The role of oral bacteria in inflammatory bowel disease

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Abstract | Over the past two decades, the importance of the microbiota in health and disease has become evident. Pathological changes to the oral bacterial microbiota, such as those occurring during periodontal disease, are associated with multiple inflammatory conditions, including inflammatory bowel disease. However, the degree to which this association is a consequence of elevated oral inflammation or because oral bacteria can directly drive inflammation at distal sites remains under debate. In this Perspective, we propose that in inflammatory bowel disease, oral disease-associated bacteria translocate to the intestine and directly exacerbate disease. We propose a multistage model that involves pathological changes to the microbial and immune compartments of both the oral cavity and intestine. The evidence to support this hypothesis is critically evaluated and the relevance to other diseases in which oral bacteria have been implicated (including colorectal cancer and liver disease) are discussed.

The gastrointestinal tract traverses from mouth to anus and harbours diverse communities of bacteria that are specifically evolved to survive in each of the ecological niches along its length. The complex mutualistic relationship between host and microorganism has evolved over many thousands of years[1] and is important in the maintenance of human health[2]. Perturbations to the host–microbiota network in the gastrointestinal tract are linked to numerous localized and systemic diseases, including inflammatory bowel disease (IBD)[3], periodontitis[4], liver disease[5] and colorectal cancer (CRC)[6].

IBD refers to a number of conditions characterized by chronic, patchy and remittent gastrointestinal inflammation. Ulcerative colitis and Crohn's disease are the most common forms of IBD but have distinct aetiologies and manifestations, with ulcerative colitis localizing to the colon and Crohn's disease occurring anywhere along the gastrointestinal tract. IBD has a high prevalence in Western societies and increasing incidence in newly industrialized nations[7]. The pathogenesis of IBD is complex and multifactorial, with genetic, environmental and microbial factors converging to initiate dysregulated immune activation towards the intestinal microbiota[8]. The role of the intestinal microbiota in IBD is an area of intense research and clinical interest, with alterations — particularly to the bacterial microbiota — well documented and specific taxa implicated in pathogenesis[8].

Genomic sequencing has identified intestinal enrichment of oral-associated bacteria as a potential microbial signature in IBD (TABLE 1). As in IBD, dysregulated host–microbiota interactions are crucial to the pathogenesis of many oral diseases, particularly periodontitis. Periodontitis is a chronic, progressing inflammatory condition that can lead to localized bone loss but is additionally linked with multiple systemic diseases[4]. Unresolved inflammation during the progression of periodontitis selects for the outgrowth of virulent bacteria that continue to drive disease[4]. Several systemic markers of inflammation are elevated in patients with periodontitis, which might provide an indirect mechanism by which oral bacteria contribute to systemic diseases[9]. Other mechanisms might include myeloid skewing of haematopoietic progenitor cell differentiation, which can further exacerbate inflammatory disease[10].

However, emerging evidence supports the hypothesis that bacteria might also translocate from the oral cavity to directly exacerbate diseases of distal locations, particularly the intestine. This Perspective highlights an accumulating body of literature that outlines a direct role for oral-associated bacteria in IBD pathogenesis. We explore the altered bacterial and immune compartments in periodontitis and IBD, proposing a model by which oral-associated species might expand in the inflamed intestinal environment to exacerbate inflammation. We highlight oral bacteria that have been associated with other diseases that have a high co-occurrence with IBD, including liver disease and CRC. In our opinion, further research is warranted to characterize the microbial and immune players involved in intestinal disease driven by oral bacteria.

Oral bacteria in the intestine

The microbiotas of the oral cavity, small intestine and large intestine have distinct bacterial compositions[11–13]. Microhabitats with divergent bacterial communities exist within each of these anatomical sites[11,12], which might not be well represented by commonly used sampling methods (BOX 1).

Intestinal bacterial dysbiosis, defined as a substantial change in the microbial population structure accompanied by a pathological change, is common in IBD with general decreases in intestinal bacterial load, diversity and stability often observed[14–16]. Signatures such as a decrease in obligate anaerobic butyrate-producing strains with a concomitant increase in facultative anaerobes have been well described[14–19]. In the following section, we evaluate the evidence suggesting that oral-associated microbial species are enriched in the intestine of patients with IBD. Studies have also implicated non-bacterial microbes and viruses in periodontitis and IBD, particularly certain fungi, including *Candida albicans*[20,21]. However, owing to the relative paucity of studies that have explored the potential role of non-bacterial species in IBD and periodontitis, we have focused this Perspective on the bacterial element of the microbiota. We discuss the increased incidence of bacterial-associated oral disease, particularly periodontitis, within IBD cohorts[22–26] and the potential effects on bacterial composition and function in the oral cavity.

Table 1 | **Oral-associated bacterial species enriched in the intestine of patients with IBD**

Species	Cohort	Method	Sample	Comments	Ref.
Campylobacter concisus	Paediatric CD, Australia	Species-specific PCR	Stool	Enriched in disease	46
Fusobacterium nucleatum	CD and UC, Canada	Isolation, culture, 16S rRNA gene sequencing	Colonic biopsy	Enriched in disease	37
F. nucleatum, *Haemophilus parainfluenzae*, *Veillonella parvula*, *Eikenella corrodens*, *Gemella morbillorum*	Paediatric CD, USA	16S rRNA gene sequencing	Ileal and rectal biopsies, stool	Enriched in disease; associated with disease progression; oral-associated species better represented in biopsy samples than in stool; changes observed upon antibiotic treatment	18
C. concisus	CD and UC, Denmark	Isolation, culture, PCR	Ileal and colonic biopsies	Enriched in disease	47
Streptococcus spp. and *Collinsella* spp. in UC, *Dialister* spp. and *Fusobacterium* spp. in CD	CD and UC, Spain, Belgium, UK and Germany	16S rRNA gene sequencing	Stool	Higher relative abundance of *Streptococcus* spp. in patients with postoperative recurrence when compared to patients who remained in remission	50
Rothia spp., *Streptococcus* spp., *Neisseria* spp., *Prevotella* spp., *Gemella* spp., *Klebsiella pneumoniae*, *Klebsiella aeromobilis*	CD and UC, Japan and USA	16S rRNA gene sequencing, metagenomic database analysis	Stool	Enriched *Klebsiella* spp. in disease and enrichment of virulence genes within these species	51
Veillonella dispar, *Aggregatibacter segnis*, *Campylobacter* spp., *V. parvula*, *H. parainfluenzae*	Paediatric UC, USA and Canada	16S rRNA gene sequencing	Rectal biopsies and stool	Enriched in disease; associated with disease progression; some oral-associated species better represented in biopsy samples than in stool	48
Veillonella spp., *Fusobacterium* spp., *Streptococcus* spp.	PSC, IBD (UC or CD) or PSC with concomitant IBD (PSC–IBD, which includes PSC–UC and PSC–CD), Belgium	16S rRNA gene sequencing	Stool	Abundance is associated with levels of faecal calprotectin	129
Prevotella spp. (including *P. melaninogenica* and *P. tannerae*), *Gemella* spp., *Fusobacterium* spp., *Aggregatibacter* spp., *Corynebacterium* spp.	CD and UC, USA	16S rRNA gene sequencing	Diseased and adjacent healthy colonic biopsies	Enriched in diseased biopsy samples	49
K. pneumoniae, *H. parainfluenzae*,	CD and UC, USA	Metagenomic, metatranscriptomic and metabolite profiling, 16s rRNA gene sequencing	Colonic biopsy, stool	Acylcarnitine and bile acid levels associated with *K. pneumoniae* and *H. parainfluenzae* during dysbiosis	130
Klebsiella spp.	CD and UC, Ireland	16S rRNA gene sequencing	Diseased and adjacent healthy colonic biopsies	*Klebsiella* spp. enriched in disease and has 100% 16S rRNA gene sequence identity to the antibiotic-resistant *Klebsiella* isolated from the oral cavity of a patient with CD in REF.[51]	131
F. nucleatum	CD and UC, China	16S rRNA gene sequencing	Stool	Enriched in disease; associated with disease activity	113

Key papers that show enrichment of oral-associated bacterial species in the intestine of individuals with inflammatory bowel disease (IBD) are included. CD, Crohn's disease; PSC, primary sclerosing cholangitis; rRNA, ribosomal RNA; UC, ulcerative colitis.

In the healthy intestine

Before attempting to draw conclusions on the potential intestinal enrichment of oral-associated bacteria in IBD, it is important to consider the degree to which these bacteria might colonize the healthy intestine. The oral cavity contains a number of microbial niches, which can be divided into the soft buccal, lingual and tongue mucosae and the hard supra and subgingival surfaces of the teeth; these sites have divergent microbiotas[13,27,28] (FIG. 1) defined by varying substrata and nutrient, oxygen, salivary and pH gradients[11]. Unlike the communities in the intestine, the oral bacterial microbiota is remarkably stable over time[29]. In oral mucosal sites such as the tongue dorsum, *Streptococcus* is the most abundant genus, with *Haemophilus*, *Prevotella*, *Veillonella*, *Rothia* and *Neisseria* also prevalent[29]. Some of these organisms act as consortia, forming complex organized structures that are intimately attached to host epithelial cells[30]. The tooth-adherent plaque microbial communities are the most diverse in the oral cavity and form complex multispecies biofilms[11,31]. Physical and metabolic interactions between species within this biofilm, such as the structural linkage between *Corynebacterium* spp., *Streptococcus* spp. and *Actinomyces* spp.[31], are critical for supporting healthy dynamics within the oral microbial community. Many organisms in the oral bacterial microbiota are capable of using nitrate as a terminal electron acceptor during metabolism[13],

outlining the importance of this community in processing host nitrate excreted in the saliva. However, these normally stable community structures in the mouth do change substantially in disease[32].

A study involving the analysis of large faecal and salivary datasets from different countries suggested high levels of colonization of the intestine by oral species, which purportedly account for ~2% of classifiable microbial abundance in faeces[29]. Profiling of microbial single nucleotide variants as a proxy for strain population structure demonstrated that oxygen-tolerant species were highly represented in oral bacteria that had reportedly translocated to the intestine in healthy individuals, including *Fusobacterium* spp., *Streptococcus* spp., *Veillonella* spp. and *Haemophilus* spp.[29]. However, a considerable limitation of this study is the lack of culture-based analysis to determine the presence of viable oral bacteria in the intestine. Numerous oral bacteria are swallowed daily[33,34], which might provide the material that is detected in the genomic content of stool in the absence of live cells. The oral bacteria *Dialister invisus* has, for example, been detected at the DNA level in stool; however, transcriptomic sequencing has determined that it might be transcriptionally inactive, suggestive of a non-growing or non-viable population[14]. However, viable oral-associated species, including *Streptococcus salivarius*, *Veillonella parvula*, *Fusobacterium nucleatum* and *Campylobacter concisus*, have been cultured from healthy human intestinal content[35–37], although the small sample sizes of these studies makes it difficult to conclude the prevalence in the wider population. Further research is required to establish the viability of oral bacteria in the intestine, although these culture-based studies do indicate that the presence of live organisms derived from the oral cavity might not be an isolated occurrence.

The acidic conditions of the stomach and resistance to colonization provided by the intestinal microbiota have largely been thought to prevent extensive live bacterial transmission to more distal parts of the gastrointestinal tract[38,39]. The mechanisms behind colonization resistance are manifold, including a commensal competitive advantage during homeostasis and interactions with the host immune system[39,40]. Murine models have supported the importance of colonization resistance in limiting the colonization of the intestine by oral bacteria[41]. Human oral species colonize the intestine of germ-free mice but these species are largely out-competed following co-housing with mice colonized with faecal microbiota[41]. In this model, however, increased proportions of *Streptococcus* spp. and *Porphyromonas* spp. persisted in the small intestine even upon co-housing, suggesting that this site might permit the survival of some oral bacteria[41] — perhaps because of its closer proximity to the oral cavity and lower microbiota stability in comparison to the colon.

The minimal overlap observed in microbiota composition between faecal and oral samples from multiple cohorts[42–45] suggests that, in health, colonization of the intestine by oral bacteria is limited. However, the presence of viable oral species, such as *F. nucleatum*, indicates that certain bacteria can translocate from the oral cavity to colonize the intestine[35–37].

In the IBD intestine

We now discuss the clinical data that describes the expansion of oral-associated bacteria in the intestine as an emerging microbial signature in IBD (TABLE 1). *C. concisus* and *F. nucleatum* were amongst the first oral bacteria implicated in IBD, in 2010 and 2011, respectively[37,46]. Both of these bacteria are enriched in IBD as detected not only by genomic analysis of stool but also by culture from intestinal biopsy samples[37,47] (TABLE 1). These findings suggest that viable *C. concisus* and *F. nucleatum* can translocate to the intestine to colonize the mucosal niche and that this phenomenon is associated with IBD. However, as the sample sizes of these initial studies were small, did not span multiple geographic locations and were conducted at a single time-point, the degree to which they could implicate *C. zconcisus* and *F. nucleatum* in IBD of a wider demographic was limited.

The rapid advancement of sequencing technology has provided a wealth of information that can associate specific taxa with disease over large multinational cohorts. The characterization of bacterial composition via 16S rRNA gene sequencing has been hugely popular in this regard and has provided further evidence of the association of intestinal enrichment of oral-associated bacteria with IBD (TABLE 1). This signature was first well defined in treatment-naive paediatric patients with Crohn's disease[18] in whom *F. nucleatum*, *Haemophilus parainfluenzae* and *V. parvula* were found to be enriched in the mucosa and stool[18]. Notably, other oral taxa were associated with disease severity; for example, *Veillonella* spp. and *Rothia mucilaginosa* were enriched in patients with deep ulcers[18]. Intestinal expansion of oral bacteria in treatment-naive IBD was later observed in paediatric ulcerative colitis[48]. Longitudinal analysis illustrated that severe disease in this ulcerative colitis cohort was associated with the presence of oral taxa, including *Veillonella dispar*, *V. parvula*, *H. parainfluenzae* and *Campylobacter* spp.[48]. Oral species were better represented in the mucosa than in stool – with *Fusobacterium* spp. found at twice the abundance in intestinal tissue biopsy samples than in stool[48]. Some oral bacteria might therefore highly colonize the inflamed intestinal mucosa. Indeed, *Prevotella* spp., *Streptococcus* spp., *Veillonella* spp. and *Fusobacterium* spp. are enriched in diseased colonic biopsy samples when compared to adjacent healthy tissue of an adult IBD cohort[49]. Faecal samples from diverse IBD cohorts have also illustrated intestinal enrichment of oral bacteria. *Fusobacterium* spp. are among those enriched in Crohn's disease, forming part of a microbial signature that accurately classifies disease; however, increased taxonomic resolution is needed to accurately describe oral strains[50].

Intestinal enrichment of *Klebsiella* spp., particularly *Klebsiella pneumoniae*, has been associated with IBD in multiple studies (TABLE 1). *Klebsiella* spp. are members of the *Proteobacteria* family and are considered important opportunistic pathogens of

Box 1 | Sampling challenges for defining microhabitat-specific microbiota composition

Distinct microhabitats with divergent microbiota compositions exist within the oral cavity, small intestine and large intestine. Although the microbiota consists of multiple forms of life, including bacteria, fungi, protozoa and viruses, the bacterial component has been the most well characterized and is therefore the focus of this article. Owing to ease of sampling, saliva and faeces are often used to determine the composition of the oral and intestinal microbiotas, respectively. However, these types of samples are not representative of the distinct microbial niches at these sites, with the salivary microbiota largely a combination of bacteria derived from the tongue dorsum and buccal mucosa and the faecal microbiota mostly representative of the colonic microbial community[43,132]. To determine localized changes in microbiota composition it is therefore preferable to sample sites directly as with plaque scrapings or intestinal mucosal biopsies. However, this approach introduces potential sampling bias, particularly for intestinal biopsy samples, for which only a small proportion of the tissue is analysed. The appropriateness of sampling methods must be considered when attempting to characterize localized microbiota composition.

multiple tissues. As such, their presence in the oral cavity has largely been thought to be indicative of systemic illness. However, *Klebsiella* spp. have been identified in healthy human saliva[51,52], although substantial strain variability exists when compared to isolates from the saliva of individuals with IBD[51] (BOX 2). The oral cavity could therefore act as a reservoir for opportunistic pathogens able to colonize the intestine, which might be more prevalent in individuals with chronic illnesses such as IBD.

The genomic sequencing approaches used in many of these studies have allowed for the association between the intestinal enrichment of oral taxa and IBD to be made in large longitudinal datasets over multiple sizable cohorts. As described previously, these studies must be complemented by culture-based analysis to determine the presence of viable bacteria as has been done for *C. concisus* and *F. nucleatum*[37,47]. However, the finding that oral bacteria are highly enriched in IBD biopsy samples that are cleared of faecal material suggests that these bacteria might actively colonize the intestinal mucosal niche. A direction for future studies should be meta-transcriptional analysis to determine the active functional pathways that might be

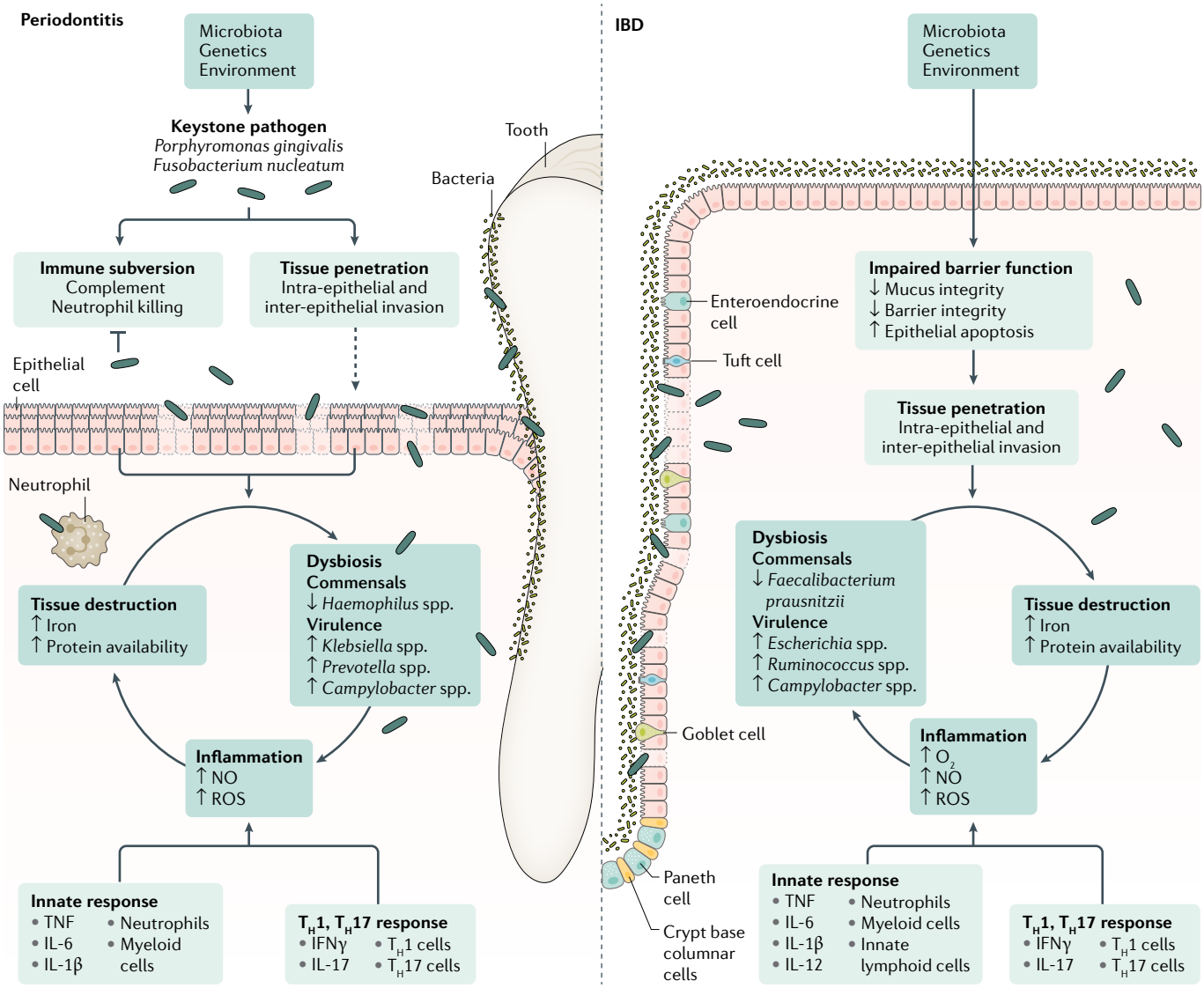

Fig. 1 | **Commonalities in the inflammatory pathology of the gingiva in periodontitis and the intestine in IBD.** In both periodontitis and inflammatory bowel disease (IBD), multiple factors converge to initiate disease. In periodontitis, the expansion of keystone pathogens able to penetrate gingival tissue and evade aspects of host immunity contributes to the emergence of dysbiosis[6]. The response to the emerging dysbiosis includes inflammation mediated by IL-1β, IL-6 and TNF, orchestrated by gingival structural cells and immune cells[70]. This environment promotes T helper 1 (T_H1) and T_H17 responses, which increase levels of reactive oxygen species (ROS) and nitric oxide (NO), contributing to further tissue destruction and T_H17 involvement in the establishment of chronic disease[70]. The subsequent increase in available degraded host proteins and haem facilitates the further expansion of virulent bacteria, including *Klebsiella* spp., *Prevotella* spp. and *Campylobacter* spp.[4]. In IBD, impaired barrier function, characterized by a reduction in the integrity of the mucus and epithelial barrier and an increase in epithelial apoptosis, is an early pathological event[3]. This promotes the dissemination of microbes into the underlying tissue[3]. As in periodontitis, this drives a pathological feedback loop between a dysbiotic microbiota and the host immune system[8]. In IBD, an influx of activated granulocytes increases O_2 concentrations, partially through the release of ROS. Pro-inflammatory cytokines drive T_H1 and T_H17 responses that promote further tissue damage and chronic disease[3]. This inflammatory environment supports the outgrowth of virulent bacterial strains, such as *Escherichia coli*, *Ruminococcus* spp. and *Campylobacter* spp., at the expense of obligate anaerobic commensals, including *Faecalibacterium prausnitzii*[3].

involved in the pathogenesis of oral bacteria in the intestine during IBD.

The oral microbiota in IBD

The potential intestinal enrichment of oral-associated bacteria in IBD promotes discussion on changes to the oral bacterial community that might be implicated in turn. IBD is associated with a bacterially driven oral disease, namely periodontitis[22–25]. Periodontitis is a chronic inflammatory disease of the tooth-supporting tissues (BOX 3), during which species diversity and bacterial load in the subgingival biofilm are substantially increased[32]. In patients with active periodontal disease, periodontitis severity and biofilm abundance are reportedly higher in individuals who also have IBD[25]. Genetic risk-association studies have identified some commonalities in pathways implicated in both diseases, including inflammasome-mediated inflammation[53,54]. However, further research is warranted, particularly in individuals who seem to have periodontitis and IBD as comorbidities, to provide insight on genetic susceptibility to both diseases and the pathways important in this association.

Despite the apparent association between periodontitis and IBD, data regarding the oral microbiota in IBD is limited. Salivary oral dysbiosis at baseline in IBD has been associated with local and systemic inflammatory markers[55,56]. *Veillonella* spp. were substantially enriched in the saliva of two IBD cohorts, correlating with increased levels of circulating lymphocytes[55,56]. *Prevotella* spp. were also enriched in the saliva of an IBD cohort and positively correlated with increased levels of salivary IL-1β[56]. *Prevotella* spp. expand during periodontitis and upregulate the expression of virulence-associated genes[57,58]. Enrichment of pathways involved in oxidative stress and virulence has also been documented in the salivary IBD microbiota[55], which might contribute to localized and systemic inflammation. The correlation of oral dysbiosis with local and systemic immune markers indicates that the interaction between the oral microbiota and immune system in IBD might be disrupted, even in the absence of obvious oral disease.

To determine compositional changes in IBD that are relevant in periodontitis it is preferable to characterize the tooth-adherent microbiota (which drives the pathology of periodontitis) rather than the total salivary microbiota (BOX 1); however, few data are available regarding this community in patients with IBD. At baseline, *Capnocytophaga* spp. and *Rothia* spp. were enriched in the subgingival biofilm of a paediatric Crohn's disease cohort[59]. Treatment of this cohort with an anti-TNF biologic agent that improved clinical outcomes reduced the biofilm abundance of *Fusobacterium* spp., *Porphyromonas* spp. and *Prevotella* spp.[59]. Mechanisms underlying anti-TNF-induced changes in the oral biofilm and how this contributed to improved clinical outcome are probably linked to the anti-inflammatory properties of this regime. Enhanced oral dysbiosis might contribute to the increased periodontitis prevalence and severity amongst individuals with IBD[22–25].

Although preliminary evidence supports enhanced oral dysbiosis at baseline and during periodontitis in IBD, higher powered longitudinal studies that consider confounding clinical, demographic and geographic factors are required. If accompanied by paired analysis at a sub-species resolution of the intestinal microbiota within the same individual, the possibility of oral seeding of the intestinal microbiota could be characterized. Combining this approach with longitudinal analysis of clinical data would determine if an association exists between oral dysbiosis, oral disease, colonization of the intestine by oral-associated bacteria and intestinal inflammation in IBD.

Oral and intestinal inflammation

At oral and intestinal sites, the interaction between the immune system, epithelium and microbiota is crucial to maintain proper tissue function and homeostasis. In periodontitis and IBD, dysregulated interactions between these compartments underlie chronic inflammatory pathology[3,4] (BOX 3; FIG. 1). In the following section, we describe the oral and intestinal immune landscape in periodontitis and IBD to highlight potential shared mechanisms that promote dysbiosis.

Oral inflammation in periodontitis

A particularly vulnerable site in the oral cavity is the junctional epithelium, a thin undifferentiated layer within the gingival crevice that attaches the mucosa to the tooth and contacts the tooth-adherent biofilm[60] (FIG. 1). To protect this highly vulnerable site, the gingival immune system is specialized for continued surveillance, activity and defence[60]. Neutrophils constitute a key defensive measure in the gingiva, controlling the microbiota through phagocytosis, degranulation, secretion of antimicrobial peptides and the formation of neutrophil extracellular traps[61].

Multiple factors, including genetic susceptibility, microbiota composition and lifestyle are thought to converge to initiate and promote periodontitis[4]. As described in BOX 3, feedback between the host immune system and a dysbiotic biofilm is central to disease pathogenesis[4] (FIG. 1). The early stages of the disease are often characterized by destructive inflammation orchestrated by IL-1β, IL-6 and TNF signalling that recruits myeloid cells, which, when activated, release reactive oxygen species and nitric oxide[62,63]. T helper 1 (T_H1)-mediated immunity has been implicated in oral inflammation in periodontitis[64]. However, the importance of T_H17-associated responses in chronic periodontitis has also become apparent[62,65] (FIG. 1), with expansion of IL-17$^+$ T memory

Box 2 | Sub-species level variability within the oral bacterial microbiota

The substantial genotype and phenotype diversity of the bacterial microbiota at the subspecies level has become apparent. A meta-analysis of salivary and faecal microbiomes (the collective genomes of the microorganisms) from healthy individuals documented a large amount of genetic diversity between individuals, whereby approximately half of the microbial genomic content was reported to be unique to each sample and partially attributed to the presence of multiple sub-species within individuals[44]. This genomic diversity is reflected in oral disease-associated bacteria, with subsequent consequences on virulence. As well characterized by Atarashi et al., phylogenetically distinct human, mouse and environmental *Klebsiella pneumoniae* strains vary in their ability to promote colonic T helper 1 responses in a murine model[51]. Genes predicted to encode components of the T6SS (Type VI Secretion System) and enzymes involved in long-chain fatty acid uptake were enriched in the T helper 1-inducing strains and in patients with inflammatory bowel disease (IBD), suggesting a potential role for these pathways in *K. pneumoniae*-mediated intestinal inflammation[51]. Strain-dependent variability in epithelial cell invasion and induction of pro-inflammatory cytokine release has also been characterized for *Fusobacterium nucleatum*[37] and *Campylobacter concisus*[133]. *C. concisus* genomic variants that contain secreted toxins and T4SS (Type IV Secretion System) homologous proteins have been identified and preliminarily associated with IBD and intestinal colonization, respectively[90,92]. Determining the genetic diversity of oral-associated bacteria implicated in IBD and how this diversity translates to virulence will be crucial for understanding the mechanisms by which these microbes might be involved in pathogenesis.

Box 3 | **Feedback between microbial dysbiosis and the host inflammatory response in periodontitis**

The pathology of periodontitis is attributed to a feedforward loop between host inflammation that drives the selective expansion of dysbiotic communities and the ability of these communities to exacerbate inflammation. The central microbial players in this pathological interaction are keystone pathogens, crucial to initially subvert the host immune response and instigate an inflammatory environment[127]. *Porphyromonas gingivalis* is the best-defined keystone pathogen in periodontitis and has multiple mechanisms by which it can subvert host immunity[127]. Other periodontal microbes, such as *Fusobacterium nucleatum*, have shown a similar capacity to subvert aspects of host immunity and might also be important in disease progression[134]. Importantly, this initial impairment of host defence facilitates the outgrowth of oral biofilm, which exacerbates inflammation and tissue destruction[127]. The ongoing inflammatory environment favours the outgrowth of inflammophilic bacteria, such as *Prevotella* spp.[4], that are present in healthy tissue but hold a selective advantage in the inflammatory state[4]. The diseased inflammatory environment can also induce transcriptional changes to promote virulence in species that are normally commensal in eubiosis as with the upregulation of iron uptake systems by *Streptococcus oralis* in periodontitis[57]. The ability of periodontal pathogens to initiate and exacerbate destructive tissue inflammation might be important in their role in inflammatory bowel disease.

cells further contributing to neutrophil activation and inflammatory bone loss[65]. In accordance with some of these cells having a circulating phenotype, activated T_H17 cells are enriched in the blood of patients with periodontitis[66].

Oral inflammation in IBD

Preliminary investigations have shown changes to the oral immune compartment in patients with IBD that might contribute to enhanced oral disease in this population. Salivary inflammatory markers, including IL-1β, IL-6 and TNF, were enriched in a Crohn's disease cohort at baseline and correlated with oral disease manifestation[67,68]. Baseline enrichment for TGFβ1 and nitric oxide has also been observed in the saliva of individuals with Crohn's disease and ulcerative colitis[69,70]. The early inflammatory response might be upregulated in the IBD oral cavity, which might contribute to the reported increased severity of oral disease in some IBD cohorts[22–26]. However, the underlying mechanisms and the subsequent effect on microbial and immune compartments are unclear. Interestingly, reduced salivary neutrophil activation and defective neutrophil chemotaxis in patients with IBD and periodontal disease have been observed[71,72]. Indeed, defects in neutrophil recruitment and function are documented in the intestinal mucosa in Crohn's disease[73]. Given the importance of neutrophils in the control of oral pathogens, potential differences in neutrophil recruitment and activity in the oral mucosa of patients with IBD could contribute to changes in the oral microbial community and disease in this population. This factor, in combination with an increased concentration of early destructive pro-inflammatory cytokines, could create a perfect storm for the enrichment of virulent bacteria in the oral cavity in IBD.

Intestinal inflammation in IBD

As in the oral cavity, the epithelial barrier forms the interface between microbial and host immune interactions in the intestine. The gut-resident immune system, which resides within and between the intestinal epithelium, is comprised of vastly complex innate and adaptive arms, which continually balance surveillance, response and tolerance to ensure protection against pathogens without hypersensitivity to commensal species and innocuous factors[74].

Epithelial and immune pathology in IBD is complex and diverse but, as with periodontitis, is driven by feedback between a dysbiotic microbiota and the host immune system that is influenced by multiple genetic and environmental factors[3] (FIG. 1). An important early event in IBD pathology is thought to be the disruption of epithelial barrier integrity[75]. Subsequent penetration of microbes into underlying tissue might then promote destructive host inflammatory responses that drive microbial dysbiosis in IBD[3]. This response is characterized by an influx of granulocytes and macrophages that exacerbate pro-inflammatory cytokine signalling[3]. As in periodontitis, T_H1-associated and T_H17-associated responses seem to underlie chronic pathology (FIG. 1), which is partially attributed to dysregulation of regulatory T cells[3,76].

Shared inflammatory mechanisms

Given that the host immune response contributes to the expansion of virulent bacteria in both periodontitis and IBD, shared inflammatory mechanisms might promote the intestinal expansion of oral disease-associated bacteria in IBD (FIG. 1). Increasing concentrations of nitrate during inflammation are of particular interest in this regard. Intestinal concentrations of nitrate, a by-product of the host inflammatory response, increase rapidly in murine colitis models[77]. Here, nitrate respiratory-sufficient Enterobacteriaceae spp. quickly outcompete obligate anaerobic commensals to exacerbate disease[77]. The oral bacterial microbiota is particularly enriched for pathways involved in nitrate reduction[13]. As with colitis, elevated nitrate concentrations in a murine periodontitis model facilitate the expansion of nitrate reductase-capable bacteria, including *Proteobacteria* spp. and *Veillonella* spp.[78]. Transcriptome analysis of the subgingival microbiota in patients with periodontitis has revealed the increased expression of nitrate reductase genes, suggesting the importance of this pathway in the expansion of virulent bacteria[79]. Intermediary and end products of the nitrate reduction pathway are enriched in the oral cavity during clinical periodontitis and in the saliva, serum and urine in IBD and correlate with disease activity[69,70,80–82], which suggests that this pathway might be upregulated in IBD. Several of the oral-associated species enriched in the IBD intestine, including *Veillonella* spp.[83], are known nitrate reducers, which might confer a selective advantage in the inflamed intestine.

The T_H17 inflammatory axis has been implicated in both periodontitis and IBD[3,62,65,76] (FIG. 1). The ability of oral migratory T_H17 cells to drive intestinal inflammation in mice has been demonstrated, highlighting a shared intermucosal inflammatory mechanism between the oral cavity and intestine[84]. In this study, the authors conclusively demonstrated transmigration of T_H17 cells from the oral lymph to the intestinal lamina propria using photoconvertible reporter mice and parabiosis experiments[84]. The ability of these oral migratory T_H17 cells to drive intestinal inflammation in an IL-1β-dependent fashion was demonstrated upon transfer into susceptible mice treated with oral *Klebsiella* spp.[84]. These findings clearly implicate both the microbial and immune compartments in the intermucosal inflammatory axis between the oral cavity and intestine. Activated T_H17 cells are enriched in the blood of patients with periodontitis, although the potential systemic consequences of this are unclear[66]. However, the increased level of circulating T_H17 in clinical periodontitis does raise the

question as to whether these cells migrate to the intestine and drive inflammation as has been demonstrated in mice[84].

Although similarities exist in the inflammatory environments in periodontitis and IBD that could contribute to the intestinal expansion of oral disease-associated bacteria in IBD, substantial differences between these diseases must also be considered in the context of disease heterogeneity, particularly in IBD. For example, in ulcerative colitis but largely not in Crohn's disease, the role of T_H2 responses has become evident, with elevated levels of IL-13, IL-15 and IL-33 thought to play a role in pathology[85]. However, a role for these cytokines and T_H2-associated immunity has not been well characterized in periodontitis. Therefore, the intestinal expansion of oral disease-associated bacteria might be more prominent and relevant in certain forms of IBD. The finding that T_H17 cells can migrate from the oral cavity during periodontitis and exacerbate murine colitis[84] highlights the fact that shared immune mechanisms might underlie both diseases. Continued work characterizing epithelial and immune profiles that associate with the intestinal expansion of oral disease-associated bacteria in IBD would help delineate the host immune factors important in this phenomenon.

A multistage model

We have highlighted the apparent oral dysbiosis, increased susceptibility to oral diseases (including periodontitis) and intestinal enrichment of oral-associated bacteria in IBD. Parallels between the inflammatory environments of periodontitis and IBD that promote the outgrowth of oral-associated bacteria and disruption to the commensal microbiota have been discussed. In many complex multifactorial diseases, theoretical models outlining events that increase the risk of pathogenesis have been described to improve our understanding of the disease. These models include a multi-hit model for IBD, whereby the convergence of multiple defects in intestinal homeostasis (such as genetic susceptibility, barrier defects and dysbiosis) is required for disease pathogenesis[86]. We now propose a model by which oral disease-associated bacteria might expand in the intestine during IBD and outline the potential pathological consequences.

This proposed model includes the following stages: first, enhanced abundance and virulence of oral disease-associated bacteria and a reduction in intestinal colonization resistance; second, translocation of these bacteria to the intestine; and third, colonization of the intestine by these oral disease-associated bacteria and exacerbation of disease in IBD (FIG. 2). Importantly, unlike a multi-hit model, we propose that these events must happen in sequence for the final outcome to occur.

An experimental basis for this model was described by Kitamoto et al.[84], in whose study periodontitis worsened intestinal disease in a murine colitis model. Oral and intestinal expansion of oral disease-associated bacteria, namely *Klebsiella* spp. and *Enterobacter* spp., exacerbated colitis through innate and adaptive inflammatory mechanisms involving both oral and intestinal immunity. The microbial and immune axis described in this pioneering study provides a framework to explore other experimental and clinical data regarding the multistage model.

Stage 1

Oral expansion of disease-associated bacteria in IBD. The first stage of this model depends on the generation and expansion of

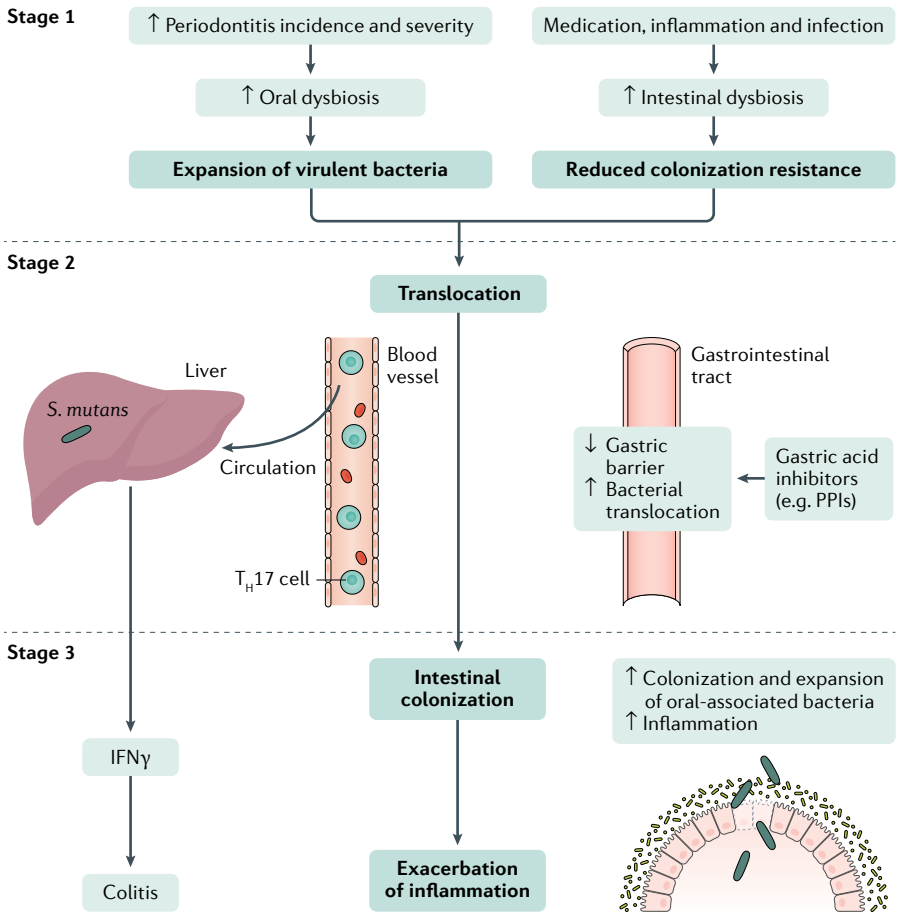

Fig. 2 | **The multistage model describing the intestinal expansion of oral-associated bacteria in IBD.** The first stage is characterized by an increased abundance and virulence of oral bacteria[75]. The increased incidence and severity of periodontitis in patients with inflammatory bowel disease (IBD), accompanied by exacerbated dysbiosis and inflammation, might support this expansion of virulent bacteria. This step coincides with a reduction in intestinal colonization resistance, which can be caused by multiple factors, including inflammatory relapse and medications such as antibiotics[20,48,100,101]. The second stage describes how oral-associated bacteria might then translocate to the intestine via the circulation or through the gastrointestinal tract. In mouse models, intravenous *Streptococcus mutans* localizes to the liver and exacerbates colitis though IFNγ signalling[104]. Other oral bacteria, such as *Fusobacterium nucleatum*, can survive intracellularly in immune cells, which might facilitate the circulatory route[106]. Oral reactive T helper 17 (T_H17) cells that arise during periodontitis also travel in the blood to the intestinal mucosa[75]. Other oral bacteria might travel via the gastrointestinal tract. This route of transmission is enhanced by a reduction in the gastric barrier, which can occur following the use of gastric acid secretion inhibitors such as proton-pump inhibitors (PPIs)[109–113]. Oral-associated bacteria that are well adapted to an inflammatory environment might then be able to colonize the disrupted intestinal environment and interact with host epithelial and immune modules to exacerbate inflammation[75].

disease-associated bacteria in the oral cavity (FIG. 2). As described, periodontitis increases the load of virulent bacteria in the oral cavity. We have highlighted the increased incidence and severity of periodontitis, oral dysbiosis and increased biofilm in IBD (see earlier). In the periodontitis–colitis model described by Kitamoto et al.[84], the intestinal expansion of oral bacteria was dependent on prior periodontitis, demonstrating the importance of oral dysbiosis for translocation of these bacteria. Although this model suggests oral to intestinal transmission of oral disease-associated bacteria, evidence of direct translocation is not conclusive.

The presence of genetically identical microbial strains in each site strongly indicates oral to intestinal translocation. Although this idea has not been widely explored in IBD, salivary and faecal microbiota single nucleotide variant analysis from other large multi-cohort databases suggests that strains able to translocate are enriched for oral disease-associated bacteria, including *F. nucleatum*, and that these strains are associated with diseases such as CRC[29] (BOX 4). Indeed, identical oral and intestinal *F. nucleatum* strains have been recorded in CRC[87]. In the context of IBD, identical strains of *C. concisus*, enriched in both the oral and intestinal mucosa in IBD[47], have been identified[47,88,89]. This finding has determined an oral *C. concisus* genomic variant, containing a 6-base pair insertion into the secreted enterotoxin B homologue *Csep1* gene (*Csep1-6bpi*), which is potentially enriched in IBD[88,90,91]. An enteric strain containing the *Csep1-6bpi* gene has been isolated from an individual with ulcerative colitis[92]; however, further work is required to determine the effect of *Csep1-6bpi* on *C. concisus* pathogenicity, virulence and intestinal colonization. Metagenomic and metatranscriptomic analysis of oral and intestinal samples from larger cohorts at fine taxonomic resolution will be necessary to determine the presence and enrichment of identical oral bacterial strains at both sites in IBD, which might also define microbial adaptations that promote oral–intestinal transmission.

Disruption to the intestinal microbiota reduces colonization resistance. The second component of the initial phase of the multistage model postulates that intestinal microbiota disruption is required for colonization by oral-associated bacteria (FIG. 2). Although the healthy intestinal microbiota is largely thought to outcompete oral strains (see earlier section), disruption to the intestinal environment permits intestinal enrichment of oral disease-associated bacteria following periodontitis as demonstrated by Kitamoto et al.[84]. Multiple factors might reduce intestinal colonization resistance in IBD, including medication (FIG. 2).

Commonly used medications, including proton-pump inhibitors (PPIs)[93] and antibiotics[94,95], can cause long-term alterations to intestinal microbiota composition. Antibiotics are frequently used in the treatment of severe periodontitis and following periodontal surgery[96]. Enrichment of oral taxa in the intestine, including *R. mucilaginosa*[48] and a tenfold increase in ileal Fusobacteriaceae[18], following antibiotic use in IBD has been observed. Antibiotics also alter the oral microbiota, including enrichment of *Fusobacterium* spp. in the saliva[94], which might further promote intestinal translocation and colonization. Intestinal translocation and colonization of oral bacteria might be exacerbated by the development of antibiotic resistance as demonstrated with an oral Crohn's disease *K. pneumoniae* isolate able to colonize the murine intestine and exacerbate colitis following antibiotic administration[51]. Although the association between antibiotic use and IBD is unclear, antibiotic use in early life is consistently implicated in the development of paediatric IBD[97]. The contribution of oral disease-associated bacteria in this context is not known; however, these bacteria seem to be enriched in the intestine of paediatric patients with IBD[18,48].

Stage 2

Translocation to the intestine. Stage 2 in the proposed multistage model involves translocation of oral disease-associated bacteria to the intestine. The route of translocation has not been conclusively determined and might vary depending on the bacterium involved. Bacteraemia, the presence of bacteria in the circulation, has been argued to occur during periodontitis owing to intimate contact of biofilm with damaged tissue, with some evidence that bacteraemia is enhanced by periodontal procedures[98]. In a mouse model, oral *Streptococcus mutans* (of which specific salivary serotypes are enriched in IBD) aggravates colitis following intravenous but not gastrointestinal travel[99]. However, the worsening of colitis in this model was driven by IFNγ-mediated inflammation via localization to the liver and not the intestine[99] (FIG. 2). Bacteraemia is not reported in some experimental periodontitis models[84] and is infrequent in hospitalized patients with IBD[100]. However, the ability of periodontal pathogens, such as *F. nucleatum*, to evade the immune system and survive intracellularly in immune cells[101] makes this route of transmission hypothetically feasible. Indeed, the enrichment of *F. nucleatum* in tumours from locations outside of the gastrointestinal tract, such as mammary tissue[102], suggests that the circulation might be the primary means of travel for this bacterium.

An alternative route of transmission is via the gastrointestinal tract (FIG. 2). Interestingly, disruption of the gastric barrier might increase intestinal colonization by oral bacteria (FIG. 2). When colonized

Box 4 | The role of oral bacteria in other systemic diseases

Oral bacteria have been increasingly implicated in multiple systemic diseases via diverse mechanisms[134,135]. Two diseases of particular interest in the context of inflammatory bowel disease (IBD) are primary sclerosing cholangitis (PSC) and colorectal cancer (CRC). PSC is characterized by inflammation of the bile ducts, which can progress to severe liver fibrosis and liver cirrhosis[136]. The aetiology of PSC is unknown but this disease has a high co-occurrence with IBD, which is present in 60–80% of patients with PSC[137]. Changes in the oral microbiota were apparent in a small paediatric PSC cohort, including an increase in *Prevotella* spp.[138]. Intestinal enrichment of oral bacteria has been reported in PSC, with increased abundances of *Rothia mucilaginosa*, *Veillonella parvula*, *V. dispar* and *Streptococcus* spp.[139]. These oral bacteria might be important in the pathology of both IBD and PSC. Whether these bacteria play a role because of systemic signalling pathways involved in the gut–liver axis or because of localization of oral bacteria to the liver (as demonstrated with *S. mutans*[99]) is yet to be determined.

CRC is one of the most common forms of cancer, to which multiple factors, including diet, lifestyle and genetic disposition, are thought to contribute. IBD has been identified as a major risk factor in the development of CRC[140]. The role of the microbiota in CRC has become an area of substantial research interest[141], with oral dysbiosis and periodontitis associated with CRC[142,143]. Several oral bacteria are enriched in mucosal CRC samples, including *Fusobacterium nucleatum*, *Haemophilus* spp. and *Rothia* spp.[143]. Indeed, substantial evidence has implicated a mechanistic role for *F. nucleatum* in CRC, including binding to epithelial residues upregulated in CRC[144], promotion of epithelial proliferation[116] and inhibition of immune cell-mediated toxicity towards tumours[126]. These mechanisms might also be implicated in the role of *F. nucleatum* in IBD.

with human faecal microbiota, germ-free mice that are genetically altered to have a higher gastric pH have increased intestinal colonization of some oral-associated species such as *S. salivarius*[103]. Sequencing of faecal microbiota from patients who use drugs that increase gastric pH, including PPIs, has determined an enrichment of oral bacteria[104–107]. These bacteria include *R. mucilaginosa*, *S. salivarius*, *H. parainfluenzae*, *S. mutans* and *V. parvula*, the levels of which positively correlate with the inflammatory marker calprotectin[104–107]. Longitudinal analysis has demonstrated an increased abundance of *Streptococcus* spp. and *Enterobacteria* spp. after PPI use, although a higher taxonomic classification is needed to assign oral strains[108]. PPIs are also directly toxic to certain intestinal commensals[93], which might promote oral bacterial colonization through the disruption of colonization resistance. Interestingly, PPI use might alter the oral microbiota as demonstrated by increased periodontal *Fusobacterium* spp. abundance in a small healthy cohort[109]. PPIs and other gastric acid inhibitors are preliminarily associated with worsening disease in patients with IBD, with one H2 receptor antagonist seeming to double the risk of surgery or hospitalization in a Crohn's disease cohort[110–112]. Determining whether intestinal expansion of oral bacteria is related to gastric acid inhibitor-induced exacerbation of IBD requires longitudinal microbial and clinical analysis of this cohort.

Stage 3

Having discussed the evidence for the translocation of oral bacteria to the intestine in IBD, we now highlight the potential direct mechanisms by which these bacteria might be causative agents of intestinal inflammation. As such, the final stage of the multistage model suggests that, once in the intestine, the inflammatory environment in IBD permits the expansion of oral disease-associated bacteria that hold a selective advantage in this state (see earlier section), through which they might then exacerbate inflammation and contribute to IBD (FIG. 3).

We explore this idea through three oral-associated bacteria, *F. nucleatum*, *Klebsiella* spp. and *C. concisus* (FIG. 3). All are enriched in the IBD intestine and both *F. nucleatum* and *K. pneumoniae* exacerbate colitis in mouse models[51,84,113]. Although these taxa are phylogenetically diverse, commonalities exist in their possible pathological interaction with the host intestine.

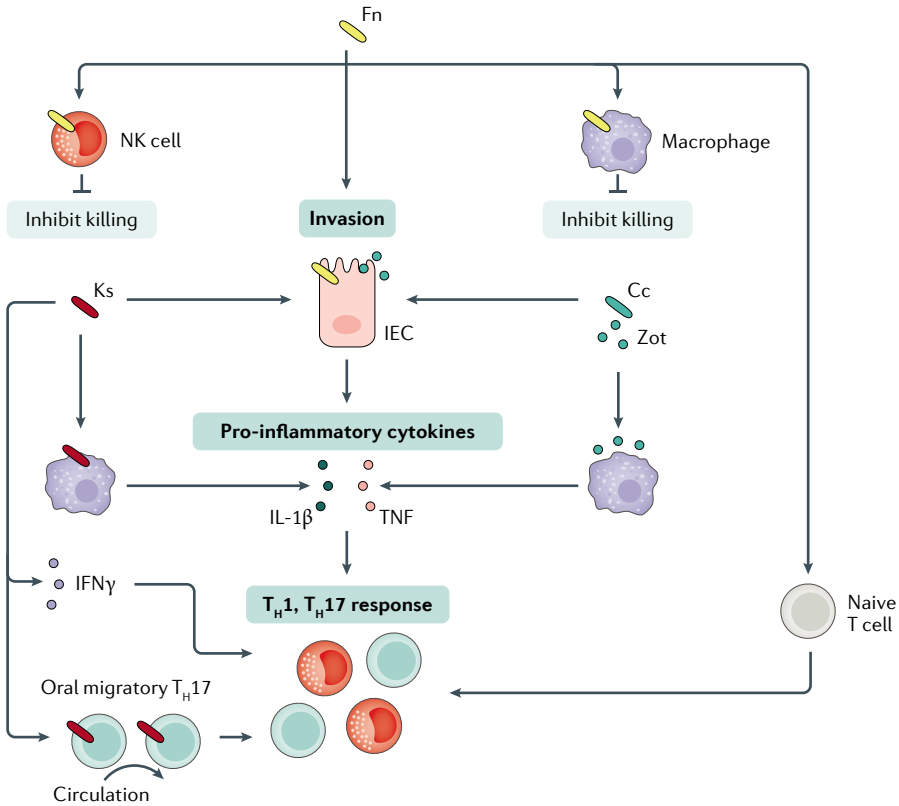

Fig. 3 | **Mechanisms by which oral-associated bacteria might mediate intestinal inflammation.** The oral-associated *Klebsiella* spp., *Fusobacterium nucleatum* and *Campylobacter concisus* have multiple mechanisms by which they might promote intestinal inflammation. All three species have been reported to invade intestinal epithelial cells and drive pro-inflammatory cytokine release[39,57,97,119–125]. Pro-inflammatory cytokine release is augmented by the zonula occludens toxin (Zot) released by *C. concisus*[124,129]. Both *Klebsiella* spp. and *C. concisus* interact with macrophages to promote the release of IL-1β and TNF, respectively[75,129]. *F. nucleatum* also can subvert aspects of innate immunity, with the ability to reduce the killing capacity of macrophages and natural killer (NK) cells[106]. *Klebsiella* spp. and *F. nucleatum* can also promote pro-inflammatory T helper 1 (T_H1) and T_H17 responses. *Klebsiella* spp. drives the accumulation of colonic T_H1 cells via IFNγ in murine models[51]. *Klebsiella* spp. can also activate T_H17 cells that have migrated from the oral cavity during periodontitis in a murine model[75]. *F. nucleatum* directly promotes the differentiation of T_H1 and T_H17 cells from naive $CD4^+$ T cells in a murine model[57]. IEC, intestinal epithelial cell.

Colonization of the intestine. We propose that one such similarity is the interaction with the intestinal epithelium to disrupt barrier integrity and instigate inflammation (FIG. 3). The increased abundance of oral disease-associated bacteria, such as *F. nucleatum*, in mucosal intestinal samples in IBD suggests adaption to this niche[48]. Indeed, *K. pneumoniae* invades the colonic mucus layer in mono-colonized mice[114]. *F. nucleatum*, *K. pneumoniae* and *C. concisus* invade human intestinal epithelial cell lines in a strain-dependent fashion (BOX 2), with intestinal IBD isolates being substantially more invasive[37,89,113,115–121]. These microbes disrupt junction protein expression and localization, which might increase epithelial barrier permeability to exacerbate disease[37,89,113,115–120]. The induction of pro-inflammatory cytokines, including IL-8, IL-1β and TNF, from human intestinal epithelial cells by *F. nucleatum*, *K. pneumoniae* and *C. concisus* might promote further inflammatory pathology and tissue destruction[120,122–124] (FIG. 3). This pathology might be augmented in the case of *C. concisus* through the secreted zonula occludens toxin (Zot)[120,125] (FIG. 3).

Exacerbation of disease. Following *F. nucleatum*, *Klebsiella* spp. and *C. concisus* disruption to the epithelial barrier, these microbes might interact with the gut-associated immune system to drive disease (FIG. 3). In the innate immune arm, *Klebsiella* spp. activate intestinal mononuclear phagocyte IL-1β signalling to exacerbate colitis in a mouse model[84]. *C. concisus* also activates macrophage inflammasome signalling, partially mediated by the toxin

zot, to enhance pro-inflammatory TNF and IL-8 signalling[125]. However, *F. nucleatum* can subvert aspects of host innate immunity, which is particularly relevant in CRC (BOX 4). *F. nucleatum* blocks natural killer cell killing capacity through direct binding to an inhibitory receptor[126] and survives inside macrophages whilst reducing their capacity to induce lymphocyte-mediated killing[101] (FIG. 3). The importance of host immune subversion for the expansion and pathology of oral disease-associated bacteria has been characterized in periodontitis[127] but is not known in the context of IBD.

F. nucleatum, *Klebsiella* spp. and *C. concisus* might also promote intestinal pathology through interactions with adaptive immunity (FIG. 3). *K. pneumoniae* induces the colonic accumulation of T_H1 cells, supported by IFNγ signalling, in genetically susceptible mice[51]. A correlation between the enrichment of *K. pneumoniae* genes involved in T_H1 induction and IBD suggests that this finding might be relevant in a human setting[51] (BOX 2). A novel adaptive immune axis between the oral cavity and intestine was characterized in the Kitamoto et al. periodontitis–colitis model[84]. In this model, T_H17 cells that arise in the oral cavity during periodontitis migrate to the intestine (FIG. 2) and, upon recognition of oral disease-associated bacteria, including *Klebsiella* spp., instigate the T_H17-associated and T_H1-associated responses that drive colitis[84]. Although this finding has yet to be investigated in a human setting, clinical periodontitis increases circulating T_H17 cell numbers[66]. *F. nucleatum* is also able to induce T_H1 and T_H17 differentiation from $CD4^+$ T cells to exacerbate colitis in a mouse model[113]. Given the importance of T_H1 and T_H17 inflammation in IBD, the ability of oral-associated bacteria to drive expansion of this compartment provides further evidence of their possible role in pathology.

Intestinal colonization and exacerbation of inflammation by oral-associated bacteria is probably dependent on many complex interactions with host microbial, epithelial and immune compartments. Characterizing these interactions and the effect of exogenous factors, such as medication, will be crucial in understanding the mechanisms underlying the role of oral disease-associated bacteria in IBD.

Conclusions

The implication of oral-associated bacteria in IBD highlights the importance of the axis between the oral and intestinal microbial and immune compartments. The direct mechanism (described in this Perspective) through which oral bacteria might exacerbate intestinal inflammation in IBD does not preclude the contribution of periodontitis-associated systemic inflammation described elsewhere[9,10]. The involvement of oral bacteria in other diseases, such as CRC and liver cirrhosis, suggests that this axis might be relevant in settings outside of IBD (BOX 4). Indeed, analysis of stool metagenomic sequencing from 34 independent studies investigating multiple diseases, such as rheumatoid arthritis, type 2 diabetes mellitus and IBD, identified enrichment of several oral-associated species, including *F. nucleatum*, *K. pneumoniae* and *Streptococcus gordonii*, in non-healthy samples[128]. Certain oral taxa, such as *F. nucleatum*, seem to be involved in multiple systemic diseases. Such microbes should be a priority for future research to identify differences in strain, host genetics and environment that might dictate how oral bacteria can promote systemic disease.

Future research should focus on clarifying our understanding of the pathological role of the oral microbiota in IBD and to translate these findings into clinical benefit. Correlation of the oral and intestinal microbiotas at a high taxonomic resolution with clinical phenotypes in longitudinal datasets of large multinational IBD cohorts, could help further identify the oral bacterial signatures associated with disease. Functional analysis will be crucial to identify the pathways and mechanisms of virulence enriched in oral bacteria in IBD. Moreover, these approaches should be combined with experimental models, such as that used by Kitamoto et al.[84], to deconstruct the possible causative role of oral bacteria in intestinal inflammation. This approach might provide targets for therapeutic intervention to limit the expansion of virulent oral bacteria during inflammation. Our multistage model provides several therapeutic avenues whereby the initial oral expansion of virulent bacteria, their intestinal translocation or their intestinal colonization could be targeted. Although the efficacy of these approaches will probably be dependent on the multiple complex and distinct factors that underlie disease aetiology, targeting oral-associated bacteria might alleviate disease in a proportion of individuals with IBD and other associated diseases.

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1. Davenport, E. R. et al. The human microbiome in evolution. *BMC Biol.* **15**, 1–12 (2017).
2. Flint, H. J., Scott, K. P., Louis, P. & Duncan, S. H. The role of the gut microbiota in nutrition and health. *Nat. Rev. Gastroenterol. Hepatol.* **9**, 577–589 (2012).
3. Ni, J., Wu, G. D., Albenberg, L. & Tomov, V. T. Gut microbiota and IBD: causation or correlation? *Nat. Rev. Gastroenterol. Hepatol.* **14**, 573–584 (2017).
4. Lamont, R. J., Koo, H. & Hajishengallis, G. The oral microbiota: dynamic communities and host interactions. *Nat. Rev. Microbiol.* **16**, 745–759 (2018).
5. Tilg, H., Cani, P. D. & Mayer, E. A. Gut microbiome and liver diseases. *Gut* **65**, 2035–2044 (2016).
6. Wong, S. H. & Yu, J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 690–704 (2019).
7. Ng, S. C. et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* **390**, 2769–2778 (2018).
8. de Souza, H. S. P. & Fiocchi, C. Immunopathogenesis of IBD: current state of the art. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 13–27 (2016).
9. Hajishengallis, G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat. Rev. Immunol.* **15**, 30–44 (2015).
10. Chavakis, T., Mitroulis, I. & Hajishengallis, G. Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation. *Nat. Immunol.* **20**, 802–811 (2019).
11. Mark Welch, J. L., Dewhirst, F. E. & Borisy, G. G. Biogeography of the oral microbiome: the site-specialist hypothesis. *Annu. Rev. Microbiol.* **73**, 335–358 (2019).
12. Donaldson, G. P., Lee, S. M. & Mazmanian, S. K. Gut biogeography of the bacterial microbiota. *Nat. Rev. Microbiol.* **14**, 20–32 (2016).
13. Lloyd-Price, J. et al. Strains, functions and dynamics in the expanded Human Microbiome Project. *Nature* **550**, 61–66 (2017).
14. Schirmer, M. et al. Dynamics of metatranscription in the inflammatory bowel disease gut microbiome. *Nat. Microbiol.* **3**, 337–346 (2018).
15. Halfvarson, J. et al. Dynamics of the human gut microbiome in inflammatory bowel disease. *Nat. Microbiol.* **2**, 17004 (2017).
16. Vandeputte, D. et al. Quantitative microbiome profiling links gut community variation to microbial load. *Nature* **551**, 507–511 (2017).
17. Andoh, A. et al. Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. *J. Gastroenterol.* **46**, 479–486 (2011).
18. Gevers, D. et al. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* **15**, 382–392 (2014).
19. Ohkusa, T. et al. Fusobacterium varium localized in the colonic mucosa of patients with ulcerative colitis stimulates species-specific antibody. *J. Gastroenterol. Hepatol.* **17**, 849–53 (2002).
20. Sokol, H. et al. Fungal microbiota dysbiosis in IBD. *Gut* **66**, 1039–1048 (2017).
21. Peters, B. A., Wu, J., Hayes, R. B. & Ahn, J. The oral fungal mycobiome: characteristics and relation to periodontitis in a pilot study. *BMC Microbiol.* **17**, 157 (2017).
22. She, Y. Y. et al. Periodontitis and inflammatory bowel disease: a meta-analysis. *BMC Oral. Health* **20**, 67 (2020).
23. Singhal, S. et al. The role of oral hygiene in inflammatory bowel disease. *Dig. Dis. Sci.* **56**, 170–175 (2011).
24. Vavricka, S. R. et al. Periodontitis and gingivitis in inflammatory bowel disease: a case-control study. *Inflamm. Bowel Dis.* **19**, 2768–2777 (2013).
25. Habashneh, R. A., Khader, Y. S., Alhumouz, M. K., Jadallah, K. & Ajlouni, Y. The association between inflammatory bowel disease and periodontitis among

Jordanians: a case-control study. *J. Periodontal. Res.* **47**, 293–298 (2012).
26. Koutsochristou, V. et al. Dental caries and periodontal disease in children and adolescents with inflammatory bowel disease: a case-control study. *Inflamm. Bowel Dis.* **21**, 1839–1846 (2015).
27. Xu, X. et al. Oral cavity contains distinct niches with dynamic microbial communities. *Environ. Microbiol.* **17**, 699–710 (2015).
28. Caselli, E. et al. Defining the oral microbiome by whole-genome sequencing and resistome analysis: the complexity of the healthy picture. *BMC Microbiol.* **20**, 120 (2020).
29. Schmidt, T. S. et al. Extensive transmission of microbes along the gastrointestinal tract. *eLife* **8**, e42693 (2019).
30. Wilbert, S. A., Mark Welch, J. L. & Borisy, G. G. Spatial ecology of the human tongue dorsum microbiome. *Cell Rep.* **30**, 4003–4015.e3 (2020).
31. Welch, J. L. M., Rossetti, B. J., Rieken, C. W., Dewhirst, F. E. & Borisy, G. G. Biogeography of a human oral microbiome at the micron scale. *Proc. Natl Acad. Sci. USA* **113**, E791–E800 (2016).
32. Curtis, M. A., Diaz, P. I. & Van Dyke, T. E. The role of the microbiota in periodontal disease. *Periodontology 2000* **83**, 14–25 (2020).
33. Sender, R., Fuchs, S. & Milo, R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol.* **14**, e1002533 (2016).
34. Humphrey, S. P. & Williamson, R. T. A review of saliva: normal composition, flow, and function. *J. Prosthet. Dent.* **85**, 162–169 (2001).
35. van den Bogert, B. et al. Diversity of human small intestinal Streptococcus and Veillonella populations. *FEMS Microbiol. Ecol.* **85**, 376–388 (2013).
36. Kirk, K. F. et al. Molecular epidemiology and comparative genomics of Campylobacter concisus strains from saliva, faeces and gut mucosal biopsies in inflammatory bowel disease. *Sci. Rep.* **8**, 1902 (2018).
37. Strauss, J. et al. Invasive potential of gut mucosa-derived Fusobacterium nucleatum positively correlates with IBD status of the host. *Inflamm. Bowel Dis.* **17**, 1971–1978 (2011).
38. Giannella, R. A., Broitman, S. A. & Zamcheck, N. Gastric acid barrier to ingested microorganisms in man: studies in vivo and in vitro. *Gut* **13**, 251–256 (1972).
39. Lawley, T. D. & Walker, A. W. Intestinal colonization resistance. *Immunology* **138**, 1–11 (2013).
40. Sequeira, R. P., McDonald, J. A. K., Marchesi, J. R. & Clarke, T. B. Commensal Bacteroidetes protect against Klebsiella pneumoniae colonization and transmission through IL-36 signalling. *Nat. Microbiol.* **5**, 304–313 (2020).
41. Li, B. et al. Oral bacteria colonize and compete with gut microbiota in gnotobiotic mice. *Int. J. Oral. Sci.* **11**, 10 (2019).
42. Segata, N. et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biol.* **13**, R42 (2012).
43. Eren, A. M., Borisy, G. G., Huse, S. M. & Mark Welch, J. L. Oligotyping analysis of the human oral microbiome. *Proc. Natl Acad. Sci. USA* **111**, E2875–2884 (2014).
44. Tierney, B. T. et al. The landscape of genetic content in the gut and oral human microbiome. *Cell Host Microbe* **26**, 283–295.e8 (2019).
45. Carr, V. R. et al. Abundance and diversity of resistomes differ between healthy human oral cavities and gut. *Nat. Commun.* **11**, 693 (2020).
46. Man, S. M. et al. Campylobacter concisus and other Campylobacter species in children with newly diagnosed Crohn's disease. *Inflamm. Bowel Dis.* **16**, 1008–1016 (2010).
47. Kirk, K. F., Nielsen, H. L., Thorlacius-Ussing, O. & Nielsen, H. Optimized cultivation of Campylobacter concisus from gut mucosal biopsies in inflammatory bowel disease. *Gut Pathog.* **8**, 27 (2016).
48. Schirmer, M. et al. Compositional and temporal changes in the gut microbiome of pediatric ulcerative colitis patients are linked to disease course. *Cell Host Microbe* **24**, 600–610.e4 (2018).
49. Dinakaran, V. et al. Identification of specific oral and gut pathogens in full thickness colon of colitis patients: implications for colon motility. *Front. Microbiol.* **10**, 3220 (2019).
50. Pascal, V. et al. A microbial signature for Crohn's disease. *Gut* **66**, 813–822 (2017).
51. Atarashi, K. et al. Ectopic colonization of oral bacteria in the intestine drives T_H1 cell induction and inflammation. *Science* **358**, 359–365 (2017).
52. Baker, J. L. et al. Klebsiella and Providencia emerge as lone survivors following long-term starvation of oral microbiota. *Proc. Natl Acad. Sci. USA* **116**, 8499–8504 (2019).
53. Sayad, A. et al. Genetic susceptibility for periodontitis with special focus on immune-related genes: a concise review. *Gene Rep.* **21**, 100814 (2020).
54. Graham, D. B. & Xavier, R. J. Pathway paradigms revealed from the genetics of inflammatory bowel disease. *Nature* **578**, 527–539 (2020).
55. Xun, Z., Zhang, Q., Xu, T., Chen, N. & Chen, F. Dysbiosis and ecotypes of the salivary microbiome associated with inflammatory bowel diseases and the assistance in diagnosis of diseases using oral bacterial profiles. *Front. Microbiol.* **9**, 1136 (2018).
56. Said, H. S. et al. Dysbiosis of salivary microbiota in inflammatory bowel disease and its association with oral immunological biomarkers. *DNA Res.* **21**, 15–25 (2015).
57. Szafrański, S. P. et al. Functional biomarkers for chronic periodontitis and insights into the roles of Prevotella nigrescens and Fusobacterium nucleatum; a metatranscriptome analysis. *NPJ Biofilms Microbiomes* **1**, 15017 (2015).
58. Kumar, P. S., Griffen, A. L., Moeschberger, M. L. & Leys, E. J. Identification of candidate periodontal pathogens and beneficial species by quantitative 16S clonal analysis. *J. Clin. Microbiol.* **43**, 3944–3955 (2005).
59. Kelsen, J. et al. Alterations of the subgingival microbiota in pediatric Crohn's disease studied longitudinally in discovery and validation cohorts. *Inflamm. Bowel Dis.* **21**, 2797–2805 (2015).
60. Moutsopoulos, N. M. & Konkel, J. E. Tissue-specific immunity at the oral mucosal barrier. *Trends Immunol.* **39**, 276–287 (2018).
61. Dutzan, N., Konkel, J. E., Greenwell-Wild, T. & Moutsopoulos, N. M. Characterization of the human immune cell network at the gingival barrier. *Mucosal Immunol.* **9**, 1163–1172 (2016).
62. Pan, W., Wang, Q. & Chen, Q. The cytokine network involved in the host immune response to periodontitis. *Int. J. Oral. Sci.* **11**, 30 (2019).
63. Herrero, E. R. et al. Dysbiotic biofilms deregulate the periodontal inflammatory response. *J. Dent. Res.* **97**, 547–555 (2018).
64. Hajishengallis, G., Shakhatreh, M.-A. K., Wang, M. & Liang, S. Complement receptor 3 blockade promotes IL-12-mediated clearance of porphyromonas gingivalis and negates its virulence in vivo. *J. Immunol.* **179**, 2359–2367 (2007).
65. Dutzan, N. et al. A dysbiotic microbiome triggers TH17 cells to mediate oral mucosal immunopathology in mice and humans. *Sci. Transl. Med.* **10**, eaat0797 (2018).
66. Suárez, L. J., Vargas, D. E., Rodrïguez, A., Arce, R. M. & Roa, N. S. Systemic Th17 response in the presence of periodontal inflammation. *J. Appl. Oral. Sci.* **28**, e20190490 (2020).
67. Aleksandra Nielsen, A., Nederby Nielsen, J., Schmedes, A., Brandslund, I. & Hey, H. Saliva Interleukin-6 in patients with inflammatory bowel disease. *Scand. J. Gastroenterol.* **40**, 1444–1448 (2005).
68. Szczeklik, K., Owczarek, D., Pytko-Polończyk, J., Kęsek, B. & Mach, T. H. Proinflammatory cytokines in the saliva of patients with active and nonactive Crohn's disease. *Pol. Arch. Med. Wewn.* **122**, 200–208 (2012).
69. Rezaie, A. et al. Alterations in salivary antioxidants, nitric oxide, and transforming growth factor-β1 in relation to disease activity in Crohn's disease patients. *Ann. N. Y. Acad. Sci.* **1091**, 110–122 (2006).
70. Rezaie, A. et al. Study on the correlations among disease activity index and salivary transforming growth factor-β1 and nitric oxide in ulcerative colitis patients. *Ann. N. Y. Acad. Sci.* **1095**, 305–314 (2007).
71. Lamster, I. B., Rodrick, M. L., Sonis, S. T. & Falchuk, Z. M. An analysis of peripheral blood and salivary polymorphonuclear leukocyte function, circulating immune complex levels and oral status in patients with inflammatory bowel disease. *J. Periodontol.* **53**, 231–238 (1982).
72. van Dyke, T. E., Dowell, V. R., Offenbacher, S., Snyder, W. & Hersh, T. Potential role of microorganisms isolated from periodontal lesions in the pathogenesis of inflammatory bowel disease. *Infect. Immun.* **53**, 671–677 (1986).
73. Fournier, B. M. & Parkos, C. A. The role of neutrophils during intestinal inflammation. *Mucosal Immunol.* **5**, 354–366 (2012).
74. Mowat, A. M. & Agace, W. W. Regional specialization within the intestinal immune system. *Nat. Rev. Immunol.* **14**, 667–685 (2014).
75. Antoni, L., Nuding, S., Wehkamp, J. & Stange, E. F. Intestinal barrier in inflammatory bowel disease. *World J. Gastroenterol.* **20**, 1165–1179 (2014).
76. Friedrich, M., Pohin, M. & Powrie, F. Cytokine networks in the pathophysiology of inflammatory bowel disease. *Immunity* **50**, 992–1006 (2019).
77. Winter, S. E. et al. Host-derived nitrate boosts growth of E. coli in the inflamed gut. *Science* **339**, 708–711 (2013).
78. Nassar, M. et al. GAS6 is a key homeostatic immunological regulator of host-commensal interactions in the oral mucosa. *Proc. Natl Acad. Sci. USA* **114**, E337–E346 (2017).
79. Duran-Pinedo, A. E. et al. Community-wide transcriptome of the oral microbiome in subjects with and without periodontitis. *ISME J.* **8**, 1659–1672 (2014).
80. Goggins, M. G. et al. Increased urinary nitrite, a marker of nitric oxide, in active inflammatory bowel disease. *Mediators Inflamm.* **10**, 69–73 (2001).
81. Avdagić, N. et al. Nitric oxide as a potential biomarker in inflammatory bowel disease. *Bosn. J. Basic Med. Sci.* **13**, 5–9 (2013).
82. Ali, O. T. et al. Nitrite and nitrate levels of gingival crevicular fluid and saliva in subjects with gingivitis and chronic periodontitis. *J. Oral Maxillofac. Res.* **5**, e5 (2014).
83. Hyde, E. R. et al. Metagenomic analysis of nitrate-reducing bacteria in the oral cavity: implications for nitric oxide homeostasis. *PLoS One* **9**, e88645 (2014).
84. Kitamoto, S. et al. The intermucosal connection between the mouth and gut in commensal pathobiont-driven colitis. *Cell* **182**, 447–462.e14 (2020).
85. Bamias, G. & Cominelli, F. Role of type 2 immunity in intestinal inflammation. *Curr. Opin. Gastroenterol.* **31**, 471–476 (2015).
86. Maloy, K. J. & Powrie, F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. *Nature* **474**, 298–306 (2011).
87. Komiya, Y. et al. Patients with colorectal cancer have identical strains of Fusobacterium nucleatum in their colorectal cancer and oral cavity. *Gut* **68**, 1335–1337 (2018).
88. Mahendran, V. et al. Delineation of genetic relatedness and population structure of oral and enteric Campylobacter concisus strains by analysis of housekeeping genes. *Microbiology* **161**, 1600–1612 (2015).
89. Ismail, Y. et al. Investigation of the enteric pathogenic potential of oral Campylobacter concisus strains isolated from patients with inflammatory bowel disease. *PLoS One* **7**, e38217 (2012).
90. Chung, H. K. L. et al. Genome analysis of Campylobacter concisus strains from patients with inflammatory bowel disease and gastroenteritis provides new insights into pathogenicity. *Sci. Rep.* **6**, 38442 (2016).
91. Wang, Y. et al. Campylobacter concisus genomospecies 2 is better adapted to the human gastrointestinal tract as compared with Campylobacter concisus genomospecies 1. *Front. Physiol.* **8**, 543 (2017).
92. Liu, F. et al. Genomic analysis of oral Campylobacter concisus strains identified a potential bacterial molecular marker associated with active Crohn's disease. *Emerg. Microbes Infect.* **7**, 64 (2018).
93. Maier, L. et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* **555**, 623–628 (2018).
94. Zaura, E. et al. Same exposure but two radically different responses to antibiotics: resilience of the salivary microbiome versus long-term microbial shifts in feces. mBio **6**, e01693-15 (2015).
95. Shaw, L. P. et al. Modelling microbiome recovery after antibiotics using a stability landscape framework. *ISME J.* **13**, 1845–1856 (2019).
96. Oswal, S., Ravindra, S., Sinha, A. & Manjunath, S. Antibiotics in periodontal surgeries: A prospective randomised cross over clinical trial. *J. Indian. Soc. Periodontol.* **18**, 570–574 (2014).
97. Bernstein, C. N. Is antibiotic use a cause of IBD worldwide? *Inflamm. Bowel Dis.* **26**, 448–449 (2020).
98. Horliana, A. C. R. T. et al. Dissemination of periodontal pathogens in the bloodstream after periodontal procedures: a systematic review. *PLoS One* **9**, e98271 (2014).
99. Kojima, A. et al. Aggravation of inflammatory bowel diseases by oral streptococci. *Oral. Dis.* **20**, 359–366 (2014).

100. Goren, I. et al. Risk of bacteremia in hospitalised patients with inflammatory bowel disease: a 9-year cohort study. *United European Gastroenterol. J.* **8**, 195–203 (2020).
101. Xue, Y. et al. Indoleamine 2,3-dioxygenase expression regulates the survival and proliferation of Fusobacterium nucleatum in THP-1-derived macrophages. *Cell Death Dis.* **9**, 355 (2018).
102. Parhi, L. et al. Breast cancer colonization by Fusobacterium nucleatum accelerates tumor growth and metastatic progression. *Nat. Commun.* **11**, 3295 (2020).
103. Seedorf, H. et al. Bacteria from diverse habitats colonize and compete in the mouse gut. *Cell* **159**, 253–266 (2014).
104. Zhernakova, A. et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science* **352**, 565–569 (2016).
105. Imhann, F. et al. Proton pump inhibitors affect the gut microbiome. *Gut* **65**, 740–748 (2016).
106. Jackson, M. A. et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut* **65**, 749–756 (2016).
107. Vich Vila, A. et al. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. *Nat. Commun.* **11**, 362 (2020).
108. Hojo, M. et al. Gut microbiota composition before and after use of proton pump inhibitors. *Dig. Dis. Sci.* **63**, 2940–2949 (2018).
109. Mishiro, T. et al. Oral microbiome alterations of healthy volunteers with proton pump inhibitor. *J. Gastroenterol. Hepatol.* **33**, 1059–1066 (2018).
110. Schwartz, N. R. M. et al. Proton pump inhibitors, H2 blocker use, and risk of inflammatory bowel disease in children. *J. Pediatr. Pharmacol. Ther.* **24**, 489–496 (2019).
111. Juillerat, P. et al. Drugs that inhibit gastric acid secretion may alter the course of inflammatory bowel disease. *Aliment. Pharmacol. Ther.* **36**, 239–247 (2012).
112. Shah, R., Richardson, P., Yu, H., Kramer, J. & Hou, J. K. Gastric acid suppression is associated with an increased risk of adverse outcomes in inflammatory bowel disease. *Digestion* **95**, 188–193 (2017).
113. Liu, H. et al. Fusobacterium nucleatum exacerbates colitis by damaging epithelial barrier and inducing aberrant inflammation. *J. Dig. Dis.* **21**, 385–398 (2020).
114. Caballero, S. et al. Distinct but spatially overlapping intestinal niches for vancomycin-resistant enterococcus faecium and carbapenem-resistant Klebsiella pneumoniae. *PLoS Pathog.* **11**, e1005132 (2015).
115. Rubinstein, M. R. et al. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. *Cell Host Microbe* **14**, 195–206 (2013).
116. Rubinstein, M. R. et al. Fusobacterium nucleatum promotes colorectal cancer by inducing Wnt/β-catenin modulator Annexin A1. *EMBO Rep.* **20**, e47638 (2019).
117. Maroncle, N., Balestrino, D., Rich, C. & Forestier, C. Identification of Klebsiella pneumoniae genes involved in intestinal colonization and adhesion using signature-tagged mutagenesis. *Infect. Immun.* **70**, 4729–4734 (2002).
118. Hsu, C. R. et al. Klebsiella pneumoniae translocates across the intestinal epithelium via rho GTPase-and phosphatidylinositol 3-kinase/Akt-dependent cell invasion. *Infect. Immun.* **83**, 769–779 (2015).
119. Lee, I. A. & Kim, D. H. Klebsiella pneumoniae increases the risk of inflammation and colitis in a murine model of intestinal bowel disease. *Scand. J. Gastroenterol.* **46**, 684–693 (2011).
120. Deshpande, N. P. et al. Campylobacter concisus pathotypes induce distinct global responses in intestinal epithelial cells. *Sci. Rep.* **6**, 34288 (2016).
121. Kaakoush, N. O. et al. The pathogenic potential of Campylobacter concisus strains associated with chronic intestinal diseases. *PLoS One* **6**, e29045 (2011).
122. Tang, B. et al. Fusobacterium nucleatum-induced impairment of autophagic flux enhances the expression of proinflammatory cytokines via ROS in Caco-2 cells. *PLoS One* **11**, e0165701 (2016).
123. Dharmani, P., Strauss, J., Ambrose, C., Allen-Vercoe, E. & Chadee, K. Fusobacterium nucleatum infection of colonic cells stimulates MUC2 mucin and tumor necrosis factor alpha. *Infect. Immun.* **79**, 2597–2607 (2011).
124. Pope, J. L. et al. Microbial colonization coordinates the pathogenesis of a Klebsiella pneumoniae infant isolate. *Sci. Rep.* **9**, 3380 (2019).
125. Mahendran, V. et al. Examination of the effects of Campylobacter concisus zonula occludens toxin on intestinal epithelial cells and macrophages. *Gut Pathog.* **8**, 18 (2016).
126. Gur, C. et al. Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity* **42**, 344–355 (2015).
127. Hajishengallis, G., Darveau, R. P. & Curtis, M. A. The keystone-pathogen hypothesis. *Nat. Rev. Microbiol.* **10**, 717–725 (2012).
128. Gupta, V. K. et al. A predictive index for health status using species-level gut microbiome profiling. *Nat. Commun.* **11**, 4635 (2020).
129. Vieira-Silva, S. et al. Quantitative microbiome profiling disentangles inflammation- and bile duct obstruction-associated microbiota alterations across PSC/IBD diagnoses. *Nat. Microbiol.* **4**, 1826–1831 (2019).
130. Lloyd-Price, J. et al. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* **569**, 655–662 (2019).
131. Ryan, F. J. et al. Colonic microbiota is associated with inflammation and host epigenomic alterations in inflammatory bowel disease. *Nat. Commun.* **11**, 1512 (2020).
132. Tang, Q. et al. Current sampling methods for gut microbiota: a call for more precise devices. *Front. Cell Infect. Microbiol.* **10**, 151 (2020).
133. Man, S. M. et al. Host attachment, invasion, and stimulation of proinflammatory cytokines by Campylobacter concisus and other non-Campylobacter jejuni Campylobacter species. *J. Infect. Dis.* **202**, 1855–1865 (2010).
134. Brennan, C. A. & Garrett, W. S. Fusobacterium nucleatum — symbiont, opportunist and oncobacterium. *Nat. Rev. Microbiol.* **17**, 156–166 (2019).
135. Mohammed, H. et al. Oral dysbiosis in pancreatic cancer and liver cirrhosis: a review of the literature. *Biomedicines* **6**, 115 (2018).
136. Karlsen, T. H., Folseraas, T., Thorburn, D. & Vesterhus, M. Primary sclerosing cholangitis – a comprehensive review. *J. Hepatol.* **67**, 1298–1323 (2017).
137. De Vries, A. B., Janse, M., Blokzijl, H. & Weersma, R. K. Distinctive inflammatory bowel disease phenotype in primary sclerosing cholangitis. *World J. Gastroenterol.* **21**, 1956–1971 (2015).
138. Iwasawa, K. et al. Dysbiosis of the salivary microbiota in pediatric-onset primary sclerosing cholangitis and its potential as a biomarker. *Sci. Rep.* **8**, 5480 (2018).
139. Bajer, L. et al. Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis. *World J. Gastroenterol.* **23**, 4548–4558 (2017).
140. Sebastian, S. et al. Colorectal cancer in inflammatory bowel disease: results of the 3rd ECCO pathogenesis scientific workshop (I). *J. Crohns Colitis* **8**, 5–18 (2014).
141. Ternes, D. et al. Microbiome in colorectal cancer: how to get from meta-omics to mechanism? *Trends Microbiol.* **28**, 401–423 (2020).
142. Kim, G. W. et al. Periodontitis is associated with an increased risk for proximal colorectal neoplasms. *Sci. Rep.* **9**, 7528 (2019).
143. Flemer, B. et al. The oral microbiota in colorectal cancer is distinctive and predictive. *Gut* **67**, 1454–1463 (2018).
144. Abed, J. et al. Fap2 mediates Fusobacterium nucleatum colorectal adenocarcinoma enrichment by binding to tumor-expressed Gal-GalNAc. *Cell Host Microbe* **20**, 215–225 (2016).

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