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EDITORIAL

Fusobacterium nucleatum in colorectal cancer: Association or causality?☆

Fusobacterium nucleatum en el carcinoma colorrectal: ¿asociación o causalidad?

Colorectal cancer (CRC) is the third most common neoplasm worldwide and the second cause of cancer death in both men and women.[1,2] The causes of CRC are complex and varied. Genetic factors have been estimated to contribute to the development of CRC in 10 to 20% of cases,[3,4] and environmental factors may play a significant role in the pathogenesis of sporadic CRC. A diet high in red meat and fat and low in fiber, smoking, heavy drinking, and a sedentary lifestyle increase the risk for CRC.[5] The gut microbiota has recently been recognized as a determining factor for the development of CRC. With the advent of molecular techniques for analyzing the microbiota, the fact that patients with CRC present with intestinal dysbiosis characterized by an increase in cancer-associated bacteria, such as genotoxic *Escherichia coli*, enterotoxigenic *Bacteroides fragilis*, *Fusobacterium nucleatum* (*F. nucleatum*), and other agents, has been confirmed.[5–7] *F. nucleatum* is a fusiform, Gram-negative anaerobe that mainly colonizes the oral cavity, where it behaves as an essential symbiotic bacterium for the oral microenvironment.[8] Numerous studies utilizing fecal samples and biopsies that analyzed the composition of the gut microbiota through culture-independent molecular techniques in case series in Asia, Europe, North America, and South America, have shown the abundance of *F. nucleatum* in patients with adenomas and carcinomas, in samples of the colonic mucosa adjacent to those lesions, as well as lymph node and liver metastases in CRC.[9,10]

In this issue of the *Revista de Gastroenterología de México*, Cuellar-Gómez et al.[11] present a study on 30 Mexican patients with CRC, in which they determined the presence of *F. nucleatum* in tumor tissue, peritumor tissue, and normal colonic mucosa, utilizing the quantitative polymerase chain reaction (qPCR) analysis. The authors showed that *F. nucleatum* was more abundant in tumor and peritumor tissues than in normal colonic mucosa, regardless of CRC location, whether in the right colon or left colon. This is the first study that shows the association of *F. nucleatum* with CRC in Mexican patients.

F. nucleatum is rarely located in a healthy gut and different researchers have proposed 2 routes for explaining the translocation of said microorganism from the mouth to the colon.[9,12] The first route is through the blood circulation, given that the intravenous injection of the bacterium into a peripheral vein of experimental animals in a CRC murine model was shown to favor tumor colonization. The other translocation route of the bacterium, after its ingestion, is through the digestive tract to the colon, a mechanism that has also been demonstrated in murine models. In addition, in a CRC tumor, *F. nucleatum* can invade the cancerous cells and reach the lymph nodes and liver, through the portal and lymphatic circulation.

On the other hand, the mechanisms by which *F. nucleatum* induces carcinogenesis are not yet well-defined. However, there is evidence that the microorganism participates in the mechanisms of inflammation, immune regulation, genotoxin production, and the production of metabolites that are harmful to the intestinal epithelium. *F. nucleatum* has also been suggested to favor resistance to chemotherapy agents. The bacterium promotes the expression of several inflammatory genes, such as nuclear factor kappa B, and cytokines, such as IL-6, IL-8, IL-10, IL-18, and tumor necrosis factor-alpha (TNF-α). That phenomenon favors a proinflammatory microenvironment that accelerates CRC progression.[9,13] In their work, Cuellar-Gómez et al. studied the possible association of *F. nucleatum* with IL-17, IL-10, and IL-23 production, finding that IL-23 levels were lower in the tumor tissue than in the normal colonic mucosa. Nevertheless, there was no correlation between the abundance of *F. nucleatum* and interleukin levels in the different

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tissue samples.[11] That finding differs from results from other studies, suggesting that the role of *F. nucleatum* in the production of cytokines, inflammation, and tumorigenesis is still to be defined.

Interestingly, the possibility that *F. nucleatum* DNA levels in tumor tissue or in fecal samples could be used as biomarkers in the diagnosis, prognosis, and treatment of CRC has been analyzed. Different studies have shown that the presence of *F. nucleatum* in fecal samples is significantly higher in patients with premalignant lesions than in normal subjects, as well as higher in patients with CRC than in those with premalignant lesions. Likewise, serum antibodies produced by *F. nucleatum* proteins have been proposed as a test for the opportune detection of CRC. In a recent meta-analysis, *F. nucleatum* levels were associated with poor survival in patients with CRC, and the abundance of *F. nucleatum* appeared to be a factor of resistance to chemotherapeutic agents, such as 5-fluorouracyl or oxaliplatin. However, further research is required.[9,13]

In summary, there is consistent evidence of the association between *F. nucleatum* and CRC. Nevertheless, further investigation is still required to define whether *F. nucleatum* is a first category carcinogen, i.e., that it causes CRC. In addition, future studies could clarify whether *F. nucleatum* or its products can be used as biomarkers for the different stages of CRC.

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Conflict of interest

The author declares that there is no conflict of interest.

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