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Fusobacterium nucleatum as a biomarker in colorectal cancer

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ABSTRACT

Introduction: Colorectal cancer is often associated with ectopic colonization of the gastrointestinal tract by the oral commensal bacterium *Fusobacterium nucleatum*. This microorganism uses virulence factors to stimulate cell growth and facilitate selective colonization, and its early, noninvasive detection is critical for patient survival.
Objectives: This article aims to summarize the pathogenic mechanisms of *F. nucleatum*, provide a detailed assessment of its role in treatment resistance, and discuss new molecular diagnostic technologies for personalized therapy.
Methodology: A search was conducted in the PubMed, Scopus, and Web of Science databases, encompassing English articles published between January 2021 and May 2026. Initially, 130 articles were identified. Following the exclusion of 105 ineligible records and manual addition via cross-referencing, 38 studies were included.
Results: The combination of fecal immunochemical tests with risk assessment algorithms and other tumor markers improves overall diagnostic accuracy. A high abundance of the bacterium in carcinoma is associated with a poorer prognosis, right-sided colon location, deoxyribonucleic acid repair deficiencies, and high-methylation phenotypes. The microorganism promotes an immunosuppressive microenvironment and induces resistance to first-line treatments (fluorouracil and combination chemotherapy), resulting in drug degradation and activation of anti-apoptotic pathways.
Conclusion: The bacterium acts simultaneously as a key diagnostic biomarker and an inhibitor of therapeutic efficacy, necessitating the use of highly sensitive molecular diagnostic methods. Strategies aimed at eliminating this microorganism, using specific antimicrobials or prebiotics, represent a promising approach to overcoming drug resistance.

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INFORMAÇÃO DO ARTIGO

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RESUMO

Introdução: O cancro colorretal associa-se frequentemente à colonização ectópica do trato gastrointestinal pela bactéria comensal oral *Fusobacterium nucleatum*. Este microrganismo utiliza fatores de virulência para estimular o crescimento celular e facilitar a colonização seletiva, sendo a sua deteção precoce não invasiva crítica para a sobrevivência do doente.
Objetivos: O artigo visa resumir os mecanismos patogénicos da *F. nucleatum*, avaliar detalhadamente o seu papel na resistência ao tratamento e discutir novas tecnologias de diagnóstico molecular para a personalização terapêutica.
Metodologia: Realizou-se uma pesquisa nas bases de dados PubMed, Scopus e Web of Science, contemplando artigos em inglês publicados entre janeiro de 2021 e maio de 2026. Identificaram-se 130 artigos. Após a exclusão de 105 registos inelegíveis e a adição manual por referenciação cruzada, 38 estudos foram incluídos.
Resultados: A combinação de testes imunoquímicos fecais com algoritmos de avaliação de risco e outros marcadores tumorais melhora a precisão diagnóstica global. A elevada abundância da bactéria no carcinoma associa-se a um pior prognóstico, localização no cólon direito, deficiências na reparação do ácido desoxirribonucleico e fenótipos de alta metilação. O microrganismo promove um microambiente imunossupressor e induz resistência a tratamentos de primeira linha (fluorouracilo e quimioterapia combinada), resultando na degradação de fármacos e ativação de vias antiapoptóticas.
Conclusões: A bactéria atua simultaneamente como biomarcador diagnóstico essencial e inibidor da eficácia terapêutica, exigindo a aplicação de métodos de diagnóstico molecular de alta sensibilidade. Estratégias focadas na eliminação deste microrganismo, utilizando antimicrobianos específicos ou prebióticos, representam uma abordagem promissora para reverter a resistência aos fármacos.

Introduction

Colorectal cancer (CRC) is a malignant tumor that develops in the colon or rectum, often arising from polypoid lesions that undergo dysplasia and subsequent malignant transformation.[1] It is the third most common cancer worldwide, with an annual incidence of more than 1.9 million cases.[2] Its incidence rises sharply after the age of 50-55, and mortality increases after the age of 45-50.[3]

This condition is associated with eating habits typical of the Western diet.[4] In addition, recent studies reveal a strong association with the pathogen *Fusobacterium nucleatum*, an anaerobic commensal that normally resides in the oral cavity but, through its migration and ectopic colonization of the gastrointestinal tract, is found in elevated levels in cases of CRC, both in tumor tissues and in fecal samples.[5]

The bacterium employs various molecular mechanisms through which it utilizes its virulence factors. For example, the *adhesin* FadA, which binds to E-cadherin, activates signaling pathways that stimulate cell growth; while the lectin Fap2 facilitates selective colonization by interacting with molecules that are overexpressed in malignant cells.[6]

Recent studies indicate that different strains of the genus *Fusobacterium* exhibit distinct strain-specific pathogenic behaviors.[7] It is important to identify subspecies in order to provide personalized treatments and accurate diagnosis.[8]

The detection of this microorganism as a biomarker depends on early-stage diagnosis, since patient survival is linked to rapid diagnosis.[9] Research into the use of different fecal markers and the quantification of microbial DNA represents a promising, non-invasive strategy for identifying high-risk microbial patterns.[10] This approach allows for more effective screening of individuals and avoids more complex procedures, such as colonoscopy.[11]

This review article aims to summarize the pathogenic mechanisms of *F. nucleatum*, evaluate its role in treatment resistance, and discuss the potential of new molecular diagnostic technologies for personalizing the treatment of CRC.

Methodology

To prepare this narrative review, a comprehensive literature search was conducted in the major electronic scientific databases, namely PubMed/MEDLINE, Scopus, and Web of Science. The search focused on identifying relevant literature on the role of *Fusobacterium nucleatum* in the context of oncology. The keywords used for the search were "colorectal cancer," "Fusobacterium nucleatum," "biomarkers," and "chemoresistance." The selection of articles was strictly limited to those published between January 2021 and May 2026, aiming to cover the most recent developments in diagnostic technologies and clinical treatment strategies. The selection of articles was based on strict eligibility criteria to ensure they were up-to-date and had undergone proper scientific review. As inclusion criteria, publications written entirely in English and published in peer-reviewed journals were required. Original research studies, meta-analyses, and systematic reviews assessing the prognostic impact of the bacterium were considered, as well as studies focused on inflammatory and immunological pathways. Additionally, clinical trials and survival

analyses comparing the efficacy of different first-line chemotherapy regimens (FOLFOX and CAPOX) in the presence of this microorganism in the carcinoma were included, alongside current clinical guidelines in the field of gastrointestinal oncology. Conversely, the exclusion criteria applied were preclinical studies not directly related to colorectal neoplasms, articles without full-text versions available, publications in languages other than English, isolated case reports, and studies with statistically insignificant sample sizes.

The initial literature search in the databases yielded a total of 130 articles. Following a primary screening of titles and abstracts, 105 records were excluded for not meeting the pre-established eligibility criteria. The remaining 25 articles were fully reviewed and selected for inclusion. Beyond the initial database screening, cross-referencing bibliographies identified 13 additional records that enriched the clinical framework. This review synthesizes data from 38 curated references.

Results

The urgency of early CRC detection makes the use of non-invasive and well-tolerated methods to detect biomarkers essential.[12]

Fecal biomarkers

In order to effectively screen for colorectal cancer (CRC), various non-invasive fecal biomarkers are used, which can be broadly divided into conventional faecal occult blood tests (fecal immunochemical test [FIT] and fecal occult blood testing [FOB]), tumor-derived protein markers (carcinoembryonic antigen [CEA], carbohydrate antigen 19-9 [CA19-9] and transferrin [TRF]), and microbiome-based biomarkers.[13] As a prominent microbiome-based biomarker, the quantification of F. *nucleatum* in faeces has demonstrated significant diagnostic potential.[10] When evaluated as a standalone biomarker, it has a combined sensitivity of 0.71 (29% diagnostic failure rate), a specificity of 0.77 (23% false-positive rate) and an area under the curve (AUC) of 0.81.[14] Despite its good overall diagnostic accuracy, reliance solely on this bacterial marker leaves a considerable gap in the reliability of the diagnosis, making it essential to combine different complementary methods.[15] For example, combining conventional screening methods, such as FIT, with a questionnaire-based risk assessment (QRA) increases the detection rate for CRC from 13.2% to 18.2%, offering a more effective clinical strategy than FIT alone.[16] Combining the detection of *F. nucleatum* with conventional and tumor-derived biomarkers (FOB, TRF, CEA, CA19-9) dramatically improves diagnostic performance. This multi-parameter approach increases the overall accuracy to 0.87 and the AUC to 0.93.[13] Clinically, this high AUC represents an excellent diagnostic tool that substantially minimizes false negatives, thereby enabling the detection of more cancers at an early stage. At the same time, it reduces false positives, thus sparing patients from unnecessary and invasive procedures, such as colonoscopy.[11]

Features of intratumoral F. nucleatum

F. nucleatum may induce tumorigenesis by a number of mechanisms. On one hand it has been proposed that carcinogenesis induction may arise through the activation of β-catenin signaling via the FadA adhesion factor, mediated by the induction of Annexin A1.[17] Also elevated *F. nucleatum* levels show a strong correlation with the CpG island methylation phenotype (CIMP-high) and with the presence of mutations in the BRAF gene.[18] In this regard it is also interesting to note that one of the most significant findings was the independent association between elevated levels of *F. nucleatum* and a deficiency in DNA mismatch repair (dMMR) status.[19] Furthermore, a number of immune mediated mechanisms may also play important roles. It has been demonstrated that the Fap2 lectin interacts directly with the inhibitory receptor TIGIT (T-cell immunoreceptor with Ig and ITIM domains), which is expressed on natural killer (NK) cells and tumor-infiltrating T lymphocytes. This binding inhibits the cytotoxic activity of these defense cells, which promotes an immunosuppressive microenvironment that protects malignant cells from immune surveillance and favors the progression of CRC.[20]

Taken together, these findings may provide the mechanistic support to explain the association of an high abundance of *F. nucleatum* in tumor tissue with poorer clinical outcome in some reports.[21]

Anatomical relationships

Anatomical variability of CRC correlates with the distribution of the microorganism in the gastrointestinal tract. Scientific evidence indicates that the bacterial load of *F. nucleatum* tends to be significantly higher in carcinomas located in the proximal colon (right colon) compared to the distal colon or rectum.[22] This biological asymmetry suggests that the diagnostic sensitivity of tests based on fecal markers or microbial DNA quantification may vary depending on the primary anatomical location of the carcinoma, a factor that must be considered when designing population-based screening strategies.[23]

Tumor microenvironment and chemoresistance

Actively involved in shaping the tumor microenvironment, this microorganism modulates the expression of inflammatory genes and microRNAs. These include the cytokine IL-6, the tumor necrosis factor TNF-α, and the microRNA miR-21.[24]. This recurring mechanism induces the exosomal secretion of the tumor-suppressor microRNA miR-122-5p. This enables tumor cells to migrate and metastasize to other organs.[25]

The finding that F. nucleatum presence is associated with a higher rate of treatment failure may be associated with its ability to induce chemoresistance.[26] This resistance is due to the microorganism's intratissue presence, which severely compromises the effectiveness of first-line treatments. The interaction of this bacterium with the rest of the resident microbiota can inactivate 5-FU by degrading the drug.[27] Also, it actively promotes cell survival by releasing metabolites that activate inflammatory pathways and

upregulate anti-apoptotic genes, thereby directly counteracting cell death.[28]

Since 5-fluorouracil (5-FU) serves as the therapeutic standard for first-line clinical interventions, *F. nucleatum*-mediated chemoresistance directly threatens the efficacy of these combined protocols. In chemotherapy for CRC, the FOLFOX and CAPOX regimens are frequently used.[29] Studies evaluating 5-year overall survival indicate that the FOLFOX regimen generally demonstrates a survival advantage over CAPOX in both non-metastatic and metastatic disease settings.[30] However, in terms of patient safety, CAPOX chemotherapy presents a lower toxicity profile, making it a better-tolerated option.[31] Therapeutic equivalence is observed when these regimens are combined with cetuximab in patients with *RAS/BRAF wild-type* mCRC.[32] It is however important to note that the comparative efficacy of different treatment regimens varies significantly depending on the clinical stage and molecular profile of the carcinoma.[33]

Discussion

Although the role of *Fusobacterium nucleatum* as a diagnostic biomarker and a driver of chemoresistance is increasingly recognized, translating these findings into routine clinical practice presents significant challenges. The literature shows that combining the quantification of *F. nucleatum* with conventional markers (FIT) and tumor-derived proteins dramatically improves diagnostic accuracy, overcoming the limitations of the tests when used in isolation.[13,14,16] However, a critical limitation to its widespread implementation is the marked spatial heterogeneity of the gastrointestinal microbiota. Evidence suggests that colonization by *F. nucleatum* is significantly higher in right-sided (proximal) carcinomas compared with distal tumors.[22] This anatomical bias constitutes a significant clinical limitation, as current fecal DNA panels may produce false-negative results for distal tumors if they are not carefully calibrated.[23] One area of significant methodological uncertainty remains the lack of universally validated bacterial load cut-offs, given that the baseline composition of the microbiome varies dramatically between different geographical and demographic populations.[34]

With the aim of overcoming the analytical limitations of standard diagnostic tools, there have been calls for a transition from real-time PCR (qPCR) to digital droplet PCR (ddPCR). Although ddPCR offers superior sensitivity for detecting low bacterial loads without the need for external calibration curves, its clinical implementation is currently hampered by higher costs and the requirement for highly specialised laboratory infrastructure. This creates a discrepancy between what is methodologically ideal and what is feasible for population-based screening for colorectal cancer.[11,34]

From a pathophysiological perspective, the evidence consistently points to *F. nucleatum* as a shaper of a tolerogenic tumor microenvironment. Rather than merely driving proliferation via the FadA/β-catenin pathway, the bacterium actively suppresses immune surveillance through the Fap2-TIGIT interaction in NK and T cells.[17,35] This simultaneously promotes cachexia and metastasis via the exosomal secretion of miR-122-5p.[20,25,36] This immunosuppressive niche directly compromises the efficacy of first-line chemotherapies, such as FOLFOX and CAPOX, through the enzymatic degradation of 5-fluorouracil (5-FU) and the activation of anti-apoptotic pathways (the ALPK1/TIFA axis).[27-30]

A major controversy in current clinical oncology is how to manage this bacteria-induced chemoresistance. Although the FOLFOX regimen generally offers a survival benefit, CAPOX has a lower profile of systemic toxicity.[30,31] However, therapeutic equivalence is compromised in the presence of high intratumoral loads of *F. nucleatum*, which act as a constant mechanism for drug inactivation.[26,32] The consistent association of this microorganism with the CpG island methylation phenotype (CIMP-high), dMMR and BRAF mutations suggests that bacterial quantification could serve as an essential stratification tool for personalised therapy.[18,19] A significant challenge lies in targeting the intratumoral bacterial reservoir; whilst specific antimicrobials or bacteriophages show promise in overcoming chemoresistance, non-specific approaches risk exacerbating gut dysbiosis, thus highlighting the need for highly targeted therapeutic interventions in the future.[37,38]

Conclusion

Fusobacterium nucleatum has emerged as a critical factor in colorectal cancer, serving both as a highly specific biomarker for early, non-invasive diagnosis and as a potent driver of tumor progression and chemoresistance. The integration of advanced diagnostic technologies, such as ddPCR, along with comprehensive fecal molecular panels, is essential for accurate screening and patient stratification. Looking ahead, the targeted administration of narrow-spectrum antimicrobials and specific bacteriophages to eradicate the intratumoral reservoir of *F. nucleatum*, as well as the development of approaches based on specific prebiotics is a promising strategy that deserves further study.[37] Ultimately, combating this microbial interference arises as a vital avenue to restore drug sensitivity, maximize the effectiveness of conventional chemotherapy regimens (such as FOLFOX and CAPOX), and thereby improve patients' overall survival and long-term prognosis.[38]

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