



Unravelling the Oral–Gut Axis: Interconnection Between Periodontitis and Inflammatory Bowel Disease, Current Challenges, and Future Perspective

Himanshi Tanwar,^{a,*} Jeba Mercy Gnanasekaran,^{a,*} Devon Allison,^a Ling-shiang Chuang,^b Xuesong He,^c Mario Aimetti,^d Giacomo Baima,^d Massimo Costalonga,^e Raymond K. Cross,^{f, } Cynthia Sears,^g Saurabh Mehandru,^b Judy Cho,^b Jean-Frederic Colombel,^b Jean-Pierre Raufman,^f Vivek Thumbigere-Math^{a,h, }

^aDivision of Periodontology, University of Maryland School of Dentistry, Baltimore, MD, USA

^bDivision of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

^cDepartment of Microbiology, The Forsyth Institute, Cambridge, MA, USA

^dDepartment of Surgical Sciences, C.I.R. Dental School, University of Turin, Turin, Italy

^eDepartment of Diagnostic and Biological Sciences, School of Dentistry, University of Minnesota, Minneapolis, MN, USA

^fDivision of Gastroenterology & Hepatology, University of Maryland School of Medicine, Baltimore, MD, USA

^gDivision of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^hNational Institute of Dental and Craniofacial Research, NIH, Bethesda, MD, USA

Corresponding author: Vivek Thumbigere-Math, Division of Periodontology, University of Maryland School of Dentistry, Baltimore, MD, USA.

E-mail: vthumbigere@umaryland.edu

*These authors contributed equally to the study

Abstract

As the opposite ends of the orodigestive tract, the oral cavity and the intestine share anatomical, microbial, and immunological ties that have bidirectional health implications. A growing body of evidence suggests an interconnection between oral pathologies and inflammatory bowel disease [IBD], implying a shift from the traditional concept of independent diseases to a complex, reciprocal cycle. This review outlines the evidence supporting an ‘oral–gut’ axis, marked by a higher prevalence of periodontitis and other oral conditions in IBD patients and vice versa. We present an in-depth examination of the interconnection between oral pathologies and IBD, highlighting the shared microbiological and immunological pathways, and proposing a ‘multi-hit’ hypothesis in the pathogenesis of periodontitis-mediated intestinal inflammation. Furthermore, the review underscores the critical need for a collaborative approach between dentists and gastroenterologists to provide holistic oral–systemic healthcare.

Key Words: Periodontitis; inflammatory bowel disease [IBD]; oral bacteria; oral–gut axis; gum–gut axis; immune response; dysbiosis; ulcerative colitis; Crohn’s disease

1. Introduction

Oral pathologies can profoundly impact general health; however, oral health and general health are often incorrectly perceived as separate entities.^{1,2} Over the past four decades, several studies have highlighted the connection between the oral cavity and the rest of the body, linking gingival and periodontal inflammation with more than 50 systemic conditions, including inflammatory bowel diseases [IBD].^{1–7} A bidirectional relationship exists between periodontitis and IBD, where microbial and inflammatory changes originating in either the oral cavity or intestinal tissues can influence each other.^{3,8–33} The growing body of literature associating periodontitis with gastrointestinal [GI] disorders such as IBD and colorectal cancer has seen a remarkable surge in recent years, with over 100 relevant articles published since 2020. This review aims to augment current knowledge by providing an in-depth analysis of the underlying mechanisms contributing

to the bidirectional relationship between oral pathologies and IBD, with a particular emphasis on periodontitis. We utilize the ‘oral–gut axis’ as a framework to investigate the reciprocal relationship between the oral cavity and the GI tract. This narrative review encapsulates historical studies on oral manifestations in IBD, and explores recent advances, current knowledge gaps, and potential future directions. Furthermore, the review underscores the critical need for a collaborative approach between dentists, gastroenterologists, immunologists, and infectious disease experts/microbiologists to provide holistic oral–systemic healthcare.

2. Periodontitis

Periodontitis is a chronic inflammatory disease that affects the periodontium, encompassing tooth-supporting structures such as the gingiva, alveolar bone, and periodontal

ligament.^{7,34–36} It is ranked as the 11th most prevalent condition worldwide, affecting ~50% of adults >30 years of age and ~70.1% of adults >65 years of age.^{37–41} The hallmark symptoms of periodontitis are gingival inflammation, gingival recession, deep periodontal pockets, clinical attachment loss, and tooth mobility.^{7,34–36} If left untreated, periodontitis results in tooth loss, and is the leading cause of tooth loss in adults worldwide.^{36,37,42,43}

Periodontitis is primarily initiated by the accumulation of bacterial plaque on tooth surfaces or within the gingival sulcus, which subsequently triggers an inflammatory response.^{35,44} The host's hyper-immunoinflammatory response, in turn, leads to the destruction of tooth-supporting structures.^{45–47} The bacterial plaque/calculus associated with the initiation of periodontitis specifically contains bacteria, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Fusobacterium nucleatum*, and *Campylobacter rectus*.^{44–46,48–52} Periodontitis is a polymicrobial disease primarily driven by bacteria; however, fungi, protozoa, and viruses might also contribute to its pathogenesis.^{35,53,54}

Several risk factors have been associated with periodontitis, including poor oral hygiene, smoking, diabetes, advanced age, genetics, and certain medications.^{7,55–57} The prognosis depends on disease severity, patient compliance with treatment, and control of risk factors.⁵⁸ Through dissemination of oral pathogens and promotion of low-grade systemic inflammation, periodontitis may contribute to other systemic diseases such as IBD, cardiovascular disease, diabetes, and pre-term birth.^{27,59–63}

3. Inflammatory Bowel Disease

IBD, encompassing Crohn's disease [CD] and ulcerative colitis [UC], refers to a group of chronic, idiopathic, and recurring inflammatory disorders that affect the GI tract.^{64–66} The clinical manifestations of IBD vary depending on the location and severity of inflammation within the GI tract. CD is characterized by patchy inflammation that can affect the full thickness of the bowel wall throughout the small and large intestines.^{66–69} There may be areas of healthy tissue between inflamed sections [skip lesions]. In contrast, UC presents with continuous, uniform inflammation limited to the mucosal layer, extending from the rectum to throughout the colon.^{66–70} Common symptoms include abdominal pain, cramping, persistent diarrhoea, nausea, vomiting, weight loss, fatigue, and fever.^{64–66,71} UC is more likely to cause bloody diarrhoea,

urgency to defecate, and tenesmus.^{70–73} Approximately 25–40% of UC and CD patients may exhibit extraintestinal manifestations such as arthritis, erythema nodosum, pyoderma gangrenosum, oral lesions [discussed in detail in later sections], uveitis, hepatic steatosis, primary sclerosing cholangitis, and metabolic bone disease.^{74–91} Both UC and CD patients are at a higher risk of developing colorectal cancer, although the risk is greater in UC than in CD.^{92,93} IBD patients experience a diminished quality of life and have a lower life expectancy compared to the general population.^{94,95}

Between 1990 and 2017, the global incidence of IBD surged by 31%, affecting around 6.8 million people worldwide and becoming a major public health concern.^{96–99} The incidence of IBD varies, with highest rates observed in North America, Western Europe, and Australia.^{98,99} The prevalence of IBD in the USA is estimated to be over 1.6 million, with 780 000 diagnosed with CD and 907 000 with UC.^{97,100,101}

The aetiology of IBD remains largely unclear, but it is believed to result from a complex interplay between genetic, environmental and, microbial factors, and the host immune responses.^{102–107} Over 200 genetic loci related to immune regulation, intestinal barrier function, and other biological pathways have been associated with IBD, suggesting a strong genetic influence.^{102,108–113} Notable genetic loci include *NOD2* [one of the first genetic loci identified as a risk factor for CD], *IL23R*, *ATG16L1*, *IRGM*, *PTGER4*, *TNFSF15*, and *IRF8*.^{102,108–113} Previously, our group and others identified several single nucleotide polymorphisms [SNPs] located 1.7–60 kb downstream of *IRF8* as risk factors for UC and CD.^{111,112,114–124} [Figure 1]. *IRF8* SNPs are significantly associated with CD in Ashkenazi Jews, who have a 4- to 7-fold higher incidence of CD than non-Ashkenazi European Jews.^{120,125} *IRF8* is expressed in the intestinal epithelial cells [IECs] in a gradient pattern, with highest expression in the differentiated cell zones and low levels in the proliferating and stem cell zones.^{126,127} *IRF8* functions as a suppressor of colonic inflammation, and its deficiency in IECs disrupts the epithelial barrier, contributing to colitis-related colon tumorigenesis in both humans and mice.^{126,128,129} Beyond IECs, *IRF8* is crucial for the development and maturation of dendritic cells and macrophages,^{130–134} key to immune surveillance in the gut. *IRF8* deficiency causes conventional type 1 dendritic cells (cDC1) cells to acquire cDC2-like characteristics, impacting their antigen presentation and immune responses to bacterial antigens.^{135,136} Additionally, *IRF8* regulates Class I and Class II MHC machinery, balancing pro-inflammatory and anti-inflammatory cytokine production.^{134,137,138} *IRF8*

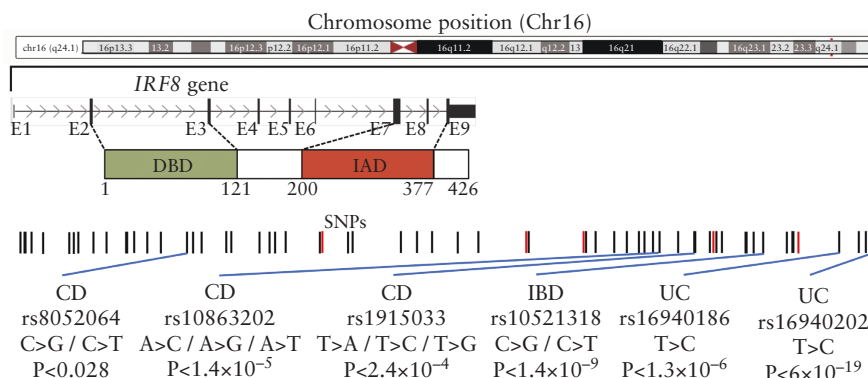


Figure 1. Schematic of *IRF8* gene structure with previously reported IBD single nucleotide polymorphisms [SNPs], genotypic changes, and p values.

also regulates pathogen-associated molecular pattern [PAMP] receptors,^{137,138} crucial for microbial recognition and gut defence. Consequently, IRF8 deficiency could disrupt gut immune homeostasis, leading to impaired responses to intestinal microbiota and exacerbating the dysbiosis and abnormal immune reactions associated with IBD. In mice, IRF8 deficiency promotes colitis mediated by Th17 and Tfh cells^{128,129} and impairs gastric innate immunity against infection.¹³⁹ Dysregulation of IRF/IFN-I signalling is extensively involved in IBD pathogenesis and targeting this pathway represents a promising intervention strategy for IBD.¹⁴⁰ Additionally, we have shown that IRF8 is also critical for periodontal homeostasis.^{141–143} Collectively, these findings highlight the importance of IRF8 in intestinal health and establish the critical value of *Irf8*-deficient mice in providing novel insights into human GI diseases.

Some of the identified risk factors for IBD include: [a] family history—individuals with a first-degree relative with IBD face a higher risk of developing the condition^{144,145}; [b] age—IBD is more commonly diagnosed in individuals under the age of 30 years, although it can occur at any age. Historically believed to be a disease of children and young adults [20–30 years], it is now recognized that 10–15% of patients develop IBD after the age of 60 years [older adults].^{146–150} The cause of older-onset IBD is unclear, but it is thought to be less associated with genetics and more influenced by age-related changes in the immune system and gut microbiome^{146,151–154}. [c] Ethnicity—IBD is more common in Caucasians and people of Ashkenazi Jewish descent^{120,125,144,155,156}; and [d] smoking—cigarette smoking increases the risk of CD and may exacerbate its progression, while it appears to have a protective effect against UC.^{157,158}

The course of IBD varies, with some experiencing periods of remission while others endure frequent relapses. IBD may lead to complications such as strictures, fistulas, or colorectal cancer.^{64–71} Disease severity and treatment response significantly influence prognosis. Currently, there is no cure for IBD, and the primary management focuses on resolving inflammation, preventing flare-ups and other complications, and improving quality of life.^{159–161}

4. Oral Manifestations of IBD

Extraintestinal manifestations of IBD, which can affect nearly all organ systems, are common in both UC and CD.^{74–79} Approximately 10–30% of IBD patients exhibit oral manifestations of the disease, which can precede, coincide with, or follow the onset of GI symptoms.^{80–82,87,88,91} Commonly observed oral manifestations include aphthous ulcers, mucosal tags, cobblestoned oral mucosa, pyostomatitis vegetans, gingivitis, periodontitis, angular cheilitis, and oral lichen planus.^{63,80–91,162–164} Additionally, some individuals may present with halitosis, atrophic glossitis, burning mouth syndrome, and xerostomia.^{80–91} Some of these lesions are more common in CD versus UC, and more frequently noted in children versus adults.¹⁶⁴

Although some IBD patients exhibit oral manifestations, the correlation is not universal. Epidemiological studies reporting a higher incidence of oral lesions in IBD patients often lack proper control groups, making it difficult to ascertain if the incidence of oral lesions is indeed increased in IBD patients beyond the general population. For example, aphthous ulcers affect 20–25% of the general population^{165,166} and it

is unclear if IBD patients experience a higher incidence of aphthous ulcers than the general population. Additionally, it is difficult to determine precisely which oral manifestations are related to IBD, and which are related to IBD therapy or other aetiologies such as nutritional deficiencies and malabsorption. It is logical to hypothesize that some of these lesions are in fact direct consequences of the disease or a secondary reaction to IBD treatment. Furthermore, oral granulomas can also result from exposure to dental materials, including retained amalgams or endodontic sealers.¹⁶⁷ Therefore, potential confounders must be meticulously excluded prior to establishing a causative link between oral lesions and IBD.

The aetiology of oral manifestations in IBD is complex and not fully understood; however, it is believed to involve a combination of genetic predisposition, immune dysregulation, and alterations in the oral microbiome.^{80–91} Several studies underscore the role of cytokine activity in both the GI and oral regions. Elevated levels of IL-6, IL-8, IL-1 β , TNF- α , and MCP-1 have been noted in saliva and gingival tissues of patients with active IBD versus non-active IBD or healthy controls.^{20,168–170} Higher levels of CXCL-9 and -10 have been identified in the buccal mucosal of children with CD compared to healthy children and adult CD patients.¹⁷¹ Mutations in IL-10RA and IL-10RB, which disrupt the IL-10/STAT3 cascade, have been associated with paediatric IBD.^{172,173} Patients deficient in IL-10 and IL-10R exhibit recurrent aphthous ulcers and subtle immunological abnormalities, including decreased CD4+/CD8+ T-cell ratios, dysregulated serum immunoglobulin levels, and dysregulated NK, B, or T cells.^{174,175} Higher concentrations of activated matrix metalloproteinase-8 [MMP-8] have been noted in the gingival crevicular fluid [GCF] of IBD patients compared to healthy controls.¹⁷⁶ Also, decreased IL-4 levels and elevated serum IL-18 levels have been noted in UC patients, with the latter positively correlated with IL-1 β in the GCF from deeper pockets.¹⁷⁷ Likewise, a significant elevation in IL-1 β concentration has been noted in GCF, alongside increased TNF- α and reduced IL-10 levels in the saliva of UC patients diagnosed with periodontitis.¹⁷⁸ Despite these findings, the contribution of these inflammatory cytokines and immune cells to the development of oral lesions in IBD patients remains unclear, necessitating further investigations.

Conversely, IBD may immunologically trigger oral manifestations, partially due to the recognition of common epitopes throughout the body. The extraintestinal manifestations of IBD could stem from a broad adaptive immune response triggered by local intestinal dysbiosis, leading to recognition of these epithelial epitopes in other organs and the oral cavity, ultimately causing extraintestinal pathologies.^{78,179–181} A molecular similarity between gut microbiota antigens and non-microbial epitopes present on cells in the oral cavity could potentially lead to immune cross-reactivity.^{182,183} Furthermore, in IBD, local immune responses to gut dysbiosis may initiate systemic T cell-mediated responses and cytokine production,^{184,185} which could potentially lead to induction of oral lesions. In response to antigenic stimulation, T cells can migrate to the oral mucosa, where CD8+ T lymphocytes, accompanied by infiltrating macrophages and neutrophils, may cause epithelial damage and ulceration commonly observed in pyostomatitis vegetans.¹⁸⁶ Overexpression of pro-inflammatory cytokines such as IL-6, IL-8, and TNF- α in pyostomatitis vegetans can potentially lead to the recruitment of inflammatory cells to UC lesions, thus synergistically contributing to the pro-inflammatory pathogenesis of

pyostomatitis vegetans and IBD.¹⁸⁶ Collectively, these studies suggest that immune system dysregulation may be an important link bridging the oral cavity and the intestines.

Several studies have suggested that oral microbial dysbiosis, and secondary inflammatory responses within the gut, might potentially contribute to oral manifestations in IBD.^{78,87,187,188} Remarkably, the periodontal inflammation in IBD does not appear to correlate with plaque accumulation, giving rise to the notion that systemic inflammation associated with IBD could induce alterations in the oral microbiome, consequently intensifying oral inflammation.^{189,190} An overabundance of specific oral bacteria, including *Streptococcus*, *Prevotella*, *Veillonella*, and *Haemophilus*, in the oral cavity is linked to inflammatory responses triggered by reduced salivary lysozyme and increased IL-1 β levels, which may be associated with gut microbial dysbiosis.²⁰ These changes are connected to heightened oxidative stress and virulence [e.g. metabolism of terpenoids, polyketides, carbohydrates, and lipids, and biosynthesis of secondary metabolites], enzyme activity [e.g. protein kinases], bacterial aggression [e.g. bacterial toxins and invasion of epithelial cells], and apoptosis in the oral region, implying a connection between oral microbial dysbiosis and IBD.¹⁵ Altered salivary lysozyme levels could be related to gut imbalance and subsequent periodontitis development.¹⁹¹ Furthermore, intestinal dysbiosis has been linked to the chronic inflammatory state and activation of gut-associated lymphoid tissue [GALT],^{192,193} which could potentially lead to extraintestinal pathologies.¹⁹⁴ The proven effectiveness of adjuvant probiotic therapy in treating oral ulcers supports the hypothesis that oral ulcers in IBD might result from a combination of intestinal dysbiosis and other factors, such as oral mucosa microtraumas.¹⁹⁵ Collectively, these findings indicate a possible correlation between oral and gut microbial dysbiosis and the occurrence of oral manifestations in IBD.

5. Historical Perspective of Oral-Gut Interconnection

Over the years, numerous case reports have contributed to our understanding of oral and gut interconnection. The first report of oral involvement in IBD, by Dudeney and Todd in 1969, described a CD patient who developed granulomatous lesions in the left buccal mucosa 16 years after the initial diagnosis.¹⁹⁶ In 1972, Bottomely *et al.* documented a case of a teenage girl with CD who exhibited gingival hyperplasia across maxillary anterior teeth, with 5–6-mm ‘pseudopockets’ indicative of a severe hyperplastic phenotype that worsened periodically.¹⁹⁷ In 1972, Croft *et al.* retrospectively analysed 332 CD patients and found that 6.1% had developed oral ulcers at some point during their illness.¹⁹⁸ In 1975, a systematic study by Asquith *et al.* involving 100 CD patients, 100 UC patients, and 100 healthy controls matched for age, sex, and denture status reported that 9% of CD and 2% of UC patients developed oral lesions with macroscopic and histological features similar to those in the GI tract.¹⁸⁷ Additionally, they noted salivary IgA production was reduced in CD patients with active bowel disease.¹⁸⁷ In 1982, Lamster *et al.* analysed polymorphonuclear leukocytes from 30 patients with active or inactive IBD and reported that those with active IBD had higher levels of circulating immune complex activity and their peripheral neutrophils exhibited greater metabolic activity compared to inactive IBD or healthy controls.¹⁹⁹ Additionally, a higher prevalence of oral pathologies was observed among

subjects with active IBD. In 1986, Van Dyke *et al.* evaluated 20 IBD patients with and without periodontal disease and found that the periodontal flora of IBD patients predominantly consisted of small, motile, gram-negative rods, closely related to the genus *Wolinella*.²⁰⁰ All 10 IBD subjects with periodontal disease exhibited serum-mediated defects in neutrophil chemotaxis, while neutrophil phagocytosis was normal. Additionally, PGE2 levels in GCF from IBD patients with periodontal disease were 4-fold higher than in adult periodontitis patients without IBD.²⁰⁰

Building upon these initial case reports, cross-sectional studies were designed to explore the positive correlation between IBD and periodontitis-afflicted individuals. In 1991, Flemmig *et al.* examined the periodontal status of 107 IBD patients and identified a 12% higher prevalence of periodontitis but a 0.6-mm lower clinical attachment loss in IBD patients when compared to the general US adult population.²⁰¹ In 2006, Grössner-Schreiber *et al.* examined 62 IBD patients and 59 healthy controls and found that IBD patients exhibited a significantly higher incidence of caries, but no distinct differences in periodontal findings.²⁰² In contrast, in 2008 Brito *et al.* examined 99 CD patients, 80 UC patients, and 74 healthy controls and found a significantly higher prevalence of periodontitis in UC [90%] and CD [82%] patients when compared to healthy controls [68%].¹⁶² Altogether, these studies provide some of the earliest evidence for the oral-gut axis, highlighting the potential connection between periodontitis and IBD. Over the next several years, similar studies have been published expanding our knowledge about periodontitis-IBD interconnection. Table 1 summarizes recent studies demonstrating associations between periodontitis and IBD.

Currently, limited evidence suggests that IBD treatment can improve periodontal disease outcomes, and vice versa, hinting that both diseases might share microbiological and immunoinflammatory pathways. IBD patients treated with anti-TNF- α biologics experienced rapid healing of apical periodontitis compared to controls.²⁰⁹ Corticosteroids, which are often used in IBD management, may confer a protective effect against periodontitis.²⁰⁴ In UC patients responsive to treatment with biologics, salivary levels of IgA and MPO increased significantly, suggesting that successful UC therapy may also boost oral defence mechanisms.²¹⁰ Furthermore, biologics used to treat other chronic inflammatory diseases appear to restrict periodontitis progression and enhance the healing response to periodontal treatment.²¹¹ Conversely, periodontitis treatment with mesenchymal stem cell-derived exosomes has been shown to attenuate experimental colitis in murine models.²¹² Clinical observations suggest that periodontal therapy can reduce intestinal levels of Enterobacteriaceae and Porphyromonadaceae, enriching Lachnospiraceae, in patients with gingivitis or mild/moderate periodontitis.²¹³ Similarly, our preliminary data [unpublished] indicate that in cases of advanced periodontitis [stage III/stage IV], periodontal therapy markedly decreases the intestinal abundance of *Bacteroides*, *Faecalibacterium*, and Lachnospiraceae. Furthermore, de Oliveira *et al.* demonstrated that in periodontitis patients who are systemically healthy, subgingival instrumentation caused an increase in intestinal levels of Actinobacteria, with a concurrent decrease in Bacteroidetes and Verrucomicrobia populations.²¹⁴ These results underscore a relationship between the oral cavity and the gut microbiota that can be modulated by changing the oral milieu with periodontal therapy. However, the full therapeutic implications

Table 1. Studies demonstrating an association between periodontitis and IBD

Study [reference number]	IBD [n]	Non-IBD [n]	Periodontitis-IBD associations	95% CI
Grossner-Schreiber <i>et al.</i> 2006 ²⁰²	IBD [62]	[59]	IBD [RR = 2.47] CAL ≥ 5 mm	1.02–5.99
Habashneh <i>et al.</i> 2012 ²⁰³	CD [59] UC [101]	[100]	CD [OR = 4.9] UC [OR = 7.0]	1.8–13.2 2.8–17.5
Vavricka <i>et al.</i> 2013 ¹⁶³	CD [69] UC [44]	[113]	CD [OR = 3.91] UC [OR = 3.94]	1.78–8.57 1.64–9.46
Chi <i>et al.</i> 2018 ²⁰⁴	CD [6657]	[26 628]	[HR = 1.36]	1.25–1.48
Yu <i>et al.</i> 2018 ²⁰⁵	CD [7] UC [20]	[108]	IBD [HR = 1.82] CD [HR = 3.95] UC [HR = 1.39]	1.09–3.03 1.59–9.82 0.69–2.46
Zhang <i>et al.</i> 2020 ²⁰⁶	CD [265] UC [124]	[265]	CD [OR = 4.46] UC [OR = 4.66]	2.50–7.95 2.49–8.71
Bertl <i>et al.</i> 2022 ²⁰⁷	IBD [1108]	[3429]	CD [OR = 1.74] UC [OR = 2.57]	1.36–2.24 1.99–3.32
Wang <i>et al.</i> 2023 ²⁰⁸	IBD [12 882]	[21 770]	IBD [OR = 1.06]	1.01–1.12
Baima <i>et al.</i> 2023 ⁶³	CD [117] UC [60]	[180]	IBD [OR = 4.48] CD [OR = 4.01] UC [OR = 4.43]	2.30–8.73 1.92–8.38 1.66–11.81

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio; HR, hazard ratio; RR, relative risk; CI, confidence interval; CAL, clinical attachment loss.

of these changes on IBD and the usefulness of assaying oral secretions as a potential biomarker for IBD requires further investigation. Taken together, these findings indicate that the immune-modulating effect of certain drugs may not only improve IBD outcomes, but also reduce inflammation within periodontal tissues. Moreover, periodontitis treatment could influence gut microbiota. Nonetheless, it is crucial to note that medications used in IBD management that result in immunosuppression, such as corticosteroids, thiopurines, anti-TNF- α , Janus kinase inhibitors, and other biologics, could increase the risk of opportunistic infections in the oral cavity.⁸⁹

6. A Multi-hit Model of Periodontitis-Mediated IBD Pathogenesis

Every day, the average adult generates and ingests ~1.5 L of saliva, which contains $\sim 1.5 \times 10^{12}$ oral bacteria.^{28,215–218} More than 99% of these bacteria are inactivated as they pass through the stomach.^{218,219} In healthy individuals, several defence mechanisms prevent ingested oral bacteria from colonizing the gut and promoting IBD. These include: [a] the physical barrier provided by the mucus layer and IECs,²²⁰ [b] bacterial clearance by mucus,²²¹ [c] competition between resident gut microbes and exogenous microbes invading from the mouth,^{222,223} and [d] neutralization of oral bacteria by gastric acid and pepsin.^{224,225} However, when these defence mechanisms are compromised by factors such as genetics, systemic disorders, medications, lifestyle, or ageing, oral microbes can potentially infiltrate the intestine and trigger immune responses, leading to IBD development.^{3,8,223,226–232}

The mucus layer rich in antimicrobial peptides and secretory immunoglobulins prevents direct contact between oral pathogens and the intestinal epithelium, creating a hostile environment for potential invaders.^{233,234} Conditions such as cystic fibrosis, stress, infection, an unhealthy diet, and ageing can disrupt the mucus layer, facilitating bacterial penetration.^{153,235–237} Beneath the mucus, the IEC barrier, fortified by occludins, claudins, and other junction proteins, provides

another layer of protection.²³⁸ Disruption of the IEC barrier can result in a 'leaky' gut, permitting microorganisms and intestinal contents to infiltrate the mucosal barrier and initiate inflammation.²³⁹ Further, the resident commensal gut microbiota resist exogenous oral pathogen colonization through nutrient competition and niche occupation.^{222,240,241} These microbes ferment dietary fibres, producing short-chain fatty acids (SCFAs) that serve as an energy source for colonocytes and exhibit anti-inflammatory properties.²⁴² However, a shift in microbial equilibrium, or dysbiosis, frequently triggered by antibiotic overuse or dietary changes, can exacerbate IBD risk.²⁴³ Chemical barriers, including gastric acid and pepsin in the stomach, help thwart opportunistic pathogens.^{224,225} However, hypochlorhydria or prolonged use of proton pump inhibitors disrupt the production of gastric acid and pepsin, which may predispose individuals to bacterial overgrowth and infections such as from *Clostridium difficile*.²⁴⁴ Collectively, the compromised mucus layer and epithelial barriers, coupled with a dysbiotic gut microbiota and heightened immune responses, can increase the risk for IBD. Based on these findings, we propose a multi-hit model to illustrate how periodontitis and related oral bacteria may enhance the susceptibility to IBD [Figure 2].

6.1. Stage 1: Initiation of oral dysbiosis

In a host exhibiting homeostatic oral and gut compartments, oral bacteria neither proliferate nor infiltrate the gut, thus maintaining a state of health. The onset of periodontitis causes oral dysbiosis, leading to the expansion of virulent oral bacteria.²⁴⁵ There is an enrichment of gram-negative bacteria that can thrive under anaerobic conditions, such as those found in the gut. The oral microbiome is subject to constant environmental perturbations, such as those from food, drinks, smoking, and oral hygiene practices, which affect the pH, temperature, oxygen levels, and nutrient profiles within the mouth.^{46,246} The oral microbiota exhibits evolutionary adaptations to environmental perturbations,²⁴⁷ which are reminiscent of the survival strategies employed by GI

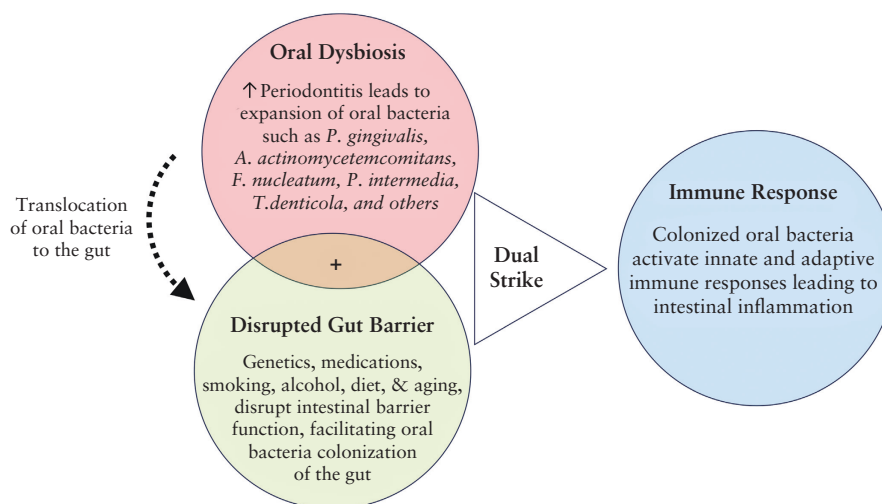


Figure 2. One hit, not enough wit—a multi-hit model. [Red circle] The onset of periodontitis leads to an expansion of pathogenic oral bacteria. These bacteria can translocate to the intestine, either via ingestion or through the circulatory system. Normally, ingested oral bacteria are inactivated as they pass through the stomach. [Green circle] Several factors, such as genetic disorders, medications, diet, smoking, alcohol, ageing, and stress, may disrupt intestinal barrier function and shift the gut microbiota in the long-term. This disruption can reduce colonization resistance, facilitating the establishment of oral bacteria in the gut. [Blue circle] Once established in the gut, oral bacteria activate both innate and adaptive immune responses leading to intestinal inflammation. Oral dysbiosis or disrupted gut barrier alone are insufficient to predispose the host to IBD. Both a sufficient load of oral pathogens and disrupted barrier function are necessary for oral pathogens to successfully colonize the gut, which then activates immune responses leading to intestinal inflammation.

microbiota. In a biofilm state, *Po. gingivalis* can endure acidic conditions, showing resilience to simulated gastric fluids.²⁴⁸ Detection of genetically identical strains of *F. nucleatum* and *Campylobacter concisus* in both the oral cavity and the intestines of IBD and colorectal cancer patients indicates microbial adaptations that promote oral-to-gut transmission.^{14,249}

6.2. Stage 2: Oral bacteria translocation and intestinal colonization

The next stage involves oral bacteria translocation to the intestine, either via ingestion or through the circulatory system [bacteraemia]. Normally, more than 99% of swallowed oral microorganisms are inactivated as they pass through the stomach.^{218,219} However, several conditions such as gastric ulcers, gastro-oesophageal reflux disease, genetic disorders, an unhealthy diet, ageing, stress, and the use of tobacco, alcohol, antibiotics, non-steroidal anti-inflammatory drugs, and/or proton-pump inhibitors may disrupt the intestinal barrier function and perturb the gut microbiota ecosystem, thus disrupting colonization resistance and facilitating the establishment of oral bacteria in the gut.^{153,235–237,243,244,250–252} A 10-fold increase in ileal Fusobacteriaceae was noted following antibiotic usage.¹⁸ Similarly, increased intestinal colonization of oral bacteria was noted in individuals who were using proton pump inhibitors.^{253,254} Additionally, periodontitis can lead to bacteraemia, with *Po. gingivalis*, *F. nucleatum*, *Tr. denticola*, and *Pr. intermedia* capable of evading immune surveillance and proliferating within the immune cells,^{35,255} and potentially exacerbating IBD development.

6.3. Stage 3: Induction of intestinal inflammation

In homeostasis, gut-resident microbes promote development of bacterium-specific tolerogenic responses against commensals that do not elicit intestinal inflammation.^{256,257} However, when certain exogenous oral pathogens colonize the gut, they can opportunistically elicit pathogenic immune

responses. After epithelial disruption, ingested oral bacteria can interact with gut-associated immune cells stimulating production of pro-inflammatory cytokines such as IL-17, IL-1 β , and IFN- γ .^{8,17} Furthermore, oral pathogen-reactive Th17 cells that arise *de novo* in the oral cavity can migrate to the inflamed gut, where they are activated by ectopically colonized oral pathogens, and subsequently contribute to gut inflammation.⁸ Thus, periodontitis can exacerbate gut inflammation by supplying the gut with both colitogenic oral pathogens and pathogenic T cells.⁸

In summary, neither oral dysbiosis nor gut barrier disruption alone is sufficient to predispose the host to IBD. However, the simultaneous presence of oral dysbiosis [providing an adequate supply of oral pathogens] and impaired gut resistance [disrupted barrier function against oral pathogens] creates susceptible conditions for oral pathogens to colonize the gut, which then promotes intestinal inflammation by activating innate and adaptive immune responses.

7. Oral and Gut Microbiome

The oral microbiota ranks as the second-largest microbial community after the gut microbiota. It harbours more than 700 species and 1300 bacterial strains, along with a diverse array of ultrasmall Candidate Phyla Radiation bacteria, fungi, amoebae, flagellates, archaea, and viruses.^{50,53,216,258–265} In health, the oral microbiota is remarkably stable and dominated by commensal bacteria such as *Streptococcus*, *Actinomyces*, *Haemophilus*, and *Neisseria*, which maintain a dynamic equilibrium with the host, ensuring symbiosis and facilitating normal immune and metabolic functions within the oral cavity.^{35,44,46,260,266} However, when this balance is disrupted, it can lead to dysbiosis, resulting in periodontitis.^{35,44,46,51,260,266} Oral dysbiosis is characterized by the overgrowth of anaerobic bacteria such as *Po. gingivalis*, *Ta. forsythia*, *Tr. denticola* [collectively referred to as the ‘red

complex'], and other species within the phyla Firmicutes, Proteobacteria, Spirochaetes, and Bacteroidetes.^{35,44,46,51,260,266} These dysbiotic bacteria produce virulence factors that promote tissue destruction, impair host immune defences, and disrupt the oral microbial community's stability.⁴⁴ While the dysbiotic oral microbiota enriched in virulence factors triggers periodontitis, it is the host's hyperactive immunoinflammatory responses to the altered microflora that cause major destruction of tooth-supporting structures.^{45,47}

Po. gingivalis is a keystone periodontal pathogen, which adheres to mucus membranes, the periodontal pocket epithelium, and other bacterial surfaces through adhesion factors such as fimbriae, haemagglutinins, proteases, and adhesins.^{267–269} *Po. gingivalis* produces a range of virulence factors, including endotoxins (e.g. lipopolysaccharide [LPS]), proteases [e.g. gingipains], outer membrane vesicles, acid and alkaline phosphatases, and organic acids, that contribute to the degradation of host proteins and evasion of host immune defences.^{268–271} Consequently, this leads to clinical manifestations such as oedema, neutrophil infiltration, and haemorrhage. In addition to *Po. gingivalis*, other periodontal pathogens, such as *A. actinomycetemcomitans*, *F. nucleatum*, *Ta. forsythia*, and *Pr. intermedia*, play crucial roles in the pathogenesis of periodontitis.^{49,272–276} *A. actinomycetemcomitans* is a facultative anaerobe and its key virulence factors include leukotoxin [LtxA], which selectively targets immune cells, cytolethal distending toxin [Cdt] that induces cell cycle arrest and apoptosis in multiple cell types, and adhesins that promote bacterial attachment to host tissues and other oral microbiota.^{274–278} Additionally, its LPS triggers inflammation, and the extracellular matrix-degrading enzymes lead to tissue destruction, together orchestrating the complex pathophysiological processes underlying periodontitis. *F. nucleatum* is an anaerobic bacterium known to promote biofilm formation and support the growth of other periodontal pathogens.^{272,273,279} It produces various virulence factors, including adhesins, haemagglutinins, and proteases, that contribute to tissue destruction and evasion of host defences.^{280,281} *Ta. forsythia*, another important periodontal pathogen, produces virulence factors such as proteases [e.g. karilysin and mirolase] and surface structures such as the BspA protein, which facilitate tissue invasion and immune evasion.^{282,283} The combined actions of multiple periodontal pathogens and their virulence factors contribute to the molecular mechanisms underlying periodontitis.^{268–283}

At opposite ends of the orodigestive tract, the oral cavity and the intestine share microbial pathogenesis mechanisms. In a healthy state, the gut microbiota is composed primarily of Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, with smaller populations of Fusobacteria and Cyanobacteria contributing to the overall diversity.^{284–287} Additionally, archaea, fungi, and viruses colonize the human GI tract. This intricate microbial community maintains gut homeostasis by executing essential functions such as nutrient metabolism, immune modulation, and defence against pathogens.^{284–289} The host tissues offer a nutrient-rich environment, reciprocated by the gut microbiota through the production of SCFAs and essential vitamins, fostering a mutually beneficial symbiosis.^{287,289} However, in IBD, the gut microbiota undergoes ecological dysbiosis, characterized by reduced microbial diversity—a decrease in beneficial commensal bacteria [e.g. Firmicutes], and an increase in potentially pathogenic bacteria [e.g. Proteobacteria].^{284–287} This dysbiosis leads to reduced

production of beneficial metabolites such as SCFAs and an increase in pro-inflammatory molecules, which can further exacerbate the intestinal inflammation and compromise the intestinal barrier function.^{284–287} As a result, the delicate balance between the host and the gut microbiota is disrupted, leading to a vicious cycle of inflammation and tissue damage that characterizes IBD.

Clinical and animal studies have demonstrated an emerging microbial signature in IBD, characterized by the expansion of oral bacteria. Table 2 summarizes various clinical studies demonstrating evidence of oral bacterial species enriched in the intestinal tissues of patients with IBD and colorectal cancer [another disease implicated in the oral–gut axis]. In an early study, Van Dyke *et al.* [1986] investigated differences in the oral microbiome among IBD and periodontitis patients, and healthy controls.²⁰⁰ In IBD patients, they observed a predominant presence of gram-negative rod-shaped bacteria, closely related to the genus *Wolinella*. Interestingly, periodontitis-free IBD patients displayed a decreased bacterial load within the gingival sulcus compared to their counterparts with periodontitis. These findings suggest distinct variations in the oral microbiome of IBD patients compared to periodontitis patients and healthy controls. Meurman *et al.* [1994] found higher salivary yeast, Lactobacilli, and *Streptococcus mutans* counts in individuals with active CD compared to inactive CD.³⁰² Stein *et al.* [2010] detected higher frequencies of *C. rectus* [94.6%], *A. actinomycetemcomitans* [76.9%], *Po. gingivalis* [62.6%], *Pr. intermedia* [79.6%], and *Ta. forsythia* [64.6%] in subgingival plaque from 147 CD patients stratified for CARD15-gene mutations.³⁰³ Notably, this study did not include a control group for comparative analysis. Man *et al.* [2010] and Strauss *et al.* [2011] identified a higher abundance of *C. concisus* and *F. nucleatum* in faeces and intestinal biopsies of IBD patients, suggesting that viable *C. concisus* and *F. nucleatum* can migrate to the intestines and establish themselves in the mucosal environment.^{23,300} Docktor *et al.* [2012] investigated the oral microbiome of children and young adults with IBD by analysing tongue and buccal mucosal brushings.³⁰⁴ They found a significant decrease in Fusobacteria and Firmicutes in CD patients compared to healthy controls. In UC patients, a similar decrease in Fusobacteria was observed, while Spirochaetes, Synergistetes, and Bacteroidetes were increased compared to controls. Brito *et al.* [2013] investigated 45 untreated periodontitis patients with either CD or UC, and patients with untreated periodontitis as controls.²⁷ They found CD patients harboured significantly higher concentrations of *Bacteriodes ureolyticus*, *Campylobacter gracilis*, *Prevotella melaninogenica*, *Staphylococcus aureus*, *Staphylococcus anginosus*, *Staphylococcus intermedius*, and *Streptococcus mutans* compared to UC and controls subjects. Said *et al.* [2014] analysed saliva from 21 CD, 14 UC patients, and 24 healthy controls, and found higher abundance of Bacteroidetes, *Prevotella*, and *Veillonella* in CD and UC patients compared to healthy controls, while Proteobacteria, *Streptococcus*, and *Haemophilus* were lower.²⁰ *Neisseria* and *Gemella* were also lower in CD patients versus healthy controls. Kelsen *et al.* [2015] characterized subgingival microbiota in paediatric patients with active or non-active CD and identified 17 genera more abundant in CD patients versus healthy controls, including *Capnocytophaga*, *Rothia*, and *TM7*.³⁰⁵ Both antibiotic exposure and disease state were linked to differences in bacterial community composition. Schmidt *et al.* [2018] examined subgingival plaque

Table 2. Oral bacteria enriched in the intestines of patients with IBD and colorectal cancer

Study [reference number]	Study design	Subjects [n]	Samples	Methods	Key findings
<i>Fusobacterium</i> spp. [<i>F. nucleatum</i>]					
Strauss <i>et al.</i> 2011 ²³	Case-control	UC [4], CD [17], intermediate colitis [1], healthy controls [32], IBS [2]	Colon biopsies	Isolation, culture, 16S rRNA sequencing	<i>Fusobacterium</i> spp. abundant in patients with GI disease [64%] vs healthy controls [26%]. Highly invasive strains of <i>F. nucleatum</i> enriched in IBD patients
Castellari <i>et al.</i> 2012 ¹¹	Cross-sectional	CRC [11]	CRC biopsies and adjacent normal tissues	Isolation, culture, RNA-sequencing, qPCR	Higher abundance of <i>Fusobacterium</i> in colorectal tumour specimens
Dejea <i>et al.</i> 2014 ¹²	Cross-sectional	USA CRC/polyp [34], healthy controls [62], MAL CRC/polyp [22]	Intestinal biopsies from CRC and healthy controls	16S rRNA sequencing	<i>Fusobacterium</i> predominant in non-biofilm CRC specimens and undetected in normal tissues
Gevers <i>et al.</i> 2014 ¹⁸	Case-control	Paediatric CD [447], healthy controls [221]	Ileal and rectal biopsies, stool, serum	16S rRNA sequencing	Fusobacteriaceae enriched in treatment-naïve CD patients and associated with disease progression. Oral species better represented in biopsies vs stool. Antibiotic use amplified the microbial dysbiosis associated with CD
Dreves <i>et al.</i> 2017 ²⁹⁰	Case-control	MAL1 CRC [21], polyp [1], healthy controls [34]; MAL2 CRC [23], healthy controls [23]; USA CRC [35], polyp [4], healthy controls [60]	Stool, intestinal biopsies from CRC, polyp, and healthy tissues	16S rRNA sequencing	Oral pathogens, including <i>F. nucleatum</i> , <i>Parvimonas micra</i> , and <i>Peptostreptococcus stomatis</i> highly enriched in CRC tissues
Pascal <i>et al.</i> 2017 ²⁴	Case-control	UC [74], CD [87], healthy controls [111]	Stool	16S rRNA sequencing	<i>Fusobacterium</i> enriched in CD
Flemer <i>et al.</i> 2018 ¹³	Case-control	CRC [99], colorectal polyps [32], healthy controls [103]	Oral swab, colonic biopsies, stool	16S rRNA sequencing	<i>F. nucleatum</i> enriched in CRC, but also noted in healthy controls
Schirmer <i>et al.</i> 2018 ²²	Observational	Paediatric UC [405]	Rectal biopsies, stool	16S rRNA sequencing	<i>Fusobacterium</i> enriched and associated with disease progression, and twice higher in rectal biopsies vs stool
Dinakaran <i>et al.</i> 2018 ²⁵	Cross-sectional	Disease tissue from UC [13], CD [13], and adjacent healthy tissue [13]	Colonic biopsies	16S rRNA sequencing	<i>Fusobacterium</i> enriched in diseased colonic biopsies vs adjacent healthy tissue
Komiya <i>et al.</i> 2019 ¹⁴	Cross-sectional	CRC [14]	Saliva, colonic biopsies	Isolation, culture, PCR, 16S rRNA sequencing	Identical <i>F. nucleatum</i> strains found in saliva and colon tumours
Vieira-Silva <i>et al.</i> 2019 ²⁹¹	Case-control	PSC [64], UC [13], CD [29], healthy [1120]	Stool	16S rRNA sequencing	<i>Fusobacterium</i> abundance associated with severity of intestinal inflammation
Liu <i>et al.</i> 2020 ²⁹²	Case-control	UC [20], CD [71], healthy controls [43]	Stool	16S rRNA sequencing	<i>F. nucleatum</i> enriched and associated with disease activity in UC and CD patients. <i>F. nucleatum</i> infection in DSS-treated mice exacerbated colitis by promoting expression of IL-1 β , TNF- α , IFN- γ , IL-6, and IL-17, and fostering CD4+ T cell differentiation into Th1 and Th17 cells

Table 2. Continued

Study [reference number]	Study design	Subjects [n]	Samples	Methods	Key findings
<i>Porphyromonas</i> spp. [<i>Po. gingivalis</i>]					
Flemer <i>et al.</i> 2017 ²⁹³	Case-control	CRC [59], colon polyps [21], healthy controls [56]	Stool, CRC biopsies and adjacent normal tissues	16S rRNA sequencing	Microbiota differed in CRC vs controls. Alterations were noted throughout the colon and not restricted to cancer
Ahn <i>et al.</i> 2013 ²⁹⁴	Case-control	CRC [47], healthy controls [94]	Stool	16S rRNA sequencing	<i>Fusobacterium</i> and <i>Porphyromonas</i> were enriched in CRC, whereas <i>Clostridia</i> were decreased
Yang <i>et al.</i> 2019 ²⁹⁵	Case-control	CRC [50], healthy controls [50]	Stool	16S rRNA sequencing, gas chromatography-mass spectrometry	CRC had less microbial diversity and enriched <i>Fusobacteria</i> , <i>Parvimonas</i> and <i>Porphyromonas</i> ; 17 metabolites were specifically perturbed in CRC
Wang <i>et al.</i> 2021 ²⁹⁶	Cross-sectional	Healthy [22], CRC [23], colorectal adenoma [32]	Stool, CRC, and normal tissue biopsies	16S rRNA sequencing, qPCR	<i>Po. gingivalis</i> enriched in stool and biopsies of CRC and associated with poor prognosis. In ApcMin/+ mice, <i>Po. gingivalis</i> promoted CRC by activating NLRP3 inflammasome
Lee <i>et al.</i> 2022 ²⁹⁷	Case-control	CD [11], control [8]	Stool	16S rRNA sequencing	Porphyromonadaceae enriched in CD. <i>Po. gingivalis</i> infection in DSS-treated mice exacerbated colitis by promoting expression of TNF- α and IL-6
Dinakaran <i>et al.</i> 2018 ²⁵	Cross-sectional	Disease tissue from UC [13], CD [13], and adjacent healthy tissue [13]	Colon biopsies	16S rRNA sequencing	<i>Aggregatibacter</i> , <i>Porphyromonas</i> , <i>Prevotella</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , enriched in diseased colon biopsies vs adjacent healthy tissue
Atarashi <i>et al.</i> 2017 ¹⁷	Case-control	UC [51], CD [7], PSC [27], GERD [18], alcoholic [16], healthy controls [150]	Saliva, stool	Isolation, culture, 16S rRNA sequencing, metagenomic analysis	<i>Prevotella</i> , <i>Streptococcus</i> , <i>Neisseria</i> , <i>Rothia</i> , and <i>Gemella</i> enriched in UC, PSC, GERD and alcoholic faeces
Dinakaran <i>et al.</i> 2018 ²⁵	Cross-sectional	Disease tissue from UC [13], CD [13], and adjacent healthy tissue [13]	Colon biopsies	16S rRNA sequencing	<i>Prevotella</i> enriched in diseased colon vs adjacent healthy tissue
Prasodanan <i>et al.</i> 2021 ²¹	Population-based	IBD [189] and healthy controls [200]	Stool	Whole metagenome sequencing	Higher abundance and diversity of <i>Prevotella copri</i> in Indian and non-Western vs Western populations
Gevers <i>et al.</i> 2014 ¹⁸	Case-control	Paediatric CD [447], healthy controls [221]	Ileal and rectal biopsies, stool, serum	16S rRNA sequencing	Veillonellaceae enriched in CD and associated with disease progression. Oral species better represented in biopsies vs stool
Schirmer <i>et al.</i> 2018 ²²	Observational	Paediatric UC [405]	Rectal biopsies, stool	16S rRNA sequencing	<i>V. parvula</i> enriched and associated with disease progression, and higher in rectal biopsies vs stool
Vieira-Silva <i>et al.</i> 2019 ²⁹¹	Case-control	PSC [64], UC [13], CD [29], healthy [1,120]	Stool	16S rRNA sequencing	<i>Veillonella</i> abundance associated with severity of intestinal inflammation

Table 2. Continued

	Study [reference number]	Study design	Subjects [n]	Samples	Methods	Key findings
<i>Klebsiella</i> spp. [<i>Klebsiella pneumoniae</i>]	Atarashi <i>et al.</i> 2017 ¹⁷	Case-control	UC [51], CD [7], PSC [27], GERD [18], alcoholic [16], healthy controls [150]	Saliva, stool	Isolation, culture, 16S rRNA sequencing, metagenomic analysis	<i>Klebsiella</i> enriched in CD. Antibiotic-resistant <i>Klebsiella</i> tend to colonize when gut microbiota is dysbiotic and elicit severe inflammation in a genetically susceptible host by promoting Th1 cells
	Lloyd-Price <i>et al.</i> 2019 ²⁹⁸	Case-control	UC [38], CD [67], healthy controls [27]	Colon biopsies, stool, blood	16S rRNA sequencing, metagenomic, metatranscriptomic, proteomic, metabolomic analysis	<i>K. pneumoniae</i> and <i>Haemophilus parainfluenzae</i> levels during dysbiosis associated with acylcarnitines and bile acid levels
	Imai <i>et al.</i> 2021 ²⁹⁹	Case-control	UC [42], CD [18], healthy controls [45]	Saliva and stool	16S rRNA sequencing	Enterobacteriaceae enriched in CD patients with periodontitis
<i>Streptococcus</i> spp.	Pascal <i>et al.</i> 2017 ²⁴	Case-control	UC [74], CD [87], healthy controls [111]	Stool	16S rRNA sequencing	Higher abundance of <i>Streptococcus</i> noted in CD with post-operative recurrence compared to those who remained in remission
	Atarashi <i>et al.</i> 2017 ¹⁷	Case-control	UC [51], CD [7], PSC [27], GERD [18], alcoholic [16], healthy controls [150]	Saliva, stool	Isolation, culture, 16S rRNA sequencing, metagenomic analysis	<i>Streptococcus</i> , enriched in faeces of UC, PSC, GERD, and alcoholic patients
<i>Campylobacter</i> spp. [<i>Campylobacter concisus</i>]	Vieira-Silva <i>et al.</i> 2019 ²⁹¹	Case-control	PSC [64], UC [13], CD [29], healthy [1120]	Stool	16S rRNA sequencing	<i>Streptococcus</i> abundance associated with severity of intestinal inflammation
	Man <i>et al.</i> 2010 ³⁰⁰	Case-control	Pediatric CD [54], non-IBD [27], and healthy controls [33]	Stool	PCR	Higher prevalence of <i>C. concisus</i> noted in paediatric CD vs non-IBD and healthy controls
	Kirk <i>et al.</i> 2016 ³⁰¹	Case-control	UC [16], CD [9], IPAA [27], and healthy controls [26]	Ileum and colon biopsies	Isolation, culture, and PCR	Higher abundance of <i>C. concisus</i> noted in IBD vs control.

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IBS, irritable bowel syndrome; CRC, colorectal cancer; PSC, primary sclerosing cholangitis; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; MAL1, Malaysian cohort 1; MAL2, Malaysian cohort 2; DSS, dextran sodium sulfate; IPAA, ileal pouch-anal anastomosis.

and found a significantly lower prevalence of *Eubacterium nodatum* and *Eikenella corrodens* in 59 IBD patients compared to 59 healthy controls.¹⁷⁶ Xun *et al.* [2018] investigated oral microbial dysbiosis in saliva samples from 54 UC patients, 13 active or remissive CD patients, and 25 healthy adults. They found an enrichment of Streptococcaceae and Enterobacteriaceae in UC and Veillonellaceae in CD, and depletion of Lachnospiraceae and Porphyromonadaceae in UC, as well as Neisseriaceae and *Haemophilus* in CD patients.¹⁵ Alpha diversity was significantly lower in UC and CD patients. Recently, Kitamoto *et al.* [2020] showed that *Klebsiella* spp. from the oral cavity can translocate to the gut, where they activate the inflammasome in lamina propria macrophages, exacerbating gut inflammation.⁸

8. Shared Immunoinflammatory Responses

The pathogenesis of both periodontitis and IBD involves a complex interplay between host immunity and specific bacterial stimuli.³⁰⁶ Here, we postulate a mechanism through which oral bacteria could potentially contribute to periodontitis-mediated IBD progression, and elaborate on the mechanistic details of the roles of neutrophils, macrophages, dendritic cells [DCs], T cells, and B cells in the process. Oral pathogen-mediated immune responses that drive gut inflammation in IBD are concisely illustrated in Figure 3.

Both periodontitis^{307,308} and IBD^{309–311} have been associated with rheumatoid arthritis [RA]. Drawing parallels from their established links with RA, we can postulate the potential contribution of oral bacteria to the pathogenesis of IBD, particularly through processes involving citrullination and immune response cross-reactivity. In periodontitis, oral bacteria, such as *Streptococcus*, *Porphyromonas*, *Actinomyces* and *Prevotella* species undergo citrullination, a process catalysed by peptidylarginine deiminase [PAD] enzymes found in both microbial and human cells.^{307,308,312–314} This enzymatic action converts peptidylarginine into peptidylcitrulline, which fundamentally alters the protein structure and function.^{315–318} The altered structure is recognized by the T and B cell immune repertoire inducing epitope spreading and loss of immune tolerance.³⁰⁷ These citrullinated bacterial antigens have been implicated in triggering autoimmune responses.^{319–321} However, the potential role of gut or oral bacteria in enhancing the citrullination cascade in IBD remains unknown.³²²

We hypothesize that in IBD, citrullinated oral bacterial antigens, either translocated to the gut via ingestion or systemic circulation, could instigate a comparable autoimmune cascade seen in RA.³⁰⁷ Once in the gut, these citrullinated bacterial antigens could induce an immune response that initially targets the microbial proteins but subsequently exhibits cross-reactivity towards citrullinated human proteins in the gut.^{307,314,323,324} We hypothesize that this cross-reactivity induced by epitope spreading could contribute to the autoimmune nature of IBD, where the immune system, originally primed against bacterial antigens, erroneously targets the gut tissues due to molecular mimicry.^{325–327} Additionally, the immune response in IBD might involve the formation of anti-citrullinated protein antibodies [ACPAs],^{328–330} similar to those observed in RA,^{307,331,332} targeting the citrullinated antigens from oral bacteria. Neutrophils, forming extracellular traps [NETs] containing citrullinated proteins, could add to the antigenic load, contributing to the inflammation and tissue damage characteristic of IBD.^{333–335}

Therefore, we hypothesize that the interplay of citrullination, immune cross-reactivity, epitope spreading, chronic inflammation, and gut dysbiosis, stemming from oral bacteria and their antigens in the context of periodontal disease, could play a pivotal role in the onset and progression of IBD. The detailed roles of specific PAD isotypes, the exact nature of the citrullinated epitopes, and the specific types of immune cells and receptors involved in these processes are areas that require further investigation.

Neutrophils, as the first responders to bacterial invasion, play a pivotal role in the initial stages of periodontitis and IBD.^{35,336–340} In periodontitis, *Po. gingivalis*, through its virulence factors such as gingipains, promotes a hyperactive and sustained neutrophilic response, leading to elevated release of proteolytic enzymes and reactive oxygen species.^{35,336,341} This results in collateral tissue damage and subsequent alveolar bone loss, a hallmark of periodontitis. Moreover, *Po. gingivalis* can dysregulate neutrophil function, such as impairing NET formation and phagocytosis, leading to an imbalanced host response.^{35,336,341} In IBD, similar neutrophil dysfunctions are observed, where excessive and sustained neutrophilic infiltration in the intestinal mucosa contributes to chronic inflammation and tissue damage.^{338,339,342} Furthermore, neutrophil dysregulation, including abnormal recruitment and impaired clearance, is also seen in IBD.^{338,339,342} *Po. gingivalis* may dysregulate neutrophil function, potentially exacerbating IBD pathogenesis. Systemically circulating neutrophils in individuals with periodontitis exhibit cytokine hyper-reactivity and impaired chemotaxis, which could potentially contribute to the oral–gut axis in the context of IBD.^{199,200,343} S100A8, S100A9, and S100A12 are small calcium-binding proteins abundantly expressed by neutrophils in acute inflammation and have been implicated in immune regulation in both periodontitis and IBD.^{344–346} Higher salivary expression of S100A12 has been found in UC patients with periodontitis.³⁴⁷ The role of S100 proteins in periodontitis–IBD pathogenesis needs to be further investigated.

Macrophages, key players in the immune response, are implicated in both periodontitis and IBD. In the context of periodontitis, *Po. gingivalis* can influence macrophage polarization, favouring a pro-inflammatory [M1] phenotype over an anti-inflammatory [M2] phenotype, thus promoting inflammation and tissue damage.³⁴⁸ *E. nucleatum* also stimulates M1 macrophage polarization via the AKT2 pathway and fosters Th1 and Th17 cell expansion through STAT3 signalling.^{292,349} Similar macrophage polarization patterns are seen in IBD, contributing to a sustained inflammatory environment in the gut.^{350,351} Specifically, Enterobacteriaceae such as *Klebsiella* isolated from the oral cavity trigger IL-1 β secretion from macrophages, intensifying intestinal inflammation by mediating IL-1 signalling.⁸ Intriguingly, Enterobacteriaceae isolated from the intestines do not evoke similar IL-1 β secretion, suggesting a specific response to oral microbes.⁸

Dendritic cells [DCs] are antigen-presenting cells that bridge innate and adaptive immunity.^{352,353} DCs play a crucial role in maintaining oral tolerance to commensal bacteria and preventing unwanted inflammatory responses.³⁵⁴ However, certain periodontal pathogens, such as *Po. gingivalis* and *A. actinomycetemcomitans*, can dysregulate DC function and promote inflammation.^{355,356} In IBD, dysregulated DCs can initiate and perpetuate intestinal inflammation through an exaggerated T cell response.^{357,358} Saliva from CD and UC patients can cause intestinal inflammation in mice lacking

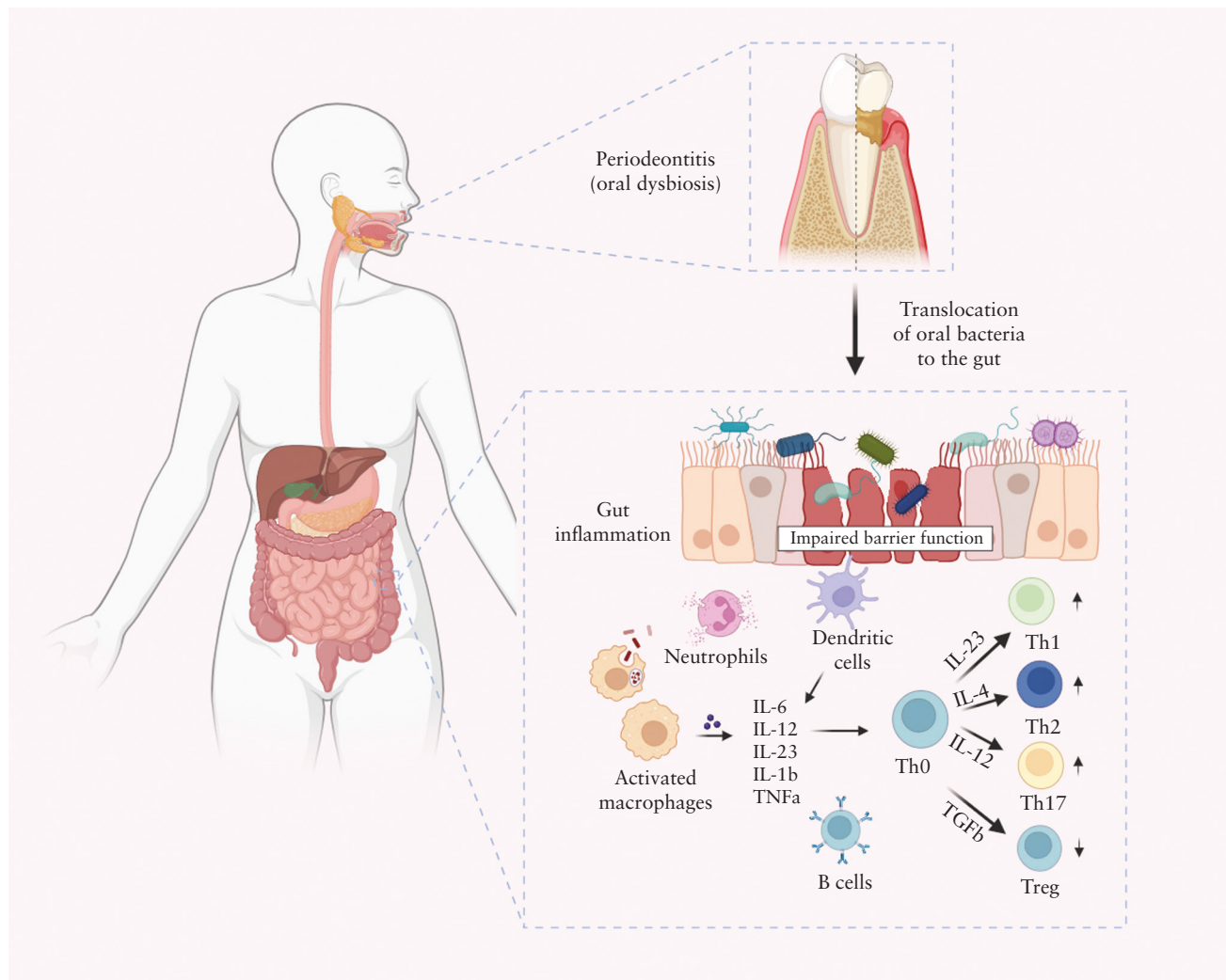


Figure 3. Oral pathogen-mediated immune responses that drive gut inflammation in IBD. Periodontitis onset triggers expansion of pathogenic oral bacteria. Constant saliva swallowing enables these bacteria to translocate to the gut. A compromised intestinal barrier function, marked by diminished mucus and epithelial barrier integrity, facilitates the penetration of oral bacteria into the sub-epithelial regions. Neutrophils, the first responders, attempt to phagocytose the ingested bacteria and release antimicrobial substances. Additionally, the antigen-presenting cells (APCs) in the gut recognize the microbial invaders through pattern recognition receptors such as Toll-like receptors (TLRs). Once activated, these cells release a cocktail of pro-inflammatory molecules: interleukin [IL]-6, IL-12, IL-23, IL-1 β , tumour necrosis factor α [TNF- α], and chemokines. Consequently, these molecules guide the differentiation of naive T helper [Th0] cells into Th1, Th2, Th17, and Treg cells. Furthermore, B cells become activated by recognizing bacterial antigens and differentiate into plasma cells, which produce antibodies specific to the oral bacterial antigens. These antibodies neutralize or opsonize bacteria and can form immune complexes, intensifying inflammation. The concerted actions of innate and adaptive immune cells lead to initiation or exacerbation of the inflammatory process in IBD, highlighting the far-reaching effects of oral bacterial dysbiosis. Figure created with BioRender.com.

IL-10 through *Klebsiella*-induced DC signalling and Th1 activation.¹⁷ In response to oral bacteria, IFN- γ + CD4+ T cells accumulate in the intestinal mucosa of these mice, as observed in humans with CD.¹⁷

T cells are key orchestrators of immune responses in both periodontitis and IBD, with their activation and subsequent modulation of inflammation serving as common pathogenic threads. *Po. gingivalis* stimulates aberrant CD4+ T cell responses, tilting the balance towards a pro-inflammatory milieu. More specifically, *Po. gingivalis* incites an increase in Th17 cell responses, characterized by distinct production of IL-17 and simultaneous modulation of the Th17/Treg ratio.^{32,359} This results in an augmentation of Th17-related transcription factors and pro-inflammatory cytokines IL-17 and IL-6 via the TLR4 pathway, paralleled by downregulation of Foxp3, TGF- β , and IL-10.³⁶⁰ Further, *Po. gingivalis* elicits

intestinal inflammation by altering the gut microbiota composition and disrupting epithelial barrier function through IL-9-producing CD4+ T cells.²³¹ These shifts towards pro-inflammatory responses and a skewed T cell landscape could contribute to IBD progression.^{32,360} *F. nucleatum* exacerbates this inflammatory cascade by compromising the integrity of the intestinal epithelial barrier, thereby increasing permeability and promoting secretion of inflammatory cytokines such as TNF- α , IFN- γ , IL-1 β , IL-6, and IL-17, and in parallel inhibiting the production of the anti-inflammatory cytokine IL-10.²⁹² Numerous studies have further delineated the shared inflammatory mechanisms between periodontitis and IBD by evaluating cytokine expression in affected tissues. For example, Menegat *et al.*³⁶¹ and Figueredo *et al.*^{170,177} identified heightened levels of IL-17A, IL-17F, IL-22, IL-23, IL-25, IL-33, INF- γ , and IL-10 in gingival tissues of patients with IBD

and chronic periodontitis. However, they found IL-1 β , IL-4, IL-10, and IL-21 to be significantly elevated in patients with active IBD, suggesting that an inflammation score based on IL-1 β , IL-6, IL-21, and sCD40L expression was higher in gingival tissues of active IBD patients. Furthermore, IBD patients treated with anti-TNF- α biologics had more rapid healing of apical periodontitis compared to controls.²⁰⁹ Collectively, these studies underscore the intertwined relationship between periodontitis and IBD and the central role of T-cell-mediated immune responses, thereby providing a clearer understanding of the common pathogenic landscape and potential targets for future therapeutics.

B cells, essential constituents of adaptive immunity that play a key role in the crosstalk between periodontitis and IBD, mediate their effects primarily through the production of antibodies against specific pathogens. *Po. gingivalis* can stimulate B cells to produce antibodies, such as IgG and IgA, but also fosters an environment of sustained inflammation in the oral cavity.^{362,363} There is emerging evidence that B cell dysregulation and inappropriate antibody responses also contribute to IBD pathogenesis.³⁶⁴ Our group recently demonstrated a highly dysregulated B cell response in UC, highlighting a potential role of B cells in disease pathogenesis.³⁶⁵ We found expansion of naive B cells and IgG+ plasma cells with curtailed diversity and maturation within the mucosal B cell compartment of UC patients.³⁶⁵

9. Animal Studies Demonstrating Periodontitis–IBD Interconnection

Animal models have been instrumental in delineating the immunoinflammatory interplay between periodontitis and IBD, suggesting potential parallels in humans. Yamazaki *et al.* demonstrated that oral inoculation of *Po. gingivalis* disrupts mouse gut microbiota and compromises intestinal barrier integrity by diminishing the expression of tight junction proteins.^{229,366} This was associated with an upsurge in colonic inflammatory cytokines [IL-6, IL-12 β , IFN- γ , and IL-17c] and higher serum endotoxin levels, suggesting a direct link between oral pathogens and systemic inflammation.^{229,366} Similarly, Liu *et al.* observed that *Po. gingivalis* inoculation in mice led to a reduction in gut microbial diversity and a marked increase in Th1 cells and associated cytokines [IFN- γ and TNF- α] in the gut and spleen.³⁶⁷ No changes were noted in tight junction proteins, and the authors posited that *Po. gingivalis* could disrupt their distribution rather than their overall expression. Zhao *et al.* showed that *Po. gingivalis* exacerbates Dextran sulphate sodium [DSS]-induced colitis in mice by promoting Th17 and IL-17 while reducing Treg and IL-10 production, an effect partially ascribed to a virulence factor of *Po. gingivalis*, peptidylarginine deiminase [PPAD].³² Sohn *et al.* reported that oral administration of *Po. gingivalis* induces ileal inflammation and alters gut microbiota composition, notably reducing microbial alpha diversity despite the absence of *Po. gingivalis* in the lower GI tract.²³¹ They documented a substantial increase in IL9+ CD4+ T cells within the small intestinal lamina propria, indicating that the inflammation might result from subsequent loss of gut microbial diversity. Qian *et al.* noted that transferring salivary microbiota from periodontitis patients into mice altered gut microbiota composition and exacerbated DSS-induced colitis via enhanced M2 polarization and Th2 cell induction.³⁶⁸ Atarashi

et al. found that *Klebsiella* species from the oral cavity of CD patients can colonize mouse intestines and provoke Th1 cell responses via the TLR4 receptor, leading to IL-10 deficiency and further amplification of intestinal inflammation.¹⁷ Notably, *Klebsiella* also promoted the expression of interferon-inducible [IFI] genes, which may facilitate colonization and subsequent recruitment of Th1 cells, thereby promoting a Th1-skewed inflammatory response reminiscent of IBD-like colitis.¹⁷ Kitamoto *et al.* revealed that in a model combining ligature-induced periodontitis and DSS treatment in mice, oral pathogen-reactive Th17 cells arise *de novo* in the oral cavity and migrate to the inflamed gut, where they are activated by ectopically colonized oral pathogens, and subsequently contribute to gut inflammation.⁸ Conversely, Nagao *et al.* found that orally administered *Po. gingivalis* is internalized by Peyer's patches and specifically activates intestinal Th17 cells influenced by the gut microbiota. These intestine-derived Th17 cells migrate from the gut to the mouth and exacerbate periodontitis.⁹ Collectively, these findings suggest that oral pathogens may contribute to the immunological and cytokine disturbances associated with human IBD by exploiting pathways similar to those documented in rodent models.

10. Current Knowledge Gaps and Future Directions

10.1. Clinical and animal studies

Although evidence supports the notion that periodontitis and IBD are interrelated, the specific mechanisms by which oral bacteria contribute to gut inflammation and vice versa are still unclear. The directionality and causality of this relationship are obscured by confounding factors. Tobacco use, a Western diet, and lifestyle are recognized risk factors for IBD, with some genes linked to mucosal barrier function and immune regulation potentially implicated.^{64,106,107,369} However, the precise role of these factors remains unclear. Much of the existing research linking periodontitis and IBD is cross-sectional, limiting our understanding of causal relationships.^{63,163,178,207,208,299,370} There is a need for longitudinal studies that can provide insights into the temporal sequence of these conditions, and whether periodontitis precedes, follows, or develops concurrently with IBD. To date, most studies have focused on bacterial dysbiosis, and the role of fungi and viruses has been neglected. It remains ambiguous whether dysbiosis acts as a primary cause of the disease or if it is simply a by-product of changes in the immune system, metabolism, or diet. Furthermore, the microbial dissimilarity between humans and mice raises questions about the applicability of murine findings to humans. The role of various immune cells and the impact of trained immunity in both conditions remains ill-defined. The influence of age on the association between periodontitis and IBD is not fully clear. Age is a significant risk factor in the pathogenesis of both conditions, and understanding its role could potentially inform prevention and treatment strategies. Further, it remains unanswered whether periodontitis treatment ameliorates IBD risk or severity, and if IBD management can reduce periodontitis occurrence. These significant knowledge gaps call for well-designed, robust, mechanistic clinical and animal studies to gain a comprehensive understanding of the interrelationships between periodontitis and IBD pathogenesis.

10.2. Concerns regarding the DSS-induced colitis model

While several animal models [at least 66 different kinds] have been employed to study IBD pathogenesis,^{371–374} we focus on the DSS-colitis model, which has been extensively used to investigate colitis pathogenesis and the potential causal link between periodontitis and IBD.^{8,32,292,360,368,371–377} However, this model has inherent limitations that may impact the interpretation and translatability of oral and gut findings. DSS administration induces acute colonic inflammation by direct chemical injury to the intestinal epithelium.^{371–374} The physical damage to the epithelial lining leads to luminal microbial ingress into the lamina propria, which stimulates innate and adaptive immune responses. This process differs from human IBD, which is a chronic condition characterized by alternating periods of inflammation and remission involving a complex interplay of genetic, environmental, and immunological factors.^{64,106,107,369} While DSS is administered to cause colonic inflammation, it can have off-target effects on periodontal tissues and oral microbiota. Oz and Ebersole [2010] found that 2% DSS alone causes periodontal inflammation and significant alveolar bone loss in BALB/c mice.^{378,379} Significant bone loss was detected as early as 7 weeks after initiation of DSS treatment, progressing to severe periodontitis by 18 weeks. The authors concluded that DSS impacts mucosal tissue in a more generalized and systemic manner, affecting both the intestine and the oral cavity. Similarly, Mello-Neto *et al.* reported that DSS-treated rats exhibited inflammatory cells extending into periodontal connective tissues, which contained significantly elevated expression of Th1/Th2-related cytokines such as IL-1 α , IL-1 β , IL-2, IL-6, IL-12, IL-13, GM-CSF, IFN- γ , and TNF- α .³⁸⁰ They concluded that DSS should be used with caution as it can lead to more widespread and indiscriminate lesions, and the increased pro-inflammatory cytokines in the gingival tissues caused by DSS alone might create an environment conducive to future alveolar bone loss. In another study, Rautava *et al.* showed that C57BL/6 male mice treated with 2% DSS for 1 week exhibited altered oral and gut microbiome composition, with a decrease in oral levels of Spirochetes, Betaproteobacteria, and *Lactobacillus*.³⁸¹ The salivary microbiota exhibited the most significant change when compared to the microbiota of the tongue and buccal mucosa. However, they noted no visible oral inflammation, and it is unclear how much of the observed effect is attributed to gender imbalance in the study. Additionally, Metzger *et al.*³⁸² and Hamdani *et al.*³⁸³ demonstrated that DSS treatment suppresses bone formation and increases bone resorption, resulting in reduced bone mass and altered bone microarchitecture. In DSS-treated mice, elevated TNF- α , IL-6, RANKL, OPG, and sclerostin corresponded with higher osteoclast surfaces and lower rates of bone formation. Collectively, these findings suggest that DSS promotes periodontal inflammation, alveolar bone loss, and altered oral microbiota.

Based on these findings, the question arises whether DSS is a confounder in studying periodontal-IBD interconnection. While seminal studies in DSS-treated mice showed that bacteria and immune cells from the oral cavity migrate to the gut and exacerbate colonic inflammation,⁸ the extent to which this inter-relationship is confounded by DSS treatment is uncertain. Previous studies investigating the periodontitis-IBD interconnection lacked evidence that DSS treatment alone did not affect periodontal tissues, the oral microbiome, and oral immune cells.^{8,32,292,360,368,375–377} This major limitation

highlights the need for future research to focus on developing more accurate and representative animal models that better mimic the complex interactions between periodontitis, oral and gut bacteria, and IBD in humans. This may involve the use of alternative mouse models exhibiting increased susceptibility to both periodontitis and IBD without the need for chemical induction.

11. Conclusions

As our understanding of periodontitis and IBD pathogenesis advances, both disorders represent a complex interplay of genetic, environmental, microbial, and immunological factors. Central to this discussion is the ‘multi-hit’ model, suggesting that a sequence of events—dysbiosis of the oral microbiota, a disrupted intestinal barrier function, and an aberrant immune response—are crucial for the development of periodontitis-associated IBD. The oral cavity may serve as a potential reservoir for intestinal pathogens. Oral bacteria and their byproducts can reach the gut through ingestion or systemic circulation. Factors such as genetics, an unhealthy diet, ageing, stress, and the use of tobacco, alcohol, or medications may disrupt intestinal barrier function, allowing the oral bacteria to colonize the gut. Once colonized, these oral bacteria can elicit excessive immune responses that promote intestinal inflammation. While current studies provide valuable insights, there is a need for longitudinal studies to provide an in-depth understanding of the periodontitis-IBD interconnection. Despite the valuable insights gained from the DSS-colitis animal models, their limitations must be carefully considered when exploring the interconnection between periodontitis and IBD. Lastly, collaboration between dentists, gastroenterologists, immunologists, and infectious disease experts/microbiologists, alongside other healthcare professionals, is necessary to provide holistic oral-systemic healthcare. Optimal dental care could reduce the supply of pathogenic oral bacteria to the gut, potentially offering innovative methods to reduce the risk and severity of IBD.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All authors have made substantial contributions to the following: [a] the conception and design of the study, or acquisition of data, or analysis and interpretation of data, [b]

drafting the article or revising it critically for important intellectual content, and [c] final approval of the version to be submitted.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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