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REVIEW ARTICLE

FUSOBACTERIUM NUCLEATUM AND COLORECTAL CANCER: FROM ORAL DYSBIOSIS TO TUMOUR PROGRESSION. A NARRATIVE REVIEW

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ABSTRACT

The relationship between oral health and systemic disease has become an important field of research in recent years. Among oral microorganisms, *Fusobacterium nucleatum* (*F. nucleatum*) has attracted considerable attention because of its frequent detection in colorectal cancer (CRC) tissue and its potential role in tumour progression. *F. nucleatum* is a Gram-negative anaerobic bacterium commonly associated with periodontal disease and oral dysbiosis. Increasing evidence suggests that this microorganism may contribute to colorectal carcinogenesis through inflammatory signalling, immune modulation, epithelial barrier disruption, and chemoresistance.

This narrative review summarizes the current evidence regarding the biological mechanisms linking *F. nucleatum* to CRC. Attention is given to bacterial adhesins such as FadA and Fap2, activation of the TLR4/MyD88/NF-κB pathway, immune escape mechanisms involving TIGIT and PD-L1, and the role of *F. nucleatum* in chemotherapeutic resistance. Clinical studies consistently demonstrate increased intratumoral abundance of *F. nucleatum* in advanced CRC stages and associations with poorer prognosis and reduced survival.

Although causality has not yet been definitively established, the available mechanistic and clinical evidence strongly supports the concept that *F. nucleatum* functions as a disease-modifying organism within the colorectal tumour microenvironment. Furthermore, these findings highlight the potential importance of periodontal health and interdisciplinary collaboration between dental and medical professionals.

Keywords: *F. nucleatum*; colorectal cancer; oral microbiome; periodontitis; tumour microenvironment; immune modulation; chemoresistance

INTRODUCTION

The association between oral health and systemic disease has gained increasing scientific attention over the past decade [1,2,3,4]. Oral microorganisms are no longer considered exclusively local pathogens, as mounting evidence demonstrates their ability to influence distant organs and systemic inflammatory processes. Periodontal disease has been associated with several systemic disorders, including cardiovascular disease, diabetes mellitus, neurodegenerative disorders, and malignancies.

Among oral pathogens, *F. nucleatum* has emerged as one of the most extensively investigated bacteria in relation to colorectal cancer (CRC) [5,6,7,8]. CRC remains one of the most common malignancies worldwide and represents a major cause of cancer-related mortality [2]. The disease develops through a complex interaction between genetic susceptibility, environmental factors, chronic inflammation, and alterations in the intestinal microbiome. *F. nucleatum* is a Gram-negative obligate anaerobic bacterium that normally resides within the oral cavity and plays an important role in periodontal biofilm maturation [9,10]. However, increasing evidence indicates that this bacterium may translocate from the oral cavity to the gastrointestinal tract and preferentially colonize colorectal tumour tissue. Multiple studies have demonstrated significantly increased levels of *F. nucleatum* within CRC tissue compared with healthy

colonic mucosa [7,11,12,13].

The objective of this narrative review is to summarize current knowledge regarding the relationship between *F. nucleatum* and colorectal cancer, with particular focus on molecular mechanisms, tumour progression, immune modulation, and potential implications for oral healthcare professionals.

Biology of *F. nucleatum*

F. nucleatum is a spindle-shaped Gram-negative anaerobic bacterium that forms part of the normal oral microbiota. Under physiological conditions, it behaves as a commensal organism; however, in dysbiosis conditions such as gingivitis and periodontitis, it may act as an opportunistic pathogen. The bacterium possesses several virulence factors that contribute to adhesion, invasion, and biofilm formation. One of the most important characteristics of *F. nucleatum* is its ability to function as a "bridge organism" within polymicrobial biofilms, connecting early and late colonizers during biofilm maturation (Fig. 1).

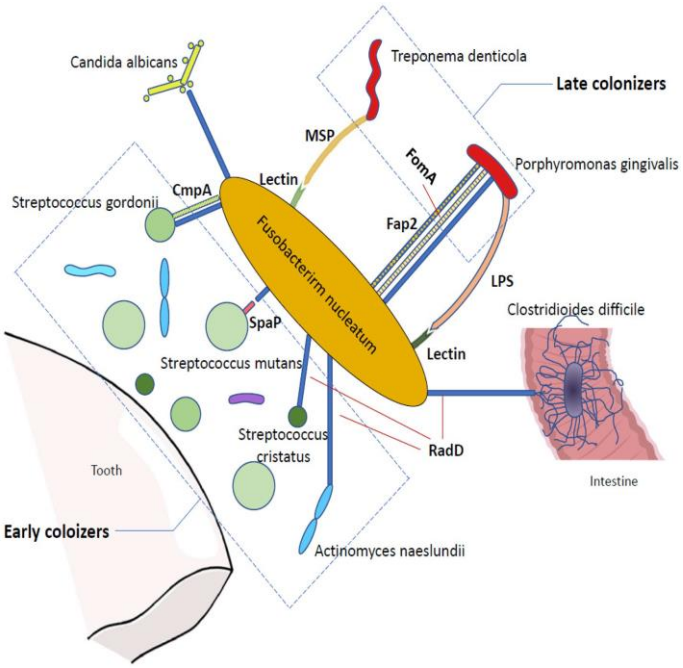

Figure 1. Schematic representation of the role of F. nucleatum in oral and intestinal microbial interactions and the adhesins and mechanisms involved that contribute to colonization and association with other microorganisms.

Several outer membrane proteins contribute to its pathogenicity [10,14,15]:

- **RadD:** mediates interspecies bacterial coaggregation and biofilm architecture;
- **FadA:** enables adhesion and invasion of epithelial cells;
- **Fap2:** interacts with host glycans and immune receptors.

These virulence factors allow *F. nucleatum* to establish close interactions with both host tissues and neighbouring microorganisms [14,16,17].

Within periodontal tissues, *F. nucleatum* contributes to chronic inflammation through activation of epithelial and immune cells, inducing production of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α.

Potential Routes from the Oral Cavity to the Colon

Several mechanisms have been proposed to explain how oral *F. nucleatum* reaches colorectal tissue.

Hematogenous dissemination

Experimental studies suggest that hematogenous spread may represent the most plausible route[9]. Periodontal inflammation compromises the integrity of gingival tissues and blood vessels, potentially allowing oral bacteria to enter the bloodstream. Animal studies demonstrated that intravenous inoculation of *F. nucleatum* resulted in significantly more efficient colonization of colorectal tumours than oral administration. Moreover, genomic analyses have shown similarities between oral and colorectal strains of *F. nucleatum*, supporting the hypothesis of oral-to-intestinal bacterial dissemination [13,18].

Gastrointestinal route

Daily swallowing of saliva containing oral bacteria may also contribute to gastrointestinal exposure. However, gastric acidity and competition with resident intestinal microbiota substantially limit bacterial survival. Consequently, the oral-intestinal route appears less efficient than hematogenous dissemination.

Nevertheless, dysbiosis, antibiotic exposure, chronic inflammation, or altered intestinal permeability may create favourable conditions for intestinal colonization.

Molecular Mechanisms Linking *F. nucleatum* to CRC

Adhesion and epithelial invasion

One of the most extensively studied virulence factors is FadA, an adhesin capable of binding to E-cadherin on epithelial cells [5,35]. This interaction disrupts epithelial integrity and activates the Wnt/β-catenin signalling

pathway. Activation of Wnt/β-catenin signalling stimulates expression of oncogenes such as *MYC* and *CCND1*, promoting cellular proliferation and tumour progression [19,20]. Additionally, Fap2 binds specifically to the Gal-GalNAc glycan motif, which is highly expressed on colorectal tumour cells [21]. This selective interaction may explain the preferential accumulation of *F. nucleatum* within colorectal tumours.

Inflammatory signalling

Following epithelial invasion, bacterial components such as lipopolysaccharides activate Toll-like receptor 4 (TLR4) on immune cells [22,23,24]. Subsequent activation of the MyD88/NF-κB signalling cascade results in production of pro-inflammatory cytokines including IL-6, IL-8, and TNF-α.

This chronic inflammatory microenvironment contributes to multiple tumour-promoting processes [24,25,26]:

- enhanced cellular proliferation;
- angiogenesis;
- genomic instability;
- inhibition of apoptosis;
- tumour progression.

The persistent inflammatory state generated by *F. nucleatum* may therefore facilitate carcinogenesis and accelerate tumour development.

Immune Modulation and Tumour Escape

An important aspect of *F. nucleatum*-associated tumour biology involves immune evasion.

The bacterial adhesin Fap2 binds to the TIGIT receptor present on T lymphocytes and natural killer (NK) cells [27]. This interaction suppresses antitumor immune activity and reduces cytotoxic responses against malignant cells. Furthermore, *F. nucleatum* has been associated with increased expression of PD-L1 within the tumour microenvironment, contributing to immune suppression.

Additional mechanisms include recruitment of:

- myeloid-derived suppressor cells (MDSCs);
- tumour-associated macrophages (TAMs).

Figure 2: Overview of TNM classification in CRC. T indicates the size of the primary tumour, N the number of involved regional lymph nodes and M the presence of metastases

Together, these mechanisms create an immunosuppressive microenvironment that favours tumour survival and progression [25,26,28].

***F. nucleatum* and Chemoresistance**

Several studies suggest that *F. nucleatum* contributes to reduced sensitivity to chemotherapy [15,16].

Particularly relevant is its association with resistance to:

- 5-fluorouracil;
- oxaliplatin.

Mechanistically, *F. nucleatum* appears to stimulate autophagy through activation of the TLR4/MyD88 pathway. Reduced expression of specific microRNAs, including miR-18a and miR-4802, has been implicated in this process. Additionally, recent studies indicate that *F. nucleatum* inhibits ferroptosis through activation of the E-cadherin/β-catenin/GPX4 axis, thereby increasing tumour cell survival under oxidative stress conditions [29].

Other investigations suggest that *F. nucleatum* may enhance stem-cell-like properties within tumour cells, further contributing to recurrence and treatment resistance.

Clinical Implications and Prognostic Value

Clinical studies consistently demonstrate increased intratumoral abundance of *F. nucleatum* in advanced CRC stages [5,30,31].

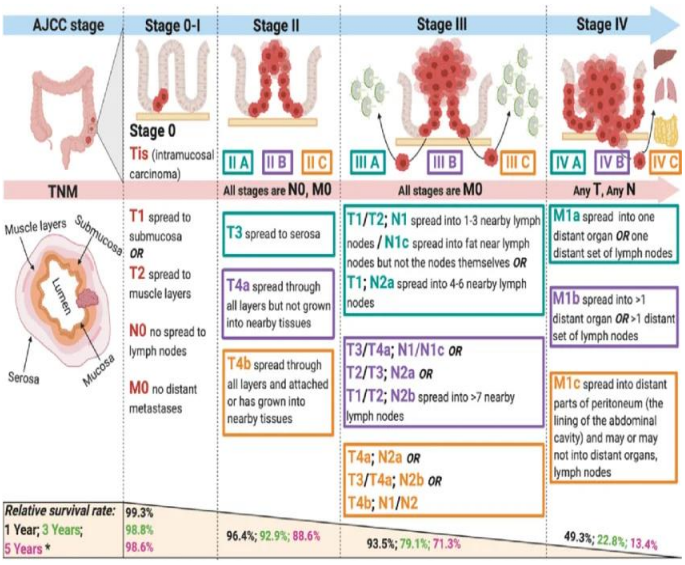

Figure 2. Overview of TNM classification in CRC. T indicates the size of the primary tumour, N the number of involved regional lymph nodes and M the presence of metastases.

Higher bacterial levels have been associated with (Fig. 2):

- advanced TNM stage;
- poorer tumour differentiation;
- microsatellite instability (MSI);
- increased recurrence risk;
- reduced overall survival.

Meta-analyses further support the association between elevated *F. nucleatum* levels and unfavourable prognosis [11,12,30,31].

Despite these findings, current evidence remains predominantly observational. Therefore, definitive causal conclusions cannot yet be established.

Nevertheless, the available mechanistic and clinical evidence strongly suggests that *F. nucleatum* acts as a disease-modifying organism that contributes to tumour progression and immune dysregulation.

Relevance for Periodontal and Oral Healthcare Professionals

Current evidence does not support the use of oral *F. nucleatum* detection as a screening tool for colorectal cancer [3]. The bacterium is frequently present in healthy individuals and lacks sufficient specificity for diagnostic purposes.

However, periodontal inflammation is associated with increased abundance of *F. nucleatum* and other pathogenic oral microorganisms. Consequently, maintenance of periodontal health may contribute to reducing systemic inflammatory burden.

Oral healthcare professionals therefore play an important role in:

- prevention and treatment of periodontal disease;
- reduction of oral dysbiosis;
- patient education regarding oral-systemic health;
- interdisciplinary collaboration with medical professionals.

Particularly in oncological patients, optimal oral health may improve quality of life and reduce complications associated with systemic inflammation.

Future Perspectives

Future research should focus on longitudinal and interventional studies capable of clarifying the causal relationship between *F. nucleatum* and colorectal carcinogenesis [3,6].

Potential future directions include innovative microbiome-targeted strategies and precision-oncology approaches [4,32,33,34]:

- microbiome-targeted therapies;
- modulation of oral dysbiosis;
- bacteriophage therapy;
- probiotic interventions;
- targeted inhibition of bacterial virulence factors.

Additionally, a deeper understanding of tumour-microbiome interactions may facilitate development of personalized therapeutic strategies.

CONCLUSION

Increasing evidence supports a significant association between *Fusobacterium nucleatum* and colorectal cancer progression. Through mechanisms involving epithelial invasion, inflammatory signalling, immune modulation, and chemoresistance, *F. nucleatum* appears capable of promoting a tumour-supportive microenvironment.

Although definitive causality has not yet been established, current mechanistic and clinical evidence strongly suggests that *F. nucleatum* functions as a disease-modifying organism within colorectal carcinogenesis.

These findings further emphasize the importance of oral health and interdisciplinary collaboration between dental and medical professionals. Periodontal management and reduction of oral dysbiosis may represent clinically relevant components of integrated patient care.

DECLARATIONS

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approval

Ethical approval was not required as this is a narrative review of published literature.

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