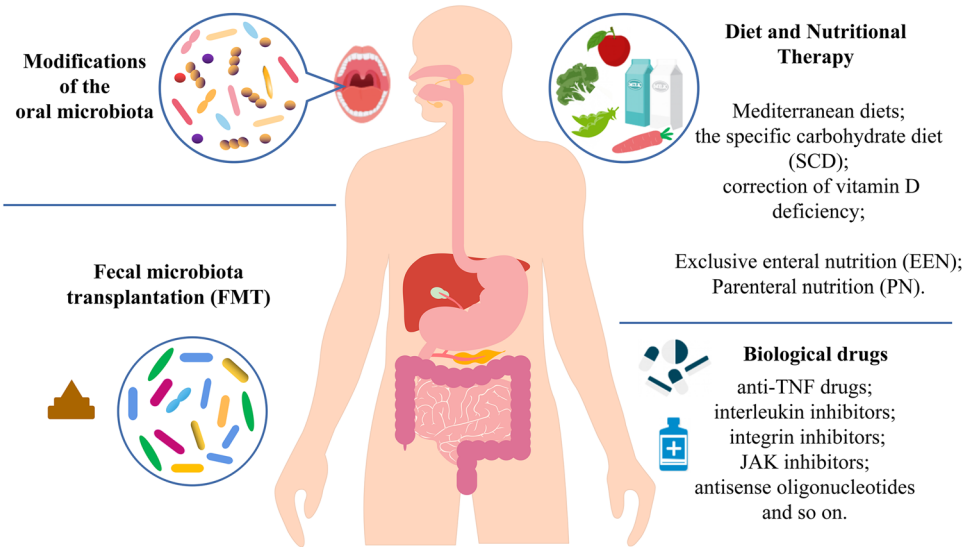

Fig. 4 Current treatment, microbiome-based strategies, and new perspectives for IBD. Microbial-based treatment strategies for IBD include fecal microbiota transplant (FMT), diet and nutritional therapy, and use of biological drugs. In view of the role of oral microbiota in the pathogenesis of IBD, modifications of the oral microbiota may serve as a potential anti-inflammatory therapy for IBD

specific inflammatory mediators. Mediterranean diets are characterized by high levels of dietary fiber and are rich in microbiota-accessible carbohydrates (MACs); these gut microbiota can ferment to produce SCFAs. Among MACs, prebiotics can enhance the growth of probiotics such as *Bifidobacterium* and *Lactobacillus* [105]. Intake of whole foods including fruits and vegetables can also reduce growth of harmful bacteria, such as *Escherichia coli* and *Enterococcus* spp. [105].

Exclusive enteral nutrition (EEN) is a completely liquid formula covering all macronutrients and micronutrients patients need and is the only established dietary intervention for CD with rigorous tests, especially for pediatric CD. EEN can induce clinical remission and mucosal healing in patients. In children with newly diagnosed CD receiving EEN for at least 6 weeks, 84% received early clinical remission at week 8, 76% had early biochemical remission, and 42% achieved mucosal healing [106].

Exclusion diets have been found effective in both UC and CD and can serve as long-term therapy. Among the exclusion diets, the specific carbohydrate diet (SCD) is the best studied. SCD is characterized by the elimination of grains, processed foods, sweeteners (except for honey), and all milk products (except for hard cheeses and fermented yogurt) for > 24 h. SCD can benefit both pediatric and adult IBD patients [107].

Parenteral nutrition (PN) eliminates the oral intake of food. PN relates to short-term avoidance of surgery but has little effect on the eventual need for surgery based on observational studies [108]. It has also been demonstrated that correction of vitamin D deficiency can reduce the requirement of future surgery for IBD patients compared to those who remained vitamin D deficient [28]. Successful dietary modifications in IBD are still in their infancy. Dietary and nutritional therapies present a unique opportunity for the treatment of IBD with challenges.

Modifications of the Oral Microbiota as Future Perspectives for IBD

Microbe-based therapies are becoming more diverse and effective, mostly based on the modification of gut microbiota. This review provides insights into the role of the oral microbiota in the pathogenesis of IBD. In light of this, IBD therapies could allow the restoration of a symbiotic microbiota in the oral cavity. Oral microbiota modification may serve as a novel anti-inflammatory therapy for IBD. Strategies targeting specific oral species are expected to improve IBD management. Future advancements in the use of probiotics to modulate the oral microbiota and antibiotics to eliminate specific oral pathogens are expected to prevent the recurrence of IBD.

Conclusion

Microbial studies of IBD have focused largely on the gut microbiota, and existing evidence points to the connection between dysbiosis of the oral microbiota and development of IBD. Predominant oral microbiota dysbiosis has been observed in IBD patients. The oral cavity is an easily accessed body site for the assessment of the microbial community, with convenient sampling, non-invasiveness, and effective interventions. Hence, the oral microbiota holds great promise for diagnostic tools.

In this review, we have summarized specific oral bacteria that may serve as new manipulators of inflammation in IBD. Thus, new therapeutic approaches targeting the oral microbiota by facilitating beneficial bacteria and eliminating pathogenic oral bacteria may be an innovative medical strategy to prevent the recurrence of IBD. This area of investigation is in its infancy and deserves more research.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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