
| REVIEW ARTICLE

***Fusobacterium nucleatum* as a Cause of Colorectal Cancer in Human**

Mohammad Salim

Retired Professor, S.G.S. Govt. Autonomous P.G. College, Sidhi (M.P.), affiliated to A.P.S. University, Rewa (M.P.), India

Corresponding Author: Mohammad Salim, **E-mail:** mmsaleem195195@gmail.com

| ABSTRACT

Fusobacterium nucleatum is an oral oncobiont associated with periodontitis and cancer in humans. High levels of *F. nucleatum* have been detected in various types of cancer, including colorectal, esophageal, pancreatic, breast, gastric, and oral cancers. Accumulating evidence indicates that this bacterium can accelerate tumorigenesis and contribute to resistance to chemotherapy. The present review examines *F. nucleatum* and its potential role in carcinogenesis in humans, with particular emphasis on the development and progression of colorectal cancer (CRC). The mechanisms involved include bacterial colonization, invasion, chronic inflammation, immune suppression, modulation of host-cell signaling, and enhancement of tumor-cell proliferation.

| KEYWORDS

Fusobacterium nucleatum, periodontitis, colorectal cancer, colonization, invasion, immune suppression, FadA, Fap2, FP100

| ARTICLE INFORMATION

ACCEPTED: August 11, 2026 **PUBLISHED:** September 26, 2026

DOI: <https://doi.org/10.61424/ijmhr.v4i3.1034>

1. Introduction

Strong associations between microorganisms and several human cancers have already been established. Two periodontal microorganisms, *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, have been identified as important microbial risk factors associated with oral, colorectal, and pancreatic cancers. *Fusobacterium nucleatum* is a common oral bacterium that is frequently detected at elevated levels in squamous cell carcinomas. It has an emerging role in the induction of inflammation and is capable of forming dental plaque biofilms in association with *Porphyromonas gingivalis* (Pignatelli *et al.* 2023; Alon-Maimon *et al.* 2022) (Figure 1).

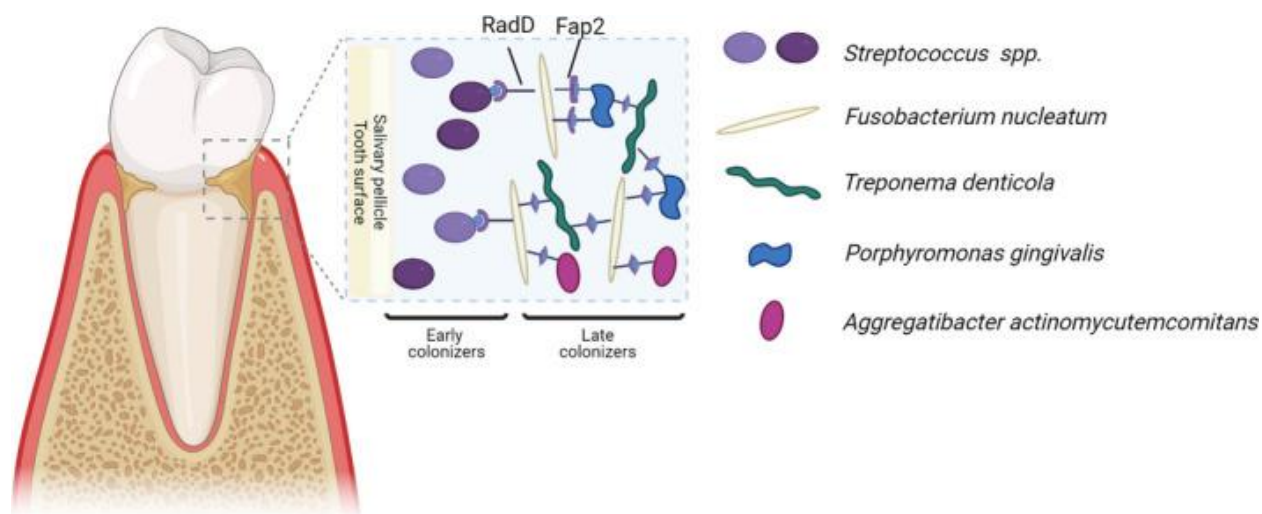


Figure 1. *Fusobacterium nucleatum* acts as a bridging organism in dental plaques. (Photo credited to Alon-Maimon *et al.* 2022.)

The bacteria is commonly found in the human oral cavity and has been closely associated with the development of colorectal cancer. Recent studies have demonstrated that specific clades of *F. nucleatum*, particularly the CRC-associated clade, are enriched in colorectal tumors. Increased numbers of this bacterium have been detected in the intestines of patients with colorectal cancer, where its presence is associated with precancerous lesions such as adenomas and may create a favorable microenvironment for tumor development (Zepeda-Rivera *et al.* 2024). Although *F. nucleatum* is not considered the sole cause of CRC, it may actively contribute to carcinogenesis by promoting chronic inflammation, evading host immune responses, and accelerating tumor-cell proliferation (Wu *et al.* 2019; Alon-Maimon *et al.* 2022; Zhao *et al.* 2022).

1.1 Colorectal Cancer and *Fusobacterium nucleatum*

Colorectal cancer is a major global health problem. A strong association between *F. nucleatum* and CRC has been reported, with considerable variation among geographical populations (Alon-Maimon *et al.* 2022). According to global cancer statistics, colorectal cancer ranks among the most frequently diagnosed cancers worldwide and represents a major cause of cancer-related mortality (Sung *et al.* 2021). The global burden of CRC continues to increase, particularly in developing and upper-middle-income countries. Changes in dietary habits, sedentary lifestyles, obesity, environmental exposures, and familial predisposition have been proposed as important contributors to this increasing incidence. Although CRC has traditionally been considered a disease predominantly affecting older adults, its incidence among younger individuals has also increased. Early-onset CRC has therefore become an important clinical and epidemiological concern. Among the microbial factors associated with intestinal dysbiosis and CRC is *F. nucleatum*, which has emerged as an important contributor to tumor development and progression (Kowsarakhizi *et al.*, 2025).

1.2 Other Cancers Associated with *F. nucleatum*

In addition to colorectal cancer, *Fusobacterium nucleatum* has been detected in association with several other human malignancies. These include gastric, pancreatic, oral, esophageal, and breast cancers (Alon-Maimon *et al.* 2022; Annegowda *et al.* 2025) (Figure 2).

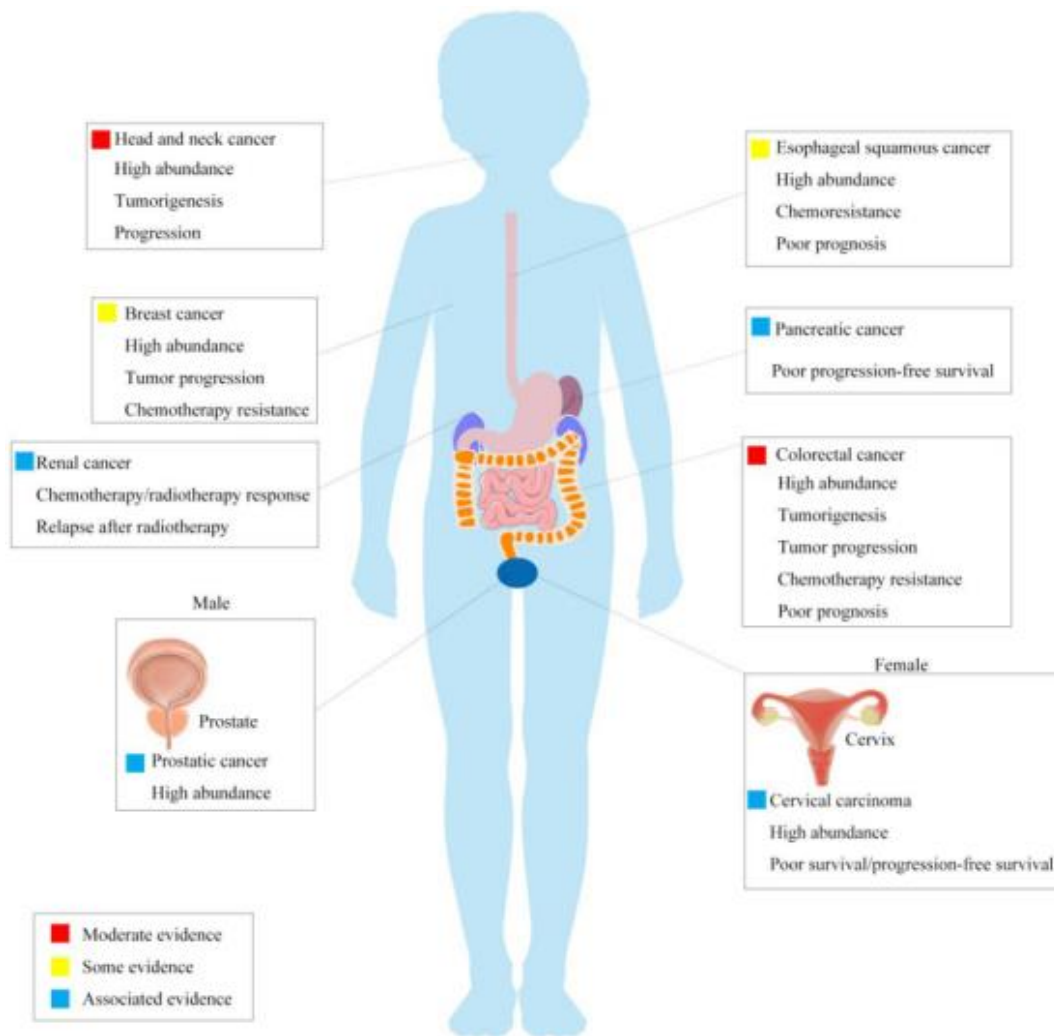


Figure 2. Various cancers associated with *Fusobacterium nucleatum*. (Photo adapted from Zhao *et al.* 2022.)

2. Diagnosis and clinical symptoms of colorectal cancer associated with *F. nucleatum*

F. nucleatum has been investigated as a potential microbial biomarker for the diagnosis and screening of colorectal cancer. Stool-based screening methods are currently used for the detection of CRC, and microbial biomarkers may provide additional diagnostic information. Fecal occult blood testing (FOBT) is a relatively inexpensive preliminary screening method for CRC. However, its sensitivity is moderate, and additional diagnostic evaluation is generally required when abnormalities are detected. Molecular detection of *F. nucleatum* in clinical specimens, including stool, can be performed using polymerase chain reaction (PCR). Immunological assays using salivary, serum, or fecal antibodies against *F. nucleatum* have also been investigated as potential approaches for CRC screening. ELISA-based assays evaluating *F. nucleatum*-specific IgA and IgG antibodies have demonstrated potential diagnostic value (Alon-Maimon *et al.* 2022).

Common clinical manifestations of colorectal cancer, particularly early-onset CRC, include abdominal pain, diarrhea, rectal bleeding, changes in bowel habits, unexplained weight loss, and iron-deficiency anemia. Early-onset colorectal cancer generally refers to CRC diagnosed in individuals younger than 50 years of age (Fritz *et al.* 2023; Saraiva *et al.* 2023).

3. Mechanism of cancer development

Fusobacterium nucleatum is a Gram-negative, non-spore-forming, anaerobic oral commensal bacterium associated with a variety of human diseases, including periodontitis, brain abscesses, cardiovascular diseases, inflammatory bowel disease, and other systemic conditions (Wang *et al.* 2021) (Figure 3).

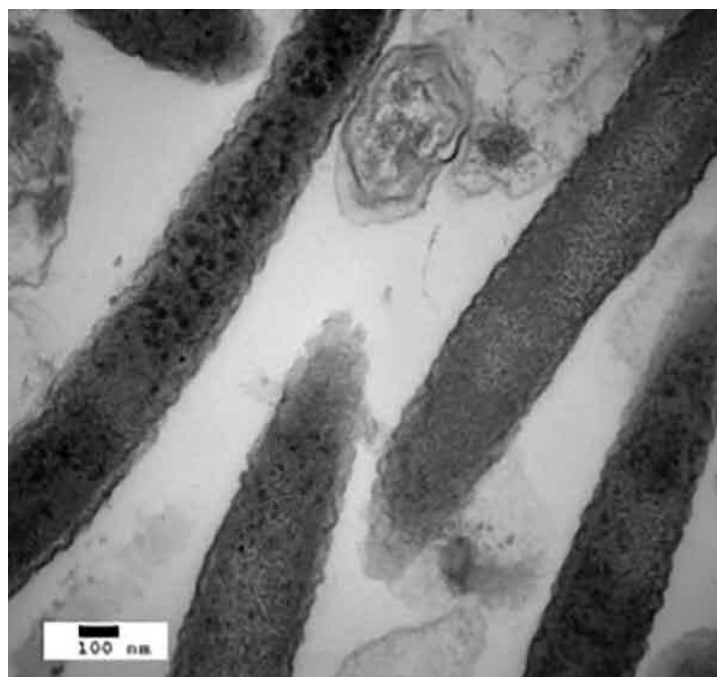


Figure 3. Electron micrograph of *Fusobacterium nucleatum*. (Credit: Microbiology Open, 2014; doi:10.1002/mbo3.204. CC BY 3.0.)

Over recent years, increasing evidence has demonstrated that *F. nucleatum* is associated with colorectal cancer through several virulence mechanisms, including bacterial colonization, invasion, modulation of host-cell signaling, induction of inflammation, and alteration of host immune responses (Wu *et al.* 2019) (Figure 4).

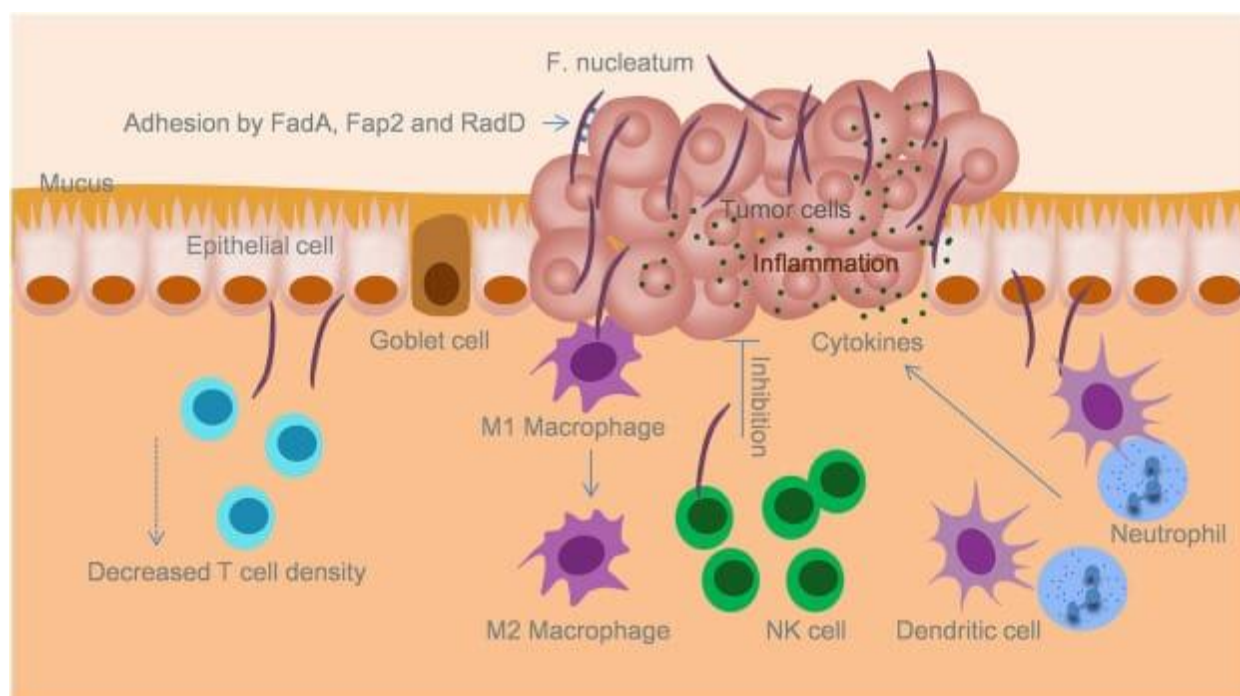


Figure 4. *Fusobacterium nucleatum* contributes to tumor development in the gut mucosa. (Photo adapted from Wu *et al.* 2019.)

F. nucleatum possesses specific surface proteins, including FadA and Fap2, which facilitate adhesion to host cells and contribute to bacterial colonization, inflammation, and tumor development. The bacterium can also suppress

the activity of natural killer (NK) cells and tumor-infiltrating T cells. Such immune modulation may impair the ability of the host immune system to recognize and eliminate malignant cells (Wu *et al.* 2019; Zhao *et al.* 2022).

Furthermore, *F. nucleatum* releases microbial metabolites such as ADP-heptose, which can activate inflammatory signaling pathways through the ALPK1/TIFA axis. Activation of these pathways promotes inflammatory and anti-apoptotic responses in colorectal cancer cells (Martin-Gallausiaux *et al.* 2023). *F. nucleatum* may enhance tumor-cell proliferation, invasion, and metastatic progression (Alon-Maimon *et al.* 2022).

Finally, infection with *F. nucleatum* may contribute to tumor initiation and promotion through persistent inflammation and the development of an immunosuppressive tumor microenvironment. The bacterium can facilitate immune evasion by inhibiting the cytotoxic activity of NK cells and altering antitumor immune responses (Zhao *et al.* 2022) (Figure 5).

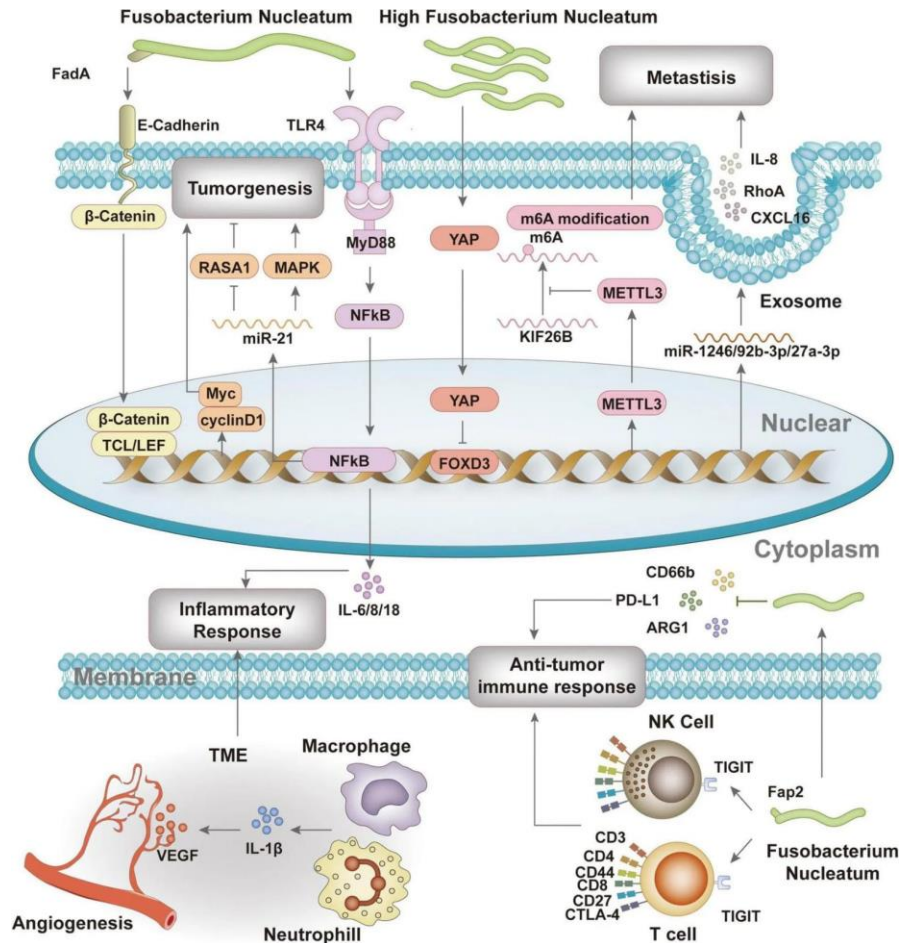


Figure 5. Developmental mechanisms of colorectal cancer associated with *Fusobacterium nucleatum* (Photo adapted from He *et al.* 2025).

4. Treatment and eradication of the disease

Treatment strategies directed against *F. nucleatum* are being investigated as potential approaches for controlling periodontal disease and microbial contributions to cancer progression. Targeted antimicrobial approaches, including the experimental agent FP100 (hygromycin A), have demonstrated activity against *F. nucleatum* and may provide a strategy for reducing the bacterium while minimizing disruption of the broader oral and intestinal microbiome (Yakar *et al.* 2024). Tea polyphenols have also been reported to inhibit the growth and virulence-associated properties of *F. nucleatum* (Lagha *et al.* 2017).

The bacterium may alter host-cell signaling pathways that support tumor growth and contribute to resistance to anticancer therapy. Its presence within tumors has been associated with reduced responsiveness to chemotherapeutic agents such as 5-fluorouracil. In addition, *F. nucleatum* can interfere with antitumor immune

responses by impairing the normal cytotoxic functions of NK cells and T cells, thereby facilitating survival and progression of abnormal tumor cells (Martin-Gallausiaux *et al.* 2023).

5. Conclusion

Fusobacterium nucleatum is an oral commensal bacterium that has emerged as an important oncobacterium associated with tumor development and progression in humans. It is commonly found in the oral cavity and may also be detected in the gastrointestinal tract and female genital tract. Under appropriate conditions, this opportunistic pathogen can cause systemic infections and has been associated with conditions such as Lemierre's syndrome, appendicitis, gingivitis, periodontitis, and inflammatory bowel disease. As a resident of the oral cavity, *F. nucleatum* may disseminate through the bloodstream or gastrointestinal tract and colonize distant tissues. Colorectal tissue represents one important site of colonization; however, elevated levels of *F. nucleatum* have also been reported in esophageal, pancreatic, breast, gastric, and oral cancers. Accumulating evidence supports an association between intestinal *F. nucleatum* and the development of colorectal cancer in humans. The bacterium can promote a pro-inflammatory microenvironment by stimulating the recruitment of inflammatory cells and the secretion of inflammatory mediators, thereby favoring colorectal tumor growth. It can also suppress components of the host immune response and contribute to immune evasion. The pathogenic effects of *F. nucleatum* involve several important virulence-associated mechanisms, including adhesion, colonization, invasion, proliferation, inflammatory signaling, immune suppression, and modulation of host-cell pathways. Collectively, these mechanisms may contribute to the initiation and progression of colorectal cancer. Nevertheless, *F. nucleatum* should be regarded as an important contributing microbial factor rather than an independent or exclusive cause of CRC. Further experimental, clinical, and epidemiological investigations are required to establish its precise causal role and to determine whether targeted eradication of the bacterium can reduce cancer incidence, progression, or therapeutic resistance.

Abbreviations

Fn — *Fusobacterium nucleatum*

CRC — Colorectal cancer

PCR — Polymerase chain reaction

GIT — Gastrointestinal tract

IBD — Inflammatory bowel disease

NK cells — Natural killer cells

IgA — Immunoglobulin A

IgG — Immunoglobulin G

FOBT — Fecal occult blood testing

ELISA — Enzyme-linked immunosorbent assay

Acknowledgements: This research work is dedicated to the memory of my father, Late Haji Mohammad Shafi.

Financial support: No financial support was received during the course of this research work.

Ethical clearance: Since this article is purely a review study and does not involve human participants, animals, or experimental interventions, ethical clearance was not required.

Conflicts of Interest: The authors declare no conflict of interest.

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Artificial Intelligence (AI) Use Disclosure: The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

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