Editorial

Going with the gut: probiotics as a novel therapy for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a leading cause of death worldwide (1). It is the most frequent primary liver tumor and usually occurs in patients affected by liver cirrhosis (1).

Nowadays, the main treatment options for HCC include surgical or locoregional approaches and systemic drugs, but despite the significant improvements in medical management the prognosis of patients with advanced HCC is still poor (1).

The term "gut microbiota" refers to the totality of microorganisms that are physiologically found in our intestinal tract. In normal conditions, it complements the biological functions of the host and contributes to the maintenance of the health and homeostasis of the whole organism.

The gut microbiota is a critical part of the gut-liver axis, which finely regulates the strict relationship between the liver and the intestine. A dysfunction of the gut barrier can occur either during a primary intestinal perturbation or secondary to liver disease, causing an increase in intestinal permeability (IP). Hence, bacterial products [e.g., lipopolysaccharide (LPS), bacterial DNA] are delivered in large, non-physiological amounts to the liver through the portal circulation (2). These pathogen-associated molecular patterns (PAMPs), interacting with the Toll-like receptors (TLRs), can trigger an inflammatory response causing detrimental effects on liver homeostasis. An imbalance in the composition and function of the gut microbiota (dysbiosis) associated with the increase in IP, which are both hallmarks of liver cirrhosis, further increase the flow of microbial toxins to the liver (3). The inability to provide a proper clearance of baneful substances and the occurrence of a secondary inflammatory response have been correlated with the progression of liver disease and the occurrence of liver cirrhosis complications (2).

As thoroughly reviewed by Wan and El-Nezami, the gut microbiota and the gut-liver axis derangement could also favor the occurrence of HCC via different mechanisms (4).

Indeed, LPS translocated from the intestinal lumen is able to activate the TLR4 on Kupffer cells, concurring to the development and the maintenance of an inflammatory, pro-oncogenic, environment. In confirmation of this, an overexpression of TLR4 in tumor tissue has been observed in HCC. Furthermore, as already demonstrated in other clinical settings, a chronic, non-resolving inflammation can "freeze" the immune system, blocking those mechanism that are critical to recognize and eliminate malignant cells, thus favoring tumor escape from the immune surveillance.

Recent studies identified a specific gut microbiota fingerprint that can be associated with the presence of early HCC, and it is now clear that bacterial metabolites such as deoxycholic acid (DCA) can favor hepatocarcinogenesis through the damage of hepatocellular DNA and liver inflammation (5-8). Finally, an increase in tissue T helper 17 (Th17) lymphocytes and the consequent overexpression of interleukin (IL) 17A correlates to inflammation, tumor angiogenesis and poor prognosis in patients with HCC (9). Interestingly, Th17 cells are mainly generated in the gut following the interaction of the immune system with the gut microbiota (10).

Therefore, the gut microbiota is involved in the process

of hepatocarcinogenesis at different levels, mainly through persistent inflammation, toxic products and immune system dysregulation.

According to these evidences, Wan and El-Nezami elegantly hypothesized a consistent role for probiotics for the treatment of HCC (4).

Indeed, probiotics exert protective effects on the intestinal mucosa, influence the gut microbiota composition, regulate the metabolism of microorganism in order to disadvantage the production and release of toxins, metabolize harmful dietary compounds and modulate the immune response (11). They also reduce the release of LPS, inhibiting the proliferation of pathogenic Gram-negative bacteria (12). Another favorable effect of probiotics is the detoxification of carcinogens, such as aflatoxin B1. Several bacterial strains can bind mycotoxins and the administration of probiotics has been correlated with a decrease in urinary excretion of aflatoxin-DNA adduct, a biomarker of liver cancer risk (13). *Bifidobacteria* and *Lactobacilli*, that are commonly found in probiotics, can produce short chain fatty acids (SCFAs). These metabolites exert a trophic effect on the intestinal mucosa, strengthening the gut barrier. Importantly, they favor a decrease in the Th17 polarization and a reduction of inflammatory cytokines, that are relevant elements in the process of tumorigenesis (14). Interestingly, tumor hypoxia due to a decrease in angiogenesis and a shift to anaerobic metabolism has been reported after treatment with probiotics (14). Probiotics can induce an upregulation of the antitumor immune response further impairing the tumor growth both directly and by inhibiting the suppression of the immune system by tumor cells (15).

Altogether, these findings strengthen the hypothesis that the modulation of the gut microbiota can protect against the development and progression of HCC, but some considerations are required.

Most of these results derive from animal models. Therefore, human studies are necessary for translating these evidences into clinical practice. The design should be particularly accurate, especially with regard to some specific steps.

Firstly, a precise choice of the probiotic to be used is crucial, as the beneficial effects are often species- and/or strain specific (16). In this regard, since the process of hepatocarcinogenesis is complex and involves multiple mechanisms, a personalized approach to the modulation of the intestinal microbiota cannot disregard the identification of a dysbiotic signature unequivocally associated with HCC. Probably, in this scenario, the use of probiotic combinations could provide better results; conversely, in most studies, commercially available probiotics mixtures have been tested. Thus, further efforts are needed for the identification of bacterial strains that specifically contrast the pathogenic mechanisms of hepatocarcinogenesis. Indeed, the ideal probiotic should supply microorganisms needed for gut homeostasis, contrast harmful bacteria proliferation and metabolism, reinforce the gut barrier preventing bacterial translocation, limit the absorption of toxins, decrease intestinal inflammation and positively modulate the immune system.

Furthermore, it is not known to what extent the administration of probiotics may change the composition and function of the intestinal microbiota, and especially how long the effects may last over time. It should also be considered that the gastrointestinal tract also harbors fungi and viruses, whose communities are interconnected with bacteria and the host. Scarce data are available about the composition and function of this network, which could become a promising tool for a future gut-targeted therapeutic approach. At present, the safety of probiotics and the simplicity of administration make them ideal for modulating the microbiota compared to other types of therapeutic interventions.

In conclusion, the use of probiotics in association with other preemptive or therapeutic procedures for the modulation of the gut microbiota of patients with HCC is currently still a dream in the drawer. However, it is time to go with our gut and design randomized controlled trials in large populations of patients to confirm the proteiform beneficial effects postulated for probiotics in this clinical setting.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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