SRHU JOURNAL OF ADVANCED RESEARCH

Strain-specific tumour colonization by *Fusobacterium nucleatum* in colorectal cancer: Linking microbial virulence, metastatic progression, and therapy resistance

Sarthak Thakur

School of Biosciences, Swami Rama Himalayan University, Jolly Grant, Dehradun, Uttarakhand, India

Keywords

Chemoresistance, colorectal cancer, Fusobacterium nucleatum, immunotherapy, metastasis, microbial biomarkers, targeted therapy, tumor microenvironment

Abstract

Colorectal cancer (CRC) is still a major challenge to global health, the bad clinical results being due to tumor progression, metastasis and resistance to anti-cancer treatments. There is growing evidence to show that Fusobacterium nucleatum, an anaerobic bacterium found in the mouth, plays a role in the development and progression of CRC as a result of its interactions with cancer cells, the immune system and the surrounding microbial environment. This review looks at the role of *F. nucleatum* in the process of colorectal carcinogenesis, in tumor colonization, in the remodeling of the microenvironment, in metastatic spread and in therapeutic resistance, as well as assessing its possible clinical applications and the current limitations of research. The bacterium can affect oncogenic signaling via the FadA–E-cadherin/β-catenin pathway, help immune evasion by interacting with inhibitory immune receptors through Fap2, and modify the inflammatory and immune-cell responses in the tumor microenvironment. Experimental evidence also associates *F. nucleatum* with metastatic progression via alterations in cellular signaling and the immune environment of the liver. Moreover, it is suggested that the bacterium may lead to chemoresistance by inhibiting apoptosis, pyroptosis and ferroptosis, while its bacterial metabolites can weaken anti-tumor immunity and decrease the sensitivity of tumors to immune checkpoint blockade. Future research needs to combine strain-resolved microbial analysis, carry out longitudinal clinical studies, use improved experimental models and adopt standardized diagnostic methods. A more in-depth understanding of the interactions between host and microbe could eventually lead to the development of reliable biomarkers and targeted therapeutic strategies for CRC associated with F. nucleatum.

Corresponding Author: thakursarthak61@gmail.com

Received: 16 July 2026, received in revised form: 5 August 2026, accepted: 2 September 2026, available online: 28 September 2026; Volume: 1; Issue: 3; Pages: 67-85.

Citation: Thakur, S., 2026. Strain-specific tumour colonization by *Fusobacterium nucleatum* in colorectal cancer: Linking microbial virulence, metastatic progression, and therapy resistance. SRHU J Adv Res. 1(3): 67-85.

DOI: [to be assigned]

This work is licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0).

1. Introduction

Colorectal cancer (CRC) stands out as one of the most common cancers globally and continues to be a leading cause of cancer-related illness and death. Even with significant progress in areas like screening, molecular classification, surgical techniques, chemotherapy, targeted therapies, and immunotherapy, many patients still face challenges such as locally advanced or metastatic disease, recurrence, or resistance to treatment. The biological diversity of CRC stems not just from genetic and epigenetic changes within the tumor cells but also from their interactions with the surrounding tumor microenvironment. Recent studies have highlighted the role of the intestinal microbiota as an additional layer of complexity, influencing everything from tumor initiation and progression to immune responses and reactions to cancer therapies. (Dekker et al., 2019; Brennan and Garrett, 2019).

The connection between the gut microbiome and CRC is particularly fascinating, as these microbial communities can affect the integrity of host epithelial cells, inflammatory responses, cellular metabolism, and immune functions. While many bacterial species have been linked to CRC, *F. nucleatum* has emerged as one of the most frequently studied microorganisms associated with tumors. This Gram-negative, anaerobic bacterium is typically found in the oral cavity, yet its increased presence in colorectal tumors has been consistently noted. Notably, its presence isn't just a byproduct of changes in microbial composition during cancer; both experimental and clinical research increasingly indicates that *F. nucleatum* can actively engage with tumor cells and the surrounding environment, playing a role in disease progression. (Brennan and Garrett, 2019; Zepeda-Rivera et al., 2024).

Several molecular mechanisms have been suggested to clarify the link between *F. nucleatum* and CRC. For instance, the bacterial adhesin FadA can bind to E-cadherin on colorectal epithelial cells, influencing β-catenin signaling. Additionally, other components from the bacterium can trigger innate immune pathways, including Toll-like receptor activation. (Rubinstein et al., 2013; Gur et al., 2015; Brennan and Garrett, 2019).

Biology and colonization of *F. nucleatum*

F. nucleatum is a Gram-negative, obligately anaerobic, non-motile and spindle-shaped bacterium, and is mainly found in the human oral cavity where it acts as an important structural component of the polymicrobial dental biofilms (Brennan and Garrett, 2019). Instead of acting only as a typical pathogen, *F. nucleatum* can function as a commensal organism under normal physiological conditions and helps in the organization of the biofilm by being able to coaggregate with a wide variety of microorganisms that colonize early and those that colonize later. The particular adhesins on its surface enable it to interact with organisms including *Streptococcus* spp., *Porphyromonas gingivalis*, *Actinomyces* spp. and other members of the oral microbiota, allowing it to act as a “bridging” organism between microbial populations that would otherwise have only weak interactions. This ecological feature is significant since it gives *F. nucleatum* the ability to set up and keep polymicrobial communities rather than depending entirely on independent colonization. (Brennan and Garrett, 2019).

The biology of *F. nucleatum* is made even more

complex by the great genetic and phenotypic diversity that exists among the subspecies usually recognized. In the past, four main subspecies- *F. nucleatum*, animalis, polymorphum, and vincentii, have been identified; yet comparative genomic studies have shown that there is enough divergence in some of the lineages to have led to a recent reclassification of the taxonomy. Significantly, this diversity seems to have biological implications, since different strains and lineages show different ecological distributions in both the oral and gastrointestinal areas. Recent analyses have shown that the population structures at the strain level can vary between the gingival and intestinal environments, which indicates that bacterial lineages may be subjected to selective pressures as they move from the oral cavity to extra-oral habitats. With regard to colorectal cancer, the Fna C2 lineage has been found to be more abundant in stool from people with colorectal cancer than in gingival samples, thus providing evidence that some lineages are better adapted to the intestinal environment. (Zepeda-Rivera et al., 2024).

The shift of *F. nucleatum* from its main habitat in the mouth to the gastrointestinal tract is an important aspect in understanding its link with colorectal cancer. Even though the exact pathway and biological factors involved in this transition are not completely known, there is evidence that populations of oral origin of *F. nucleatum* can reach sites outside the mouth and still be found in the gastrointestinal environment. Notably, the distribution of *F. nucleatum* in the mouth does not necessarily mirror that of the populations found in the intestine; gingival samples tend to show a higher overall abundance, while certain lineages, especially Fna C2, appear to be enriched in intestinal samples associated with colorectal cancer. This finding supports the idea that colonization of the intestine may involve the selective survival or expansion of certain bacterial populations rather than the indiscriminate spread of the whole oral *F. nucleatum* community. (Zepeda-Rivera et al., 2024).

The ability of *F. nucleatum* to recognize and stick to particular molecular characteristics of the tumor microenvironment may help to facilitate the colonization of colorectal tumors. This bacterium has a number of adhesins associated with its surface, such as FadA, Fap2, RadD and FomA, which are involved in interactions with host cells and with other microorganisms. Since FadA interacts with E-cadherin, it is especially relevant to the development of colorectal cancer as this interaction can lead to bacterial attachment and internalisation together with an effect on β-catenin-associated signalling. In contrast, Fap2 has been linked to the recognition of Gal-GalNAc, a glycan which can be highly expressed on colorectal tumour cells and thus may provide a molecular explanation for the preferential accumulation of *F. nucleatum* in tumour tissue. These adhesion mechanisms might therefore enable *F. nucleatum* not only to get to the intestinal tract but also to persist selectively within the tumour-associated niche. (Rubinstein et al., 2013; Abed et al., 2016; Gur et al., 2015).

A key aspect of *F. nucleatum* colonization is its association with biofilm formation. In the oral cavity, the bacterium functions as a central bridging organism that promotes the formation of complex polymicrobial biofilms. The same kind of biofilm-related behavior may also account for its ability to persist in the gastrointestinal and tumor microenvironments. More

recent studies have increasingly indicated that *F. nucleatum* can be found among the microbial communities associated with tumors rather than existing as a separate bacterial species. These communities might offer protection against environmental stresses, encourage metabolic interactions between different species, and help to increase bacterial persistence. As a result, colonization of tumors should be considered an ecological process which involves bacterial adhesion, biofilm formation, interactions with other microorganisms, and adaptation to the biochemical and immune conditions of the colorectal tumor microenvironment. (Brennan and Garrett, 2019; Dejea et al., 2014). Taken together, these observations indicate that the presence of *F. nucleatum* in colorectal tumors is not merely a function of the total bacterial abundance but rather seems to depend on a combination of strain-specific genetic characteristics, adhesion capacity, ecological adaptation, biofilm formation, and selective interactions with the tumor microenvironment. The fact that CRC-associated lineages such as Fna C2 have been identified is especially significant since it contradicts the conventional approach of viewing

Figure 1. From bacterial colonization to colorectal cancer progression. The figure summarizes the role of Fusobacterium nucleatum in tumor colonization, oncogenic signaling, tumor-microenvironment remodeling, and immune evasion. Adapted conceptually from Gur et al. (2015), Sun et al. (2019), Zepeda-Rivera et al. (2024), and Wang et al. (2025).

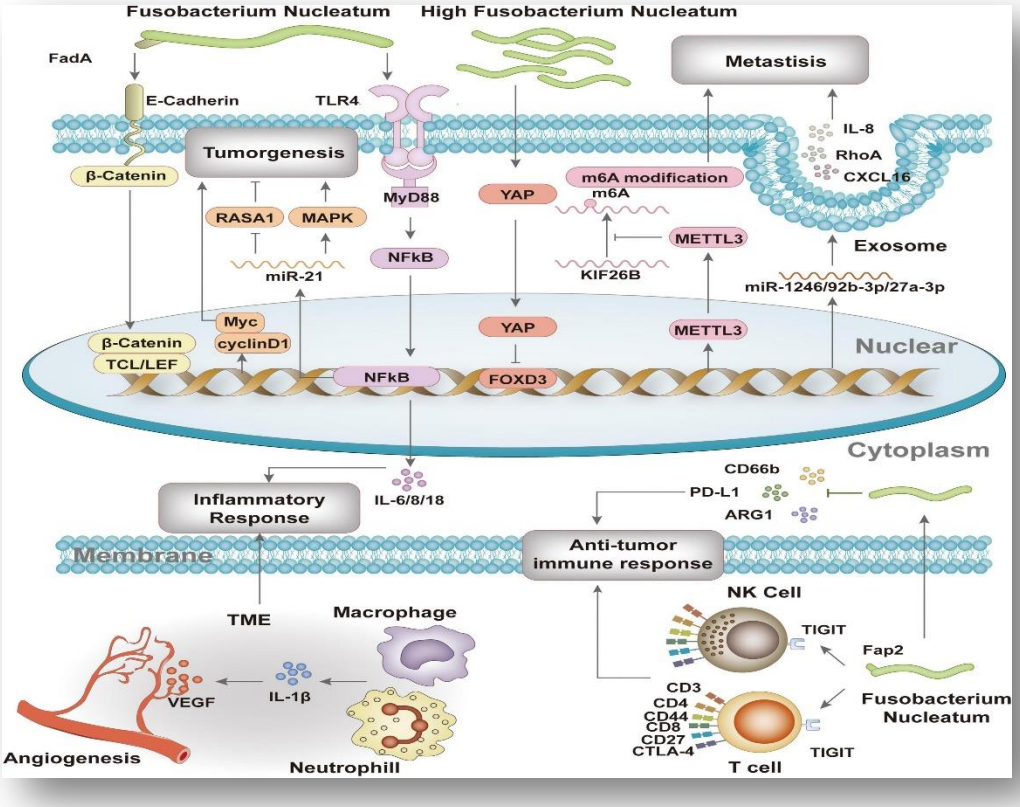


Figure 1. The process of bacterial colonization in human which leads to colorectal cancer progression.

F. nucleatum as a biologically uniform species. It therefore may be important to understand why certain bacterial lineages are able to transition from the oral cavity to the colorectal tumor environment and are then selectively retained there, as this could provide a key mechanistic connection between microbial ecology and the effects of *F. nucleatum* on tumor progression, metastasis, and therapeutic response. (Zepeda-Rivera et al., 2024; Brennan and Garrett, 2019).

F. nucleatum and promotion of colorectal cancer

There is growing evidence indicating that *F. nucleatum* (F. nucleatum) might play a role in the initiation of colorectal cancer (CRC) by changing the signaling of intestinal epithelial cells, causing inflammation, reducing immune surveillance, and interfering with the normal control of intestinal stem cells. Even though the bacterium is usually linked with the oral microbiota, its increased presence in colorectal tumors and some precancerous lesions has led to questions regarding its possible involvement in the early stages of colorectal carcinogenesis. Yet, the fact that it is found in tumor tissue does not mean that it causes cancer; present evidence shows that its effects may vary according to the host's genetic susceptibility, the inflammatory environment, and the biological properties of the bacterial strain. (Rubinstein et al., 2013; Gur et al., 2015; Wang et al., 2025).

A well-defined mechanism is the bacterial adhesin FadA, which binds to E-cadherin on the host's epithelial cells and triggers β-catenin-associated signaling. This binding can lead to the expression of genes that play a role in cellular proliferation and inflammatory responses and may thus promote the growth of abnormal epithelial cells. At the same time, *F. nucleatum* can activate Toll-like receptor-associated pathways and enhance inflammatory signaling, including that which is associated with microRNA-21. Continuous inflammatory activity might help to create an environment that is conducive to neoplastic development. The bacterium's Fap2 protein may also contribute to tumor development by interacting with receptors on immune cells, such as TIGIT, as a result of which the activity of natural killer cells and other immune cells responsible for identifying and eliminating abnormal cells is suppressed. Taken together, these mechanisms indicate that *F. nucleatum* can affect both the behavior of epithelial cells and the local immune response, producing conditions that could support early tumorigenesis. (Rubinstein et al., 2013; Kostic et al., 2013; Gur et al., 2015).

Another mechanistic explanation was given by Wang et al. (2025), who looked at the interaction between *F. nucleatum* and intestinal regenerative stem cells. Their results showed that the bacterium is able to colonize the deep parts of the intestinal crypts and interact with LY6A-positive revival stem cells, a group that is normally concerned with tissue repair. The researchers found that LY6A acts as a host-cell receptor in this interaction and that exposure to the bacterium leads to an increase in the expression of ribosomal protein S14 (RPS14). This pathway is linked to greater stem-cell proliferation and to the appearance of cells that have tumor-initiating properties. When LY6A or RPS14 was experimentally disrupted in their models, the tumor-promoting effects that were observed were reduced, which supports a functional role for this signaling pathway. Similar associations between *F. nucleatum* infection, features

of regenerative stem cells, and increased RPS14 expression were also found in human CRC samples. The results indicate that the bacterium might affect tumor initiation by disrupting the normal transition from intestinal regeneration to tissue transformation, although further research is needed to determine how far this mechanism operates during human CRC development.

It is important not to view the effects of *F. nucleatum* as independent of the host's genetic and physiological background. Experimental studies that were reviewed earlier show that bacterial exposure can lead to tumor development in susceptible models, such as those with alterations in the APC pathway. This implies that *F. nucleatum* might function as a tumor promoter that depends on the context rather than necessarily causing malignancy in normally structured intestinal tissue. Moreover, the fact that bacterial levels are linked to specific molecular characteristics of CRC, such as microsatellite instability and oncogenic changes, shows that there are associations but does not prove causation on its own. Variations in bacterial strain, colonization patterns, host genetics, and the level of inflammation may account for the fact that the relationship between *F. nucleatum* and CRC differs from one individual and experimental system to another. (Zepeda-Rivera et al., 2024; Brennan and Garrett, 2019). Taken together, the existing evidence points to a multifactorial model in which *F. nucleatum* could contribute to the initiation of colorectal tumors by the combination of epithelial signaling, inflammatory activation, immune evasion and reprogramming of regenerative stem cells. The FadA–E-cadherin/β-catenin pathway offers a mechanism by which bacterial adhesion is linked to proliferative signaling, and the Fap2–TIGIT interaction shows how immune suppression can enable abnormal cells to survive. The more recently identified LY6A–RPS14 axis broadens this model by indicating that bacterial infection can directly affect the behavior of cells taking part in intestinal repair and may thus lead to the formation of tumor-initiating populations. However, there are still important questions to be answered concerning the timing of colonization, the role of strain-specific features, and the causal significance of these mechanisms in human disease. Future research that combines longitudinal human sampling, strain-resolved microbial analysis and functional validation will be necessary to establish whether *F. nucleatum* acts as an early driver of carcinogenesis in certain subtypes of CRC or mainly serves to promote the expansion of lesions that have already been initiated by other genetic and environmental factors. (Rubinstein et al., 2013; Wang et al., 2025).

Interaction of *F. nucleatum* with the tumour microenvironment

The tumor microenvironment (TME) is a dynamic ecosystem which includes malignant epithelial cells, immune cells, stromal elements, blood vessels, cytokines, and the extracellular matrix. In the case of colorectal cancer (CRC), *F. nucleatum* has become a possible regulator of this ecosystem and affects both innate and adaptive immunity. Instead of being merely a tumor-associated bacterium, it is able to interact with the host's immune cells, modify inflammatory signalling, and create conditions that are favourable to tumor survival and progression. The way in which it exerts its

effects involves direct interactions with immune receptors, the recruitment of immunosuppressive cell populations, and alterations in the cytokine and chemokine environment. (Gur et al., 2015; Brennan and Garrett, 2019).

Chen et al. (2025) outlined a key mechanism involving the ability of *F. nucleatum* to survive within phagocytic immune cells, especially neutrophils and macrophages, and possibly use these cells as carriers to take the bacteria to tumor tissues. The researchers found that the bacterium could remain inside neutrophils by lowering the levels of intracellular reactive oxygen species (ROS) and releasing hydrogen sulfide (H_2S), which in turn helped it resist the antimicrobial defences. They also discovered that Fn1792, a lysozyme inhibitor produced by the bacterium, acts as a virulence factor by causing increased CX3CR1 expression and reducing apoptosis in the infected phagocytes. The phagocytes that were both positive for CX3CR1 and positive for PD-L1 were found to be involved in transporting the intracellular bacteria to tumor tissues. When the bacteria reached the tumor environment, both the infected cells and the tumor cells took part in recruiting more neutrophils and macrophils via the CXCL2/CXCL8–CXCR2 and CCL5–CCR5 signalling pathways. In the experimental models, the buildup of these cells was linked to more advanced tumor progression and metastasis as well as to a decreased effectiveness of immunotherapy. The idea of this phagocyte-mediated route provides a mechanism by which *F. nucleatum* might get to and survive in tumors, even though the strength of the evidence varies between the results from the experimental models and those observed in human patients.

In addition to its effects on phagocytes, *F. nucleatum* can affect the balance between antitumor immunity and tumor-promoting inflammation. The Fap2 adhesin of the bacterium binds to the inhibitory immune receptor TIGIT, which is found on natural killer (NK) cells and on certain subsets of T cells. As a result, the cytotoxic activity of immune cells is impaired, reducing the host's ability to get rid of malignant cells. The bacterium has also been linked to CEACAM1-mediated inhibitory signalling and to altered T-cell function. At the same time, inflammatory pathways such as those involving NF-κB can lead to the production of mediators like IL-6, IL-8, TNF-α and IL-17A. Even though inflammation is normally part of the host's defense mechanism, persistent or dysregulated inflammatory signalling can help tumor cells survive, cause tissue remodeling, promote invasion and facilitate metastatic progression. Therefore, *F. nucleatum* may at the same time stimulate inflammatory activity and inhibit effective antitumor immunity, resulting in a microenvironment that is inflammatory but not effective at eliminating cancer cells. (Gur et al., 2015; Chen et al., 2025).

It could also help to maintain this environment by changing the number and functional condition of the various types of immune cells in the tumor. The papers by Galasso et al. (2025) and Wuyi and Tao (2026) mention associations with myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), regulatory T cells (Tregs), Th17 cells and cytotoxic $CD8^+$ T cells. MDSCs are able to inhibit T-cell proliferation and activity, whereas M2-like macrophages might contribute to immunosuppression, angiogenesis and tissue

remodeling. Some of the different states of tumor-associated neutrophils can also lead to inflammatory damage and promote tumor progression. In the area of adaptive immunity, *F. nucleatum* has been connected with increased Th17-associated responses, less $CD8^+$ T-cell infiltration or activity, and signs of T-cell exhaustion. Such alterations can result in a reduction of immune surveillance while at the same time keeping a pro-inflammatory environment. Nevertheless, it is still unclear in several human datasets to what extent each of the changes in immune cells is directly caused by the bacterium rather than by the tumor subtype, more widespread microbial dysbiosis or other host factors. (Brennan and Garrett, 2019; Wuyi and Tao, 2026).

Another complication is the connection between *F. nucleatum*, PD-L1 expression and the response to immunotherapy. Chen et al. (2025) discovered that higher bacterial abundance was linked to an increased number of PD-L1-positive neutrophils in the blood of patients with CRC, and their experimental studies connected the infiltration of CX3CR1-positive, PD-L1-positive phagocytes with reduced efficacy of immunotherapy. The 2026 review, on the other hand, mentions evidence indicating that *F. nucleatum*-related upregulation of PD-L1 might, in some biological situations, be accompanied by greater sensitivity to PD-1/PD-L1 checkpoint blockade. These findings are not necessarily in conflict since PD-L1 expression by itself does not determine the response to treatment, the response also depending on the state and position of T cells, the tumor molecular subtype, the level of baseline immune infiltration and other characteristics of the microenvironment. As a result, bacterial abundance or PD-L1 expression should at this stage not be regarded as a standalone predictor of the benefit from immunotherapy. (Chen et al., 2025; Wuyi and Tao, 2026).

Table 1: Major mechanisms linking *F. nucleatum* to colorectal cancer progression (Brennan and Garrett, 2019; Wuyi and Tao, 2026).

Biological Process	Key Molecular Mechanism	Effect on Colorectal Cancer	Representative reference
Tumour colonisation	FadA binding to E-cadherin; Fap2 recognition of Gal-GalNAc	Promotes bacterial attachment and preferential colonisation of tumour tissue	Gur et al. (2015); Zepeda-Rivera et al. (2024)
Tumour initiation	FadA–E-cadherin/β-catenin signalling	Activates proliferative and oncogenic signalling in epithelial cells	Sun et al. (2019)
Inflammatory signalling	TLR-associated signalling and miRNA-21 regulation	May support inflammation, epithelial proliferation and tumour-promoting conditions	Sun et al. (2019)
Stem-cell	Interaction with LY6A-	Promotes stem-cell	Wang et al.

reprogramming	positive regenerative stem cells and increased RPS14 expression	proliferation and tumour-initiating traits in experimental models	(2025)
Clinical metastatic association	Intratumoral bacterial detection associated with inflammation and altered immune-cell infiltration	Associated with metastatic disease characteristics and recurrence involving multiple organs	Shigematsu et al. (2024)

Taken together, these findings point to a model in which *F. nucleatum* alters the CRC tumor microenvironment by means of a number of interconnected processes, including intracellular survival, the transport of the bacteria by phagocytes, the recruitment of immune cells via chemokine signalling, inflammatory signalling and the suppression of antitumor immunity. The mechanism involving phagocytes and the CX3CR1–PD-L1 interaction in particular offers a significant link between bacterial colonization and the recruitment of immune cells that could promote tumor progression. At the same time, the interactions involving Fap2–TIGIT, myeloid suppressor populations and modified T-cell states show how the bacterium might impair immune surveillance following colonization. However, these mechanisms should not be regarded as applicable in all CRC cases, and several of the proposed relationships are supported more adequately by experimental models or by retrospective associations than by prospective clinical evidence. It will be important for future studies to integrate spatial profiling, bacterial strain characterization, immune-cell functional analysis and longitudinal treatment outcomes in order to establish how these interactions contribute to disease progression and whether targeting the bacterium can lead to improved therapeutic responses.

Role in colorectal cancer metastasis

F. nucleatum could contribute to the metastasis of colorectal cancer (CRC) by having a series of interconnected effects on the behaviour of tumour cells, epigenetic regulation, systemic inflammation, and immune restructuring. Chen et al. (2022) showed that *F. nucleatum* increased the ability of CRC cells to migrate and invade by activating the Hippo–YAP signalling pathway, which in turn suppressed the transcription factor FOXD3 and decreased the expression of the mRNA methyltransferase METTL3. This in turn led to a lower level of N6-methyladenosine (m^6A) modification of RNA, resulting in reduced degradation of the KIF26B mRNA via YTHDF2 and consequently higher KIF26B expression, which ultimately promoted metastatic behaviour in experimental models. In addition to this cellular mechanism, Yin et al. (2022) found that giving mice *F. nucleatum* orally increased the extent of liver metastasis and reduced their survival in a mouse model of CRC. This was accompanied by higher levels of circulating inflammatory mediators, such as IL-6, TNF-α, IL-12 and IFN-γ, an increased accumulation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) in the liver, and a decreased infiltration of

natural killer (NK) cells and other T-cell populations. The study also noted a reduction in gut microbial diversity and a higher abundance of bacteria that may promote CRC, such as Enterococcus and Escherichia/Shigella, indicating that *F. nucleatum* might influence liver metastasis both directly and by disrupting the gut microbiota–liver immune axis. Human evidence was given by Shigematsu et al. (2024), who found *F. nucleatum* DNA in 42% (92 out of 218) of the CRC liver-metastasis specimens. A higher bacterial abundance was linked to increased serum C-reactive protein, fewer intratumoral $CD8^+$ and $FOXP3^+$ cells, and a greater number of metastatic organs involved in recurrence. These findings indicate a connection between the presence of the bacterium in metastatic lesions, systemic inflammation, changes in local immunity, and more widespread metastatic spread. However, the 2024 study was retrospective and observational, whereas the mechanistic and liver-metastasis findings from the earlier studies were mainly obtained from cell-based or mouse models; thus, the clinical associations do not on their own prove that the bacterium causes metastatic dissemination in humans. Together, these studies support a model in which *F. nucleatum* may promote the metastasis of CRC by making the tumour cells more aggressive through the YAP–FOXD3–METTL3–KIF26B pathway and by altering the immune and microbial environments in a way that affects metastatic colonization and recurrence. (Chen et al., 2022; Yin et al., 2022; Shigematsu et al., 2024).

F. nucleatum and chemoresistance

The bacterium *F. nucleatum* is becoming more and more involved in colorectal cancer (CRC) chemoresistance due to its ability to alter cellular survival signalling and inhibit chemotherapy-induced cell death. Zhang et al. (2019) showed that *F. nucleatum* decreased the sensitivity of CRC cells to 5-fluorouracil (5-FU) by activating the Toll-like receptor 4 (TLR4)/NF-κB signalling pathway, which in turn increased the expression of baculoviral IAP repeat-containing protein 3 (BIRC3), a protein that inhibits apoptosis. When BIRC3 levels are elevated, caspase-mediated apoptosis is suppressed, enabling the cancer cells to survive the chemotherapy. This mechanism was supported by their cell and animal experiments, and a clinical analysis of 94 patients who had received 5-FU-based adjuvant chemotherapy revealed a link between a high amount of *F. nucleatum* in the tumour and chemoresistance-related outcomes. Going beyond the role in apoptosis, Wang et al. (2024) examined the role of pyroptosis, a type of inflammatory programmed cell death, in *F. nucleatum* related chemoresistance. They found that *F. nucleatum* inhibited chemotherapy-induced pyroptosis after exposure to either 5-FU or oxaliplatin by regulating the Hippo pathway and increasing the expression of B-cell lymphoma 2 (BCL2). Higher levels of BCL2 reduced the activation and cleavage of both caspase-3 and gasdermin E (GSDME), thus suppressing GSDME-mediated pyroptosis and enhancing CRC cell survival during chemotherapy. These findings were confirmed by cell studies, patient-derived tumour organoids and animal models. The study also found that blocking YAP or BCL2 could reverse some of the resistant characteristics in experimental systems, although the partial effect of knocking out GSDME suggested that inhibition of pyroptosis does not completely account for the resistance caused by the

bacterium. In addition to these primary studies, Dadgar-Zankbar et al. (2024) reviewed the evidence connecting *F. nucleatum* to various chemoresistance mechanisms, such as inhibition of apoptosis, modulation of autophagy, changes in gene expression and modifications of the tumour microenvironment. Their review supports the idea that the effects of the bacterium on chemotherapy response result from interconnected cellular survival pathways rather than a single molecular mechanism. Together, these studies indicate that *F. nucleatum* may reduce the sensitivity of cancer cells to chemotherapy by suppressing different types of programmed cell death, especially via the TLR4/NF-κB/BIRC3 and Hippo/YAP/BCL2 signalling pathways. However, the extent to which these mechanisms contribute may differ depending on the tumour model and the treatment context, and the clinical associations should not be seen as conclusive proof that bacterial colonisation causes treatment failure in every patient. (Zhang et al., 2019; Wang et al., 2024; Li et al., 2024).

***F. nucleatum* and immunotherapy**

In the study entitled *F. nucleatum* derived succinic acid induces tumour resistance to immunotherapy in colorectal cancer, Jiang et al. (2023) examined the effect of *F. nucleatum* on the effectiveness of immune checkpoint blockade, especially that involving anti-PD-1 therapy. They discovered that among patients with metastatic colorectal cancer who did not respond to immunotherapy, there were higher levels of *F. nucleatum* and its metabolite succinic acid. As for the mechanism involved, succinic acid derived from *F. nucleatum* inhibited the cyclic GMP–AMP synthase (cGAS)–interferon-β (IFN-β) signalling pathway, which in turn decreased the production of the chemokines CCL5 and CXCL10 that attract T cells. This in turn restricted the infiltration of CD8+ cytotoxic T cells into the tumour microenvironment and diminished antitumour immunity, thus lowering the sensitivity of the tumours to anti-PD-1 treatment. The study also showed that treatment with metronidazole decreased the amount of *F. nucleatum* in the intestine and lowered succinic acid levels, leading to a restoration of sensitivity to immunotherapy in the experimental models. These results offer mechanistic evidence of a link between a bacterial metabolite and resistance to immune checkpoint inhibitors, although the therapeutic advantages of targeting *F. nucleatum* still need to be confirmed by further clinical studies. (Jiang et al., 2023).

Li and colleagues (2025), in their paper titled *F. nucleatum* Derived Outer Membrane Vesicles Promote Immunotherapy Resistance via Changes in Tryptophan Metabolism in Tumour-Associated Macrophages, looked at how outer membrane vesicles (OMVs) released by *F. nucleatum* affect antitumour immunity. Unlike the earlier study which.

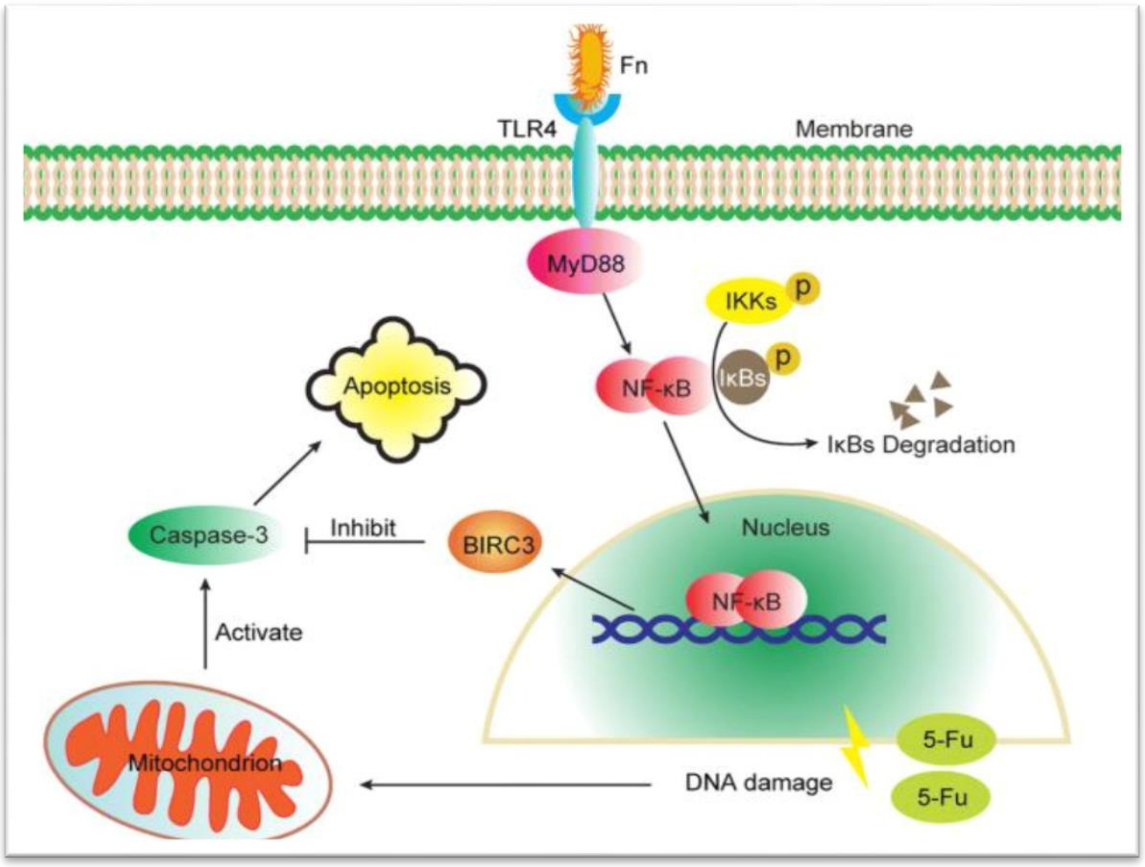


Figure 2. Proposed mechanisms of *F. nucleatum*-associated treatment resistance in colorectal cancer. The figure summarises reported mechanisms involving apoptosis, pyroptosis, ferroptosis and immunotherapy response. Adapted conceptually from Zhang et al. (2019), Wang et al. (2024), Li et al. (2024), and Jiang et al. (2023).

Focused on colorectal cancer, this one mainly looked at head and neck squamous cell carcinoma (HNSCC), so it provides relevant supportive mechanistic evidence rather than direct evidence in the case of colorectal cancer. They discovered that *F. nucleatum* derived OMVs were taken up by tumour-associated macrophages (TAMs), where bacterial tryptophanase activated the tryptophan-2,3-dioxygenase 2/aryl hydrocarbon receptor (TDO2/AHR) pathway, which in turn promoted immunosuppressive macrophage traits, increased the expression of immunosuppressive cytokines and immune checkpoint molecules, and reduced the infiltration of cytotoxic CD8+ T cells into the tumours. As a result, the tumour microenvironment became more conducive to tumour progression and less supportive of effective immune-mediated tumour destruction. In the mouse models, inhibition of TDO2 enhanced the response to anti-PD-1 therapy. The study thus indicates that bacterial products can influence the response to immunotherapy even without the need for the whole bacterium to colonise the tumour cells. Nevertheless, the results have to be confirmed specifically in colorectal cancer before the same mechanism can be assumed to apply in colorectal tumours. (Li et al., 2025).

The *F. nucleatum* playbook Wuyi and Tao (2026)

compiled the evidence showing how *F. nucleatum* alters the immune microenvironment of colorectal tumours and may thus affect the results of immunotherapy. The authors outlined several mechanisms by which immune evasion occurs, such as the interaction between the bacterial adhesin Fap2 and TIGIT on natural killer (NK) cells and cytotoxic T lymphocytes, which in turn inhibits their ability to attack the tumour. They also mentioned the recruitment of myeloid-derived suppressor cells (MDSCs), the immunosuppressive polarisation of tumour-associated macrophages, the stimulation of inflammatory Th17 responses, and the reduced infiltration or impaired function of CD8+ T cells. Such alterations could lead to immune escape and a decreased effectiveness of immune checkpoint inhibitors. Crucially, the review points out a possibly complex link between *F. nucleatum* and PD-L1 expression: even though bacterial activity might lead to immune suppression and resistance, higher PD-L1 expression could cause certain tumours to respond better to PD-1/PD-L1 blockade. However, this possibility is still dependent on the context and should not be taken to mean that *F. nucleatum* positive tumours will definitely respond better to immunotherapy. The authors consider bacterial abundance to be a potential predictive biomarker and talk about various approaches, including the use of antibiotics, bacteriophages, inhibitors of virulence factors, and combination therapies. Yet they stress that most of the human evidence is still observational and that prospective studies are required in order to determine whether *F. nucleatum* can reliably predict treatment response or act as a clinically useful therapeutic target.

Diagnostic and prognostic potential of *F. nucleatum*

F. nucleatum has become a promising biomarker for the diagnosis and prognosis of colorectal cancer (CRC) because it is often found in tumor tissues and can be detected in fecal samples. According to the studies summarized by Brennan and Garrett (2019), encouraging diagnostic performance was observed, with one meta-analysis achieving an area under the receiver operating characteristic curve (AUC) of 0.86. Nevertheless, other meta-analyses found lower accuracy, pointing to inconsistencies related to the detection methods, the groups of patients studied, and the diagnostic cut-off values used. Yu et al. (2024) and He et al. (2025) also look at the possible clinical uses of detecting *F. nucleatum*, such as enabling non-invasive CRC screening, assessing disease progression, monitoring for recurrence and predicting treatment outcomes. In a number of studies, a higher abundance of the bacterium has been linked to more advanced tumor features, metastasis, recurrence and worse survival, indicating that *F. nucleatum* might offer prognostic information in addition to standard clinical parameters such as TNM staging. With regard to cancers other than CRC, Huang et al. (2020) found that increased levels of *F. nucleatum* within the tumor were associated with poorer overall and progression-free survival in a group of 112 patients with cervical carcinoma, thus supporting further research into the bacterium's prognostic significance in different types of cancer, even though these results cannot be directly applied to CRC. Yet, despite these positive findings, the clinical usefulness of *F. nucleatum* is still restricted by differences in sample types, detection techniques, thresholds for bacterial abundance and patient

characteristics. Moreover, the fact that higher bacterial levels are associated with adverse outcomes does not mean that they have independent predictive power or that there is a causal relationship. As a result, large-scale prospective and multicenter studies, standardized detection procedures, and validation in a variety of populations are needed before *F. nucleatum* can be routinely used in CRC screening, prognostic evaluation or treatment-monitoring programmes. (Brennan and Garrett, 2019; Yu et al., 2024).

Therapeutic target of *F. nucleatum*

The idea of using treatments directed at *F. nucleatum* to slow down the progression of colorectal cancer (CRC), to prevent metastasis and to overcome treatment resistance is a promising one. New strategies go beyond standard antibiotics such as metronidazole and now involve targeted drug-delivery systems, nanomedicines, antimicrobial peptides, bacteriophage therapy, vaccines and the inhibition of bacterial virulence factors. Approaches based on nanotechnology, such as liposomal antibiotics and tumor-targeted nanoplatforms, could improve the clearance of the bacteria while at the same time reducing disturbance of the beneficial gut microbiota. A key therapeutic target is Fap2, a bacterial adhesin which binds to Gal-GalNAc structures that are frequently overexpressed on CRC cells and thus helps the bacteria to colonize the tumor. Fap2 also binds to the inhibitory immune receptor TIGIT, thereby suppressing the activity of natural killer cells and weakening the antitumor immune response. It therefore follows that interfering with the interactions mediated by Fap2 could possibly decrease bacterial accumulation in the tumors while at the same time restoring antitumor immune responses. Other suggested strategies are to target bacterial lineages associated with tumors, such as the Fna C2 clade, to eliminate intracellular bacterial reservoirs and to develop vaccines against bacterial surface proteins. Phage-based methods might allow for a more selective elimination of bacteria, while genetically attenuated or modified *F. nucleatum* has been suggested as a possible therapeutic tool, even though its safety and effectiveness are still uncertain. Nevertheless, most of these approaches are still at an experimental or preclinical level. Major challenges include achieving selective delivery to tumor-associated bacteria, the persistence of bacteria within cells, antimicrobial resistance, differences between strains, unintended effects on the gut microbiome and the potential risks linked to the use of genetically modified bacteria. As a result, future research should focus on strain-specific targeting, on improving the delivery systems and on carrying out rigorous clinical validation in order to determine whether these strategies can safely lead to an improvement in CRC treatment outcomes. (Gur et al., 2015; Zepeda-Rivera et al., 2024; Jiang et al., 2023).

Current challenges and knowledge gaps

Research into the role of *F. nucleatum* in colorectal cancer (CRC) is encountering a number of significant difficulties which prevent the transfer of results from experimental studies into clinical practice. A key area lacking in our knowledge is the great variety of strains and subspecies of the organism, since variations in genomic content, virulence factors, ability to colonize tumors and response to treatment could all affect its pathogenicity. Yet a great many of the studies have

been based on a small number of laboratory strains and might therefore have missed out on biologically distinct lineages. Moreover, the causal link between *F. nucleatum* and CRC is not well understood, especially whether the bacterium causes tumor development or instead tends to colonize an already existing tumor microenvironment. There are also limitations with the current experimental models: animal models do not adequately mimic the human gut microbiome and immune environment, and organoid systems lack important stromal and immune components. (Brennan and Garrett, 2019; Zepeda-Rivera et al., 2024).

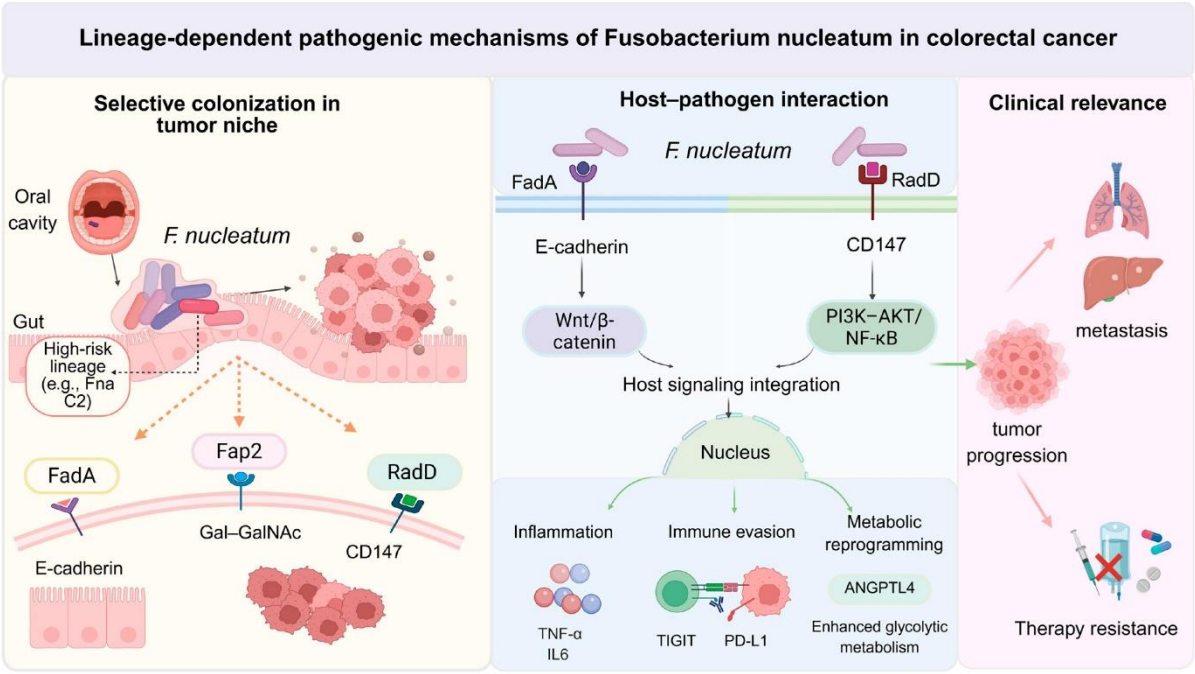


Figure 3. Strain-specific colonization and its potential influence on colorectal cancer outcomes. The figure illustrates the proposed interactions between bacterial lineage, virulence factors, host characteristics and the tumour microenvironment in influencing tumour progression, metastasis and treatment response. Adapted conceptually from Zepeda-Rivera et al. (2024), Chen et al. (2022), and Shigematsu et al. (2024).

The application of this research to clinical settings is additionally obstructed by inconsistent methods for detecting the bacteria, differing assay thresholds, variations between measurements taken from stool and those from tumor tissue, and the fact that the distribution of the bacteria within tumors is not uniform. Even though *F. nucleatum* has potential as a diagnostic, prognostic and therapeutic biomarker, its reliability and clinical usefulness must be confirmed in larger and more diverse groups of patients. Overcoming these shortcomings will demand standardized methods for detecting the bacteria and for strain typing, longitudinal clinical studies, better experimental models, integrated multi-omics approaches and validation carried out across multiple centers. In the end, it will be essential to clarify the specific functions of different strains and to distinguish between causal mechanisms and clinical associations if reliable

biomarkers and targeted therapeutic strategies against *F. nucleatum* associated CRC are to be developed. (Brennan and Garrett, 2019; Yu et al., 2024).

Table 2. Diagnostic, prognostic and therapeutic applications of *F. nucleatum* in colorectal cancer

Clinical application or strategy	Biological rationale or approach	Potential clinical significance	Major limitations and research needs	Representative reference
Faecal diagnostic biomarker	Detection of *F. nucleatum* DNA in stool samples	May support non-invasive CRC detection and screening research	Diagnostic accuracy varies with population, assay, sample processing and cut-off values	Brennan and Garrett (2019); Yu et al. (2024)
Tumour-tissue biomarker	Measurement of bacterial abundance in colorectal tumour tissue	May help characterise bacterial colonisation and tumour-associated microbial features	Tissue sampling is invasive, and intra tumoral bacterial distribution may be heterogeneous	Zepeda-Rivera et al. (2024); Yu et al. (2024)
Prognostic biomarker	Assessment of bacterial abundance alongside tumour and clinical characteristics	May provide additional information about disease progression, recurrence or survival	Independent prognostic value requires validation in well-designed clinical cohorts	Brennan and Garrett (2019); Yu et al. (2024)
Treatment-response biomarker	Evaluation of bacterial abundance in relation to chemotherapy or immunotherapy outcomes	May help identify associations between bacterial colonisation and treatment resistance	Association does not establish causation; predictive value needs prospective validation	Zhang et al. (2019); Jiang et al. (2023)
Conventional antibiotic treatment	Reduction of bacterial burden using agents such as metronidazole	May reduce bacteria-associated tumour-promoting effects in experimental settings	Potential microbiome disruption, antimicrobial resistance and uncertain clinical benefit	Jiang et al. (2023)

Conclusion

F. nucleatum has become an important factor in the biology of colorectal cancer (CRC), with growing evidence showing that its colonization of the tumor, interaction with host signaling and immunomodulatory actions are linked to the progression of the disease and to the results of treatment. Its impact goes beyond simply being present in the tumor microenvironment since it involves the activation of oncogenic pathways, changes in the functions of immune cells, the promotion of metastatic spread and the modulation of how cancer cells respond to chemotherapy and immunotherapy. New research has also shown that there is a great deal of biological variety among *F. nucleatum*, indicating that variations in bacterial traits and their interactions with the host may affect its role in the development and progression of CRC. However, it is not yet fully understood how much the bacterium directly causes carcinogenesis rather than simply colonizing an already existing tumor environment. In addition, limitations in experimental models, methods for detecting the bacterium and the design of clinical studies further hinder the comparability of the findings and their application in patient care. Even though *F. nucleatum* has potential as a diagnostic and prognostic biomarker and as a possible therapeutic target, its clinical usefulness must be thoroughly validated. Future research should focus on long-term clinical studies, the use of experimentally relevant models, standardized molecular detection methods and the integration of analyses of microbial, tumor and immune features. In the end, a clearer understanding of the complex relationship between *F. nucleatum* and its host will be necessary if reliable biomarkers are to be developed, if it is possible to identify the patients who may benefit from targeted treatments, and if it can be determined whether manipulating the microbiome can improve treatment responses and clinical outcomes in CRC.

References

Abed J, Emgård JE, Zamir G, Faroja M, Almogy G, Grenov A, Sol A, Naor R, Pikarsky E, Atlan KA, Mellul A, Chaushu S, Manson AL, Earl AM, Ou N, Brennan CA, Garrett WS, Bachrach G 2016. Fap2 mediates *F. nucleatum* colorectal adenocarcinoma enrichment by binding to tumor-expressed Gal-GalNAc. Cell Host Microbe, 20(2), 215–225. https://doi.org/10.1016/j.chom.2016.07.006

Brennan C A, Garrett W S 2019. *F nucleatum* symbiont, opportunist and onco bacterium. Nature Rev Microbio 17 156–166. https://doi.org/10.1038/s41579-018-0129-6

Chen F, Guo S, Li Y, Lu Y, Liu L, Chen S, An J, Zhang G. (2025). *F nucleatum* driven CX3CR1+ PD-L1+ phagocytes route to tumor tissues and reshape tumor microenvironment. Gut Microbes, 17(1), 2442037. https://doi.org/10.1080/19490976.2024.2442037

Chen Y, Peng Y, Yu J, Chen T, Wu Y, Shi L, Li Q, Wu J, Fu X. (2017). Invasive *F nucleatum* activates beta-catenin signal in colorectal cancer via a TLR4/P-PAK1 cascade. Oncotarget, 8(19), 31802–31814. https://doi.org/10.18632/oncotarget.15902

Dadgar-Zankbar, Elahi, Shariati Z, Khaledi A, Razavi A, Khoshbayan S. 2024. Exploring the role of *F nucleatum* in colorectal cancer: Implications for tumor proliferation and chemoresistance. Cell

Commun Signal, 22, 547. https://doi.org/10.1186/s12964-024-01909-y

Dejea CM, Wick EC, Hechenbleikner EM, White JR, Mark Welch JL, Rossetti BJ, Peterson SN, Snesrud EC, Borisy GG, Lazarev M, Stein E, Vadivelu J, Roslani AC, Malik AA, Wanyiri JW, Goh KL, Thevambiga I, Fuj K, Wan F, Llosa N, Housseau F, Romans K, Wu XQ, McAllister FM, Wu S, Vogelstein B, Kinzler KW, Pardoll DM, Sears CL. 2014. Microbiota organization is a distinct feature of proximal colorectal cancers. Proceed Nat Acad Sci, 111(51), 18321–18326. https://doi.org/10.1073/pnas.1406199111

Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. 2019. Colorectal cancer. The Lancet, 394(10207), 1467–1480. https://doi.org/10.1016/S0140-6736(19)32319-0

Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, Enk J, Bar-On Y, Stanietsky-Kaynan N, Coppenhagen-Glazer S, Shussman N, Almogy G, Cuapio A, Hofer E, Mevorach D, Tabib A, Ortenberg R, Markel G, Miklić K, Jonjic S, Brennan CA, Garrett WS, Bachrach G, Mandelboim O. 2015. Binding of the Fap2 protein of *F nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack. Immunity, 42(2), 344–355. https://doi.org/10.1016/j.immuni.2015.01.010

Shan-Shan Jiang, Yi-Le Xie, Xiu-Ying Xiao, Zi-Ran Kang, Xiao-Lin Lin, Lu Zhang, Chu-Shu Li, Yun Qian, Ping-Ping Xu, Xiao-Xu Leng, Li-Wei Wang, Shui-Ping Tu, Ming Zhong, Gang Zhao, Jin-Xian Chen, Zheng Wang, Qiang Liu, Jie Hong, Hao-Yan Chen, Ying-Xuan Chen, Jing-Yuan Fang 2023. *F nucleatum* derived succinic acid induces tumor resistance to immunotherapy in colorectal cancer. Cell Host Microbe, 31(5), 781–797.e9. https://doi.org/10.1016/j.chom.2023.04.010

Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS. 2013. *F nucleatum* potentiates intestinal tumorigenesis and modulates the tumour immune microenvironment. Cell Host Microbe, 14(2), 207–215. https://doi.org/10.1016/j.chom.2013.07.007

Bowen Li, Zixian Wei, Zhiyue Wang, Fangqi Xu, Jinhua Yang, Baiqiang Lin, Yu Chen, Hubin Wenren, Lingli Wu, Xiao Guo, Yang Liu, Yunwei Wei. 2024. *F nucleatum* induces oxaliplatin resistance by inhibiting ferroptosis through E-cadherin/β-catenin/GPX4 axis in colorectal cancer. Free Radical Bio and Medicine, 220, 125–138. https://doi.org/10.1016/j.freeradbiomed.2024.04.226

Li W, Zhang Z, Wu R, Mao M, Ji Y, Wang X, Dou S, Yan M, Chen W. 2025. *F nucleatum* derived outer membrane vesicles promote immunotherapy resistance via changes in tryptophan metabolism in tumour associated macrophages. J Extracell Vesicle, 14(4), e70070. https://doi.org/10.1002/jev2.70070

Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. 2013. *F nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signal via its FadA adhesin. Cell Host Microbe, 14(2), 195–206. https://doi.org/10.1016/j.chom.2013.07.012

Shigematsu Y, Saito R, Amori G, et al. 2024 *F nucleatum*, immune responses, and metastatic organ diversity in colorectal cancer liver metastasis. Cancer Sci, 115(10), 3248–3255. https://doi.org/10.1111/cas.16315

Sun CH, Li BB, Wang B, Zhao J, Zhang XX, Li TT, Li WB, Tang D, Qiu MJ, Wang XC, Zhu M, Qian ZR. 2019. The role of *F nucleatum* in colorectal cancer: From carcinogenesis to clinical management. Front Oncol, 9, 566. https://doi.org/10.3389/fonc.2019.00566

Wang N, Zhang L, Leng XX, Xie YL, Kang ZR, Zhao LC, Song LH, Zhou CB, Fang ZY. 2024. *F nucleatum* induces chemoresistance in colorectal cancer by inhibiting pyroptosis via the Hippo pathway. Gut Microbes, 16(1), 2333790. https://doi.org/10.1080/19490976.2024.2333790

Wuyi W, Tao P. 2026. Microbe-driven immune suppression in colorectal cancer: The Fusobacterium nucleatum playbook. Front Immuno, 17, 1795703. https://doi.org/10.3389/fimmu.2026.1795703

Yu LC, Li YP, Xin YM, Mao M, Pan YX, Qu YX, Luo ZD, Zhang Y, Zhang X. 2024. Application of *F nucleatum* as a biomarker in gastrointestinal malignancies. World Journal of Gastrointestinal Oncology, 16(6), 2271–2283. https://doi.org/10.4251/wjgo.v16.i6.2271

Zepeda-Rivera M, Minot SS, Bouzek H, Wu H, Blanco-Míguez A, Manghi P, Jones DS, LaCourse KD, Wu Y, McMahon EF, Park SN, Lim YK, Kempchinsky AG, Willis AD, Cotton SL, Yost SC, Sicinska E, Kook JK, Dewhirst FE, Segata N, Bullman S, Johnston CD. 2024. A distinct *F nucleatum* clade dominates the colorectal cancer niche. Nature, 628(8007), 424–432. https://doi.org/10.1038/s41586-024-07182-w

Zhang S, Yang Y, Weng W, Guo B, Cai G, Ma Y, Cai S. 2019. *F nucleatum* promotes chemoresistance to 5-fluorouracil by upregulation of BIRC3 expression in colorectal cancer. J Expt Clinical Cancer Res, 38, 14. https://doi.org/10.1186/s13046-018-0985-y