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Editorial

Bacteremia and colon cancer: Causality or coincidence?

Bacteriemia y cáncer de colon: ¿causa o coincidencia?

Colorectal cancer (CRC) is one of the leading causes of cancer in the world and one of the main causes of cancer mortality. In Spain, it is the most diagnosed cancer. Its incidence is increasing due to the progressive aging of the population, and due to the increasingly generalized acquisition of the "Western" way of life.

Although it usually presents as changes in bowel habit or blood in the stool, occasionally they may present as infections preceding the diagnosis of the tumor. Thus, local infections arising from perforated tumors may appear, such peritonitis, fistulas or abscesses. Additionally, intestinal flora can invade the bloodstream and cause remote infections, causing meningitis, endocarditis, liver abscesses, spontaneous gas gangrene or bacteremia of no apparent source. Occasionally, fever of unknown origin, often intermittent, can show up, which probably is due to autolimited bacteremia episodes. The isolation of certain microorganisms in blood cultures should alert us of the possibility of occult CRC, and may allow an earlier diagnosis, improving prognosis.[1]

Since the study in which Klein established a strong relationship between *Streptococcus bovis* and colonic neoplasms,[2] numerous articles have described associations of various intestinal bacteria with bacteremia/endocarditis and CRC. In addition to *S. bovis*, specifically *Streptococcus gallolyticus* subsp. *gallolyticus* (*S. gallolyticus*), a close link has been established between CRC and bacteriemia by *Clostridium septicum*,[1,3] and also, although in a lower percentage, other *Clostridia* species. bacteremia has been associated with CRC in 11%, ranging from 0 to 28%.[1] Likewise, *E. faecalis* endocarditis has been associated with an increased incidence of colonic adenomas/carcinomas.[4]

In a recent study with more than 13,000 bacteremia in Hong-Kong,[5] a significant association of some bacteria with CRC diagnosis was found, mainly during the first year after bacteremia. *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Gemella morbillorum*, *Clostridiun perfringens*, *Clostridium septicum* and *S. gallolyticus* have a stronger association with CRC than controls matched by age, sex and comorbidities, with a relative risk varying between 23.2 and 2.2 times for *C. septicum* and *C. perfringens*, respectively. Despite the high number of bacteremia analyzed, it is difficult to establish the risk of some species other than *C. perfringens* or *B. fragilis* due to their low incidence, which makes necessary to conduct more studies with a higher number of cases. It is also important that Microbiology laboratories identify precisely the different species of anaerobes as well as *S. bovis/equinus* complex members.

How do these microorganisms invade the bloodstream? The usual mechanism is exemplified by *Clostridium septicum* bacteremia. *C. septicum* reaches the blood or the peritoneum through macroscopic ulcerations or perforations of the mucosa, generally producing fulminant sepsis, secondary peritonitis or spontaneous myonecrosis, a very characteristic entity. Tumors are generally large, located mainly in the right colon, where the lower vascularization and the size of the lesions are associated with ischemia and necrosis, which decrease pH, favoring the germination of spores.[1,3] In the case of CRC related *S. gallolyticus* bacteremia the mechanism is fully distinct. In this case, tumors are generally small, usually adenomas, which do not ulcerate the mucosa and rarely produce intestinal symptoms.[3] *S. gallolyticus* has a high translocation capability in the neoplastic, although not in healthy epithelium; *S. gallolyticus* invades the bloodstream by a paracellular mechanism in a "silent" way, causing a subacute endocarditis in most cases.[6] Unlike *C. septicum*, it does not give place to explosive abdominal symptoms.[3] To my knowledge, intestinal perforation associated with *S. gallolyticus* has not been described (although it has been described in other species of the *bovis* group).

Taken together, all these data establish a clear relationship between colon neoplasms and bacteremia caused by certain microorganisms, which would take advantage of the conditions created by the tumor to invade the blood, behaving as opportunists. But can they be involved in tumor genesis? In Klein's well-honored article on *S. bovis*,[2] published 45 years ago, he stated: *"Undefined physical or biochemical factors in the gastrointestinal tract of patients with carcinoma of the colon may directly or indirectly promote the carrier state of S. bovis. Alternatively, S. bovis may play a part in producing carcinogens in the large bowel"*. Although we still do not have a definitive answer to his question, in recent years notable progresses in the knowledge of mechanisms of carcinogenesis and in the role of the intestinal flora in its development have been made.[7–11]

CRC development depends on the accumulation of genetic and epigenetic changes in a process that lasts several years. The trigger of those mutations are multiple and not fully understood, but a role played by the intestinal microbiota in these process is supported by an increasing amount of evidence.

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Most of the human microbiota resides in the large bowel, with 10^{14} cells and more than 10^3 species, and plays a vital role in human health, performing structural, immunological and metabolic functions. Its composition changes during the first year of life and then remains relatively stable throughout adult life, although there are many variations from person to person. Diet, antibiotics and some diseases, such as CRC, can vary its composition and diversity.

In experimental models of transgenic CRC-prone and wild-type mice exposed to a chemical carcinogen, both developed tumors less often when in a microorganism free setting than when they had their usual microbiota. Additionally in both groups CRC-patient microbiota transplantation promoted the intestinal carcinogenesis. In general, the intestinal microbiota of individuals with CRC compared with healthy controls shows scarcity of potentially protective taxa, and abundance of procarcinogenic taxa, as well as lower diversity.

A usual finding of CRC microbioma studies is an enrichment in *Fusobacterim nucleatum* (FN) in tumor samples.[12] FN exhibits a progressive increase, from early to advanced stages of carcinogenesis, and high concentrations of the bacteria have been associated with a worse prognosis, and in particular a high risk of lymph node involvement. In the systematic review and meta-analysis published by Villar-Ortega at al.,[13] a significantly higher presence of FN in CRC tissue samples versus healthy tissue and colo-rectal adenoma was found. However, as the authors very well say, it remains to be shown whether this association implies that this microorganism is involved in carcinogenesis.

Nevertheless, there are experimental data in animals and in vitro studies, which suggest that some strains of *B. fragilis*, *E. coli*, FN, *E. faecalis* and *S. gallolyticus* could be oncogenic by inducing DNA damage and/or interfering with DNA repair, which can be critical for tumor initiation. The specific mechanisms have been reviewed in depth,[8,12] but basically, they can act directly, creating a pro-inflammatory state or through the production of genotoxins, or indirectly by producing secondary metabolites from the components of the diet.

How do all these bacteria interact in people predisposed by genetic and/or environmental factors to the development of CRC? Is a bacterium or a consortium of them responsible? And how are they distributed over the time it takes for a cancer to develop? According to the colonic cancer model by Sears et al.,[14] there would be bacteria of the intestinal microbiota called “Alpha-bugs” which would have oncogenic capacity, through direct or indirect mechanisms. They would also be capable of remodeling the colonic flora, favoring the development of bacteria that contribute to oncogenesis and preventing the development of anti-oncogenic microbiota. In the “driver-passenger” model of Tjalsma et al.,[15] there would exist carcinogenetic bacteria (drivers) that later during the evolution of cancer, could be gradually replaced by others (passengers), which would take advantage of the environment created by the cancer. These passenger bacteria, in turn, could have the capacity to promote or suppress neoplasia. Therefore, the driver and passenger bacteria would have a different temporal association, as well as different roles in the pathogenesis of cancer.

It is possible for both models to coexist. Thus, enterotoxigenic *Bacteroides fragilis* (ETBF) and *pks+ E. coli* produce toxins that would be carcinogenic in certain murine models. Coinfection with both pathogens speeds the tumor growth and increases mortality when compared with each pathogen separately. Also, both microorganisms are present in the colon of patients with familial adenomatous polyposis in significantly higher percentages than healthy controls.[16] Thus, ETBF and *pks+ E. coli* would be “Alpha-bugs” or drivers.

Different microorganisms such as S. *gallolyticus* could profit from tumor environment. This particular species finds an ideal medium for adhesion since collagen exposure after epithelium disruption.[6] However, some data suggest that it plays an active role in cancer development and is not only an innocent passenger Some *S. gallolyticus* strains have been shown to promote colon cancer cell proliferation in specific cellular lineages, as well as in some mice species. Therefore, it appears that both the appropriate strain and host are needed for tumors to develop.[17]

From a clinical point of view, *S. gallolyticus* is associated to early stage neoplasms, most of them adenomas, while *C. septicum* bacteremia associated carcinomas are mostly advanced-stage (58% in stage III and IV) with an average size of 7 cm (compared to 1.5 cm in the case of *S. gallolyticus*),[3,18]. These data suggest that S. gallolyticus appears in intermediate stages of CRC, behaving both as a passenger and driver, while *C. septicum* appears in final stages of CRC, behaving as a mere bystander in the carcinogenesis process. Although this driver bacteria may be replaced during the tumor progression as does *Helicobacter pylori* in gastric cancer, this might not always be the case. Genes encoding the ETBF toxin have been detected in both adenomas and advanced carcinomas,[19,20] suggesting that ETBF probably remains throughout tumor development.

Survival in CRC is directly related to the stage at diagnosis CRC related bacteremia can improve the prognosis in some cases, although it only accounts for less than 1% of all CRC. CRC screening using fecal occult blood and endoscopy reduces its incidence, and reduces mortality. In the future, we might be able to identify groups of bacterial taxa or specific microbial markers that could predict the risk of developing CRC before macroscopic changes develop in the colonic epithelium[8–12] or allow for stratification of patients for therapeutic regimes. Substituting the potentially oncogenic microbiome by changing the diet, using probiotics, prebiotics or fecal transplantation could perhaps be solutions in the prevention of intestinal tumors. In the next few years, we are going to witness an important development in the knowledge of the microbiome, which may allow us to understand the mechanisms of the genesis of CRC.

References

1. Panwalker A. Unusual infections associated with colorectal cancer. Rev Infect Dis. 1988;10:347–64.
2. Klein RS, Recco R, Catalano M, Edberg S, Casey J, Steigbiel N. Association of *Streptococcus bovis* with carcinoma of the colon. N Engl J Med. 1977;13:800–2. Intern Med. 1979. PMID: 48495.
3. Corredoira J, Grau I, Garcia-Rodriguez JF, García-País MJ, Rabuñal R, Ardanuy C, et al. Colorectal neoplasm in cases of *Clostridium septicum* and *Streptococcus gallolyticus* subsp. gallolyticus bacteraemia. Eur J Intern Med. 2017;41:68–73, http://dx.doi.org/10.1016/j.ejim.2017.02.009.
4. Pericàs JM, Corredoira J, Moreno A, García-País MJ, Falces C, Rabuñal R, et al. Relationship between *Enterococcus faecalis* infective endocarditis and colorectal neoplasm: preliminary results from a cohort of 154 patients. Rev Esp Cardiol (Engl Ed). 2017;70:451–8, http://dx.doi.org/10.1016/j.rec.2016.10.013.
5. Kwong T, Kwong T, Wang X, Nakatsu G, Chow TC, Tipoe T, et al. Association between bacteremia from specific microbes and subsequent diagnosis of colorectal cancer. Gastroenterology. 2018;155:383–90, http://dx.doi.org/10.1053/j.gastro.2018.04.028, e8. Epub 2018 May 3.
6. Boleij A, Tjalsma H. The itinerary of *Streptococcus gallolyticus* infection in patients with colonic malignant disease. Lancet Infect Dis. 2013;13:719–24, http://dx.doi.org/10.1016/S1473-3099(13)70107-5. Epub 2013 Jul 5.
7. Janney A, Powrie F, Mann E. Host–microbiota maladaptation in colorectal cancer. Nature. 2020;585:509–17.
8. Vacante M, Cuini R, Basile F, Biondi A. Gut microbiota and colorectal cancer developmente: a closer look to the adenoma–carcinoma sequence. Biomedicines. 2020;8:489, http://dx.doi.org/10.3390/biomedicines8110489.
9. Knippel R, Sears C. The microbioma colorectal cancer puzzle: initiator, propagator, and avenue for treatment and research. J Natl Compr Netw. 2021;19:986–92, http://dx.doi.org/10.6004/jnccn.2021.7062.
10. Silva M, Brunner V, Tschurtschenthaler M. Microbiota and colorectal cancer: from gut to bedside. Front Pharmacol 12:760280. doi:10.3389/fphar.2021.760280.
11. Wong S, Yu j. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepat. 2019;16:690–704.
12. Brennan C, Garret W. *Fusobacterium nucleatum* – symbiont, opportunist and oncobacterium. Nat Rev Microbiol. 2019;17:156–66, http://dx.doi.org/10.1038/s41579-018-0129-6.

13. Vilar-Ortega P, Exposito-Ruiz M, Gutierrez-Soto M, Ruiz-Cabello Mnavarro-Mari J, Gutierrez-Fernandez J. La asociación entre *Fusobacterium nucleatum* y el cancer colorectal: una revisión sistematica y metaanálisis. Enf Infecc Microbiol Clin. 2022;40:224–34.
14. Sears C, Pardoll D. Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. J Infect Dis. 2011;203:306–11, http://dx.doi.org/10.1093/jinfdis/jiq061. Epub 2010 Dec 8.
15. Tjalsma H, Boleij A, Marchesi JR, Dutilh BE. A bacterial driver-passenger model for coorectal cancer: beyond the usual suspects. Nat Rev Microbiol. 2012;25:575–82, http://dx.doi.org/10.1038/nrmicro2819.
16. Dejea C, Fathi P, Craig J, Boleij A, Taddese R, Geis A. Patients with familiar adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. Science. 2018;359:592–7, http://dx.doi.org/10.1126/science.aah.3648.
17. Kumar R, et al. Streptococcus gallolyticus subsp. gallolyticus promotes colorectal tumor development. PLoS Pathog. 2017. PMID: 28704539.
18. Corredoira-Sánchez J, García-Garrote F, Rabuñal R, López-Roses L, García-País, Elena Castro E, et al. Association between bacteremia due to *Streptococcus gallolyticus* subsp. gallolyticus (*Streptococcus bovis* I) and colorectal neoplasia: a case–control study. Clin Infect Dis. 2012;55:491–6, http://dx.doi.org/10.1093/cid/cis434. Epub 2012 May 4.
19. Purcell R, Pearson J, Aitchison A, Dixon L, Frizella F, Keenan J. Colonizacion with enteroxigenic Bacteroides fragilis is associated with early-stage colorectal neoplasia. PLOS ONE 12:e0171602. doi:10.1371/journal phone.0171602.
20. Boleij A, Hechenbleikner E, Goodwing A, Badani R, Stein E, Lazarev M, et al. The *Bacteroides fragilis* toxin gene is prevalente in the colon mucosa of colorectal cancer patients. CID. 2015;60:208–15.

Juan Corredoira*, Blanca Ayuso
Unidad de Enfermedades Infecciosas, Hospital Lucus Augusti, Lugo, Spain

* Corresponding author.
E-mail address: juan.corredoira.sanchez@sergas.es (J. Corredoira).