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The Pathophysiological and Diagnostic Role of *Fusobacterium nucleatum* in Colorectal Cancer †

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Abstract: Colorectal cancer (CRC) is common cancer, and it has a high mortality rate, especially in developed countries. Lately, developing countries that adopt a westernized lifestyle have exhibited an increased incidence of deaths caused by CRC. This trend and the reduced number of genetic syndromes linked to CRC led to the conclusion that the environment and lifestyle are key elements in the pathophysiology of CRC. We are interested in the dietary component as it mediators intestinal microbiota. Studies have shown that gut microbial dysbiosis is crucial in CRC development. Various bacteria have been associated with colon tumors, but the microorganism that sparked the most interest is *Fusobacterium nucleatum* (*F. nucleatum*). This gram-negative anaerobic pathobiont is part of the normal oral flora and, in a scarce quantity, the normal gut microbiota. It is unclear if gut dysbiosis promotes carcinogenesis or if the tumoral microenvironment disturbs the microbiota. However, studies have shown that *F. nucleatum* is involved in tumor progression and metastasis. As it got more studied, F. nucleatum started being considered as a potential early-stage, noninvasive tumor biomarker for CRC. Research was conducted on the electronic database Pubmed in order to identify articles relevant to the subject, published between 2017 and 2022. Search formula included ("Colorectal cancer" OR "Colon cancer" OR "Rectal cancer") AND ("*Fusobacterium nucleatum*" or "*Fusobacterium*") and ("Microbiota" or "Intestinal Microbiota" or "Intestinal microbiome"). A total of 20 articles were selected. In the early stages of studying the relationship between CRC and intestinal microbiota, fecal samples were used. Later it was shown that mucosal tissue samples provided a better assessment of microbial diversity. As the bacteria colonize the mucosa, it is plausible that alterations in the gene expression may be caused, leading to cancer. An important pro-oncogenic mechanism of *F. nucleatum* is the proliferative effect of the β-catenin signaling cascade mediated by the adhesion of FadA protein to E-cadherin of tumoral cells. Another mechanism is the Fap2 protein-mediated suppression of the anti-tumor T-cell and natural killer cell cytotoxicity, allowing tumor growth. The impairment of host immune surveillance is also assured by releasing myeloid chemoattractants that lead to the expansion of myeloid-derived immune cells. Not only does this bacterium have proliferative effects on CRC, but it can also be found in metastases in the lymph nodes, liver, and lungs, but the mechanism needs to be further studied. Patients with abundant *Fusobacterium* usually have a poorer prognosis, the survival period being around 2 years. Currently, the diagnosis of CRC is usually made in advanced stages because of the late appearance of the symptoms. CEA and CA19-9 are the most commonly used noninvasive tumor markers but have low diagnostic capabilities. As an alternative, it is proposed the dosage of salivary *F. nucleatum* DNA, as patients with CRC register high levels of it. *Fusobacterium nucleatum* raises some interesting questions regarding the oncogenesis of colorectal cancer and its diagnosis. Further research is needed to clarify the pathogenesis of colorectal cancer and to decide if the *Fusobacterium nucleatum* is a reliable diagnostic marker.

Keywords: colorectal cancer; *Fusobacterium nucleatum*; gut microbiota.

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Conflicts of Interest

The authors declare no conflict of interest.