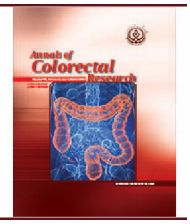
Review Article

Ann Colorectal Res 2021;9(2):47-50.

Annals of Colorectal Research
(Iranian Journal of Colorectal Research)



Oral Bacteria and Colorectal Pathology

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Received: 05-06-2021
Accepted: 11-07-2021

Abstract

Context: The oral cavity and colon are distantly located anatomically and are hence colonized by entirely divergent microbes. The mouth is affected by several pathologies, and so is the colon. Therefore, it is quite natural to investigate the potential connection between poor oral health and colorectal pathologies.
Evidence Acquisition: This article is a small attempt to identify the oral microbiota, how they translocate to the colorectal area, and how they give rise to pathology. PubMed indexed journals relating to this topic were screened and shortlisted to construct this article.
Results: The organisms generally responsible for oral diseases, particularly *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, have been found in colon disorders resulting in intestinal dysbiosis and ultimately leading to colorectal cancer.
Conclusion: If the disease pathogenesis is well understood, it will open new ways to prevent or treat colorectal pathologies. However, further studies are needed in this arena.

Keywords: Colorectal cancer, Dysbiosis, Microbiota, Periodontitis

Please cite this paper as:
Nair V. Oral Bacteria and Colorectal Pathology. *Ann Colorectal Res*. 2021;9(2):47-50. doi: 10.30476/ACRR.2021.91493.1105.

Context

The human mouth is home to a wide variety of microbial populations (1, 2). Scientists are constantly endeavoring to identify these organisms. However, only about 57% of the oral bacterial species have been christened (3). The mouth is affected by several pathologies, the most common among them being periodontitis, gingivitis, and dental caries. The organisms commonly held responsible for these oral diseases are *Porphyromonas gingivalis, Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans, Streptococcus mutans,* and *Lactobacillus spp.* (4-9). Again, several of these organisms like *Porphyromonas gingivalis, Tannerella forsythia, Capnocytophaga gingivalis,* and *Prevotella melaninogenica* have been linked with oral and esophageal cancer (10-12). Some researchers have reported that diseases in the oral cavity like periodontitis have links with several other forms of cancers in the human body (13, 14). Thus, a natural curiosity arises to know whether these oral microbes have any role to play in the colorectal area. Several bacteria, viruses, fungi, and protozoa (the intestinal microbiota) exist in the colon of healthy subjects, maintaining a balance or homeostasis in which there is no overgrowth of any particular pathogen (15). A disruption of this balance is called “dysbiosis”

(16). Dysbiosis is allied with ailments like obesity, diabetes, inflammatory bowel disease, colorectal adenomas, and colorectal cancer (CRC) (17). CRC is common in humans and has been attributed to environmental factors primarily and to a minor extent to certain hereditary or predisposing diseases like inflammatory bowel disease (18). This again highlights the role of oral and colonic microbiota in CRC pathogenesis (19).

Evidence Acquisition

Nearly 100 articles were screened by searching both online and offline in journals that were either PubMed indexed or were not. Half of these articles were eliminated as they were not related directly to the topic. This work is an assimilation of the gathered data along with two decades of experience of the author.

Results

Helicobacter pylori, Streptococcus gallolyticus, and *Escherichia coli* were initially considered the causative agents of CRC (20). However, the advancement of technology in the form of 16S rRNA pyrosequencing analysis has widened our knowledge of many more microbes (21). Tissue samples collected from the intestinal mucosa of patients with CRC showed reduced counts of *Blautia, Bifidobacterium,* and *Faecalibacterium,* besides elevated levels of *Fusobacterium, Peptostreptococcus,* and *Porphyromonas spp.* (which are the oral microbiota) (17-21). The literature indicates reductions in beneficial bacteria like *Bifidobacteria, Roseburia,* and *Faecalibacterium prausnitzii* along with elevations in the counts of 'bad' oral bacteria like *Campylobacter, Enterococcaceae,* and *Fusobacterium spp.* (22, 23).

With the motive of delving deeper into the role of microbiota, Tjalsma et al. proposed the "bacterial driver–passenger" hypothesis in 2012 (24). As per this hypothesis, some bacterial species that have pro-tumor traits (drivers) inflict damage to the DNA of the intestinal epithelial cells and initiate the development of CRC. As the microbial balance is disturbed, there is a decrease in beneficial bacteria and an upsurge in the numbers of opportunistic pathogens (passengers). The latter elicit a pro-inflammatory response and cause direct epithelial damage. The drivers cause DNA damage, the proliferation of the epithelium, and cell apoptosis. Together, the 'drivers and passengers' play a critical role in the development of CRC.

Oral Bacteria and Intestinal Dysbiosis

With an understanding that oral microbes are involved in CRC, let us now focus on some studies (25, 26). In a study by Kato et al. (2018), C57BL/6 mice were fed *P. gingivalis* W83 twice weekly for five weeks. The results showed increased counts of *Ruminococcus* and decreased *Dorea* species compared to controls (27). Similarly, Sato et al. fed *P. gingivalis* and *Prevotella intermedia* to DBA/1J mice and reported endotoxemia, systemic inflammation, disruption of the intestinal barrier, and intestinal dysbiosis (28). In a study on human subjects with liver cirrhosis, it was concluded that 54% of the intestinal microbes had originated from the oral cavity, which is a consequence of intestinal dysbiosis (29). These bacteria mainly were *Veillonella* and *Streptococcus spp.*, with *Fusobacterium, Aggregatibacter,* and *Megasphaera spp.* also being seen. Lourenco et al. analyzed the fecal samples of subjects with oral diseases (14 had gingivitis while 23 had chronic periodontitis). Compared to the healthy control group, the oral disease group showed raised levels of *Firmicutes, Euryarcheota, Proteobacteria,* and *Verrucomicrobiota* and a diminished count of *Bacteroidetes* (30). In a study on subjects with cirrhosis, Bajaj et al. highlighted the importance of periodontal therapy by demonstrating an improvement in intestinal dysbiosis, with increased levels of commensal bacteria (*Ruminococcaceae* and *Lachnospiraceae*) and decreased counts of opportunistic pathogens like *Enterobacteriaceae* (31). Based on the studies mentioned above, one can conclude that the oral bacteria *P. gingivalis* and *A. actinomycetemcomitans* have a role to play in colorectal pathologies.

Oral Bacteria and CRC

Nakatsu et al. detected abundant oral bacteria like *Fusobacterium, Gemella, Peptostreptococcus,* and *Parvimonas* in patients with CRC (32). Hale et al., in their study on patients with colon adenomas, found elevated numbers of *Actinomyces, Corynebacterium, Haemophilus, Mogibacterium,* and *Porphyromonas* as compared to the controls (33). Similar findings were reported by Liang et al. and Flemer et al. (34-36). The prophetic role of the oral microbiota in CRC pathogenesis received a shot in the arm by a report submitted by Momen-Heravi et al. (37). They found that individuals with severe chronic periodontitis (<17 teeth) showed a higher risk for CRC development along with a poor prognosis. In a cohort study, Yang et al. employed 16S rRNA gene sequencing to analyze mouth rinse samples and proved that organisms causing oral diseases like *Treponema denticola, Bifidobacteriaceae,* and *Prevotella* (*P. denticola, P. intermedia, P. oral taxon 300*) were associated with amplified risk of CRC, while *Carnobacteriaceae, Erysipelotrichaceae, Prevotella melaninogenica, Streptococcus,* and *Solobacterium* showed a reduced risk for CRC development (38).

However, the oral bacterium of importance in cases of CRC is *Fusobacterium nucleatum* (39-41). *F. nucleatum* is an anaerobic oral pathogen, a late colonizer of dental plaque, and is associated with periodontitis (42). *F. nucleatum* habitually co-habits

with another oral microbiota, *Porphyromonas spp.* (mainly *P. gingivalis*), and these two are the most commonly increased organisms in CRC (43, 44). Similar studies were reported by Tahara et al. and Gao et al., where they confirmed that these oral pathogens promote CRC tumorigenesis (45, 46). These data were in accordance with previous studies (47, 48).

So How Does Oral Microbiota Affect the Colorectal Area?

Segata et al. reported that there is roughly a 45% overlap of the fecal and oral microbiota (49). Thus, the microbial colonization of the intestine could be due to the transportation of the oral microbes. This was further confirmed by Li et al. in 2019 (50). Although the exact mechanism of bacterial transport from the oral cavity to the colon is ambiguous, there are two possible routes. The first and most obvious route is through the process of swallowing (51). For example, in chronic periodontitis, the count of *P. gingivalis* swallowed can vary from 10^8-10^{10} (52). The second route of bacterial transport could be through usual dental activities like tooth brushing or chewing (53). During oral pathological conditions, *F. nucleatum* and *P. gingivalis* traverse the ulcerated gingival pockets and enter the bloodstream (54).

Conclusion

Oral periodontopathogenic bacteria traverse from the oral cavity, reach the colon, synthesize growth and virulence factors, and progressively eradicate the beneficial bacteria. This creates instability in the intestinal microbiota balance, favoring the orally-derived opportunistic pathogens to thrive and breed, thereby resulting in intestinal dysbiosis. Mucosal adhesion and biofilm formation along with an increased concentration of toxic metabolites and greater proteolytic activity can disrupt the integrity of the colonic barrier. All the above mechanisms, added with aberrant immunity, will lead to inflammation and CRC tumorigenesis.

Further studies are required to probe deeper into the connection of the oral-colonic microbiota, especially regarding the exact role of *F. nucleatum* virulence proteins. Until then, good oral hygiene, frequent visits to dentists, and probiotics may help prevent intestinal diseases mediated by oral bacteria.

Conflicts of interests: None declared.

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