Editorial

Potential therapeutic strategies to target gut microbiota in hepatocellular carcinoma

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The gut microbiota (GM) is an assorted ecosystem, composed of viruses, fungi, protozoa, archaea, and especially bacteria, which exist in a definite symbiosis between each other and the host (human) as well. Increasing data document that GM plays key parts in human physiology, taking part in the digestive process, vitamin B synthesis, promotion of angiogenesis and nerve functionality, and notably in the maturation and modulation of the immune system. In addition, it is commonly known and accepted that the GM has an impacting role in different pathological disorders, such as gastrointestinal, hepatic, respiratory, cardiovascular and endocrine (1). In fact, different studies confirmed that the GM is involved in the pathogenesis of different pathologies, including inflammatory and irritably bowel syndrome, autism, depression, obesity, atherosclerosis, colorectal carcinoma, infectious and non-infectious chronic liver diseases (2-6).

The GM as a "virtual metabolic organ" makes axis with various extra-intestinal organs, such as brain (the most relevant), lung, cardiovascular, kidneys and the liver (7). The gut-liver axis is the result of a close (anatomical and functional) bidirectional interaction of the gastrointestinal tract and liver, primarily by the portal circulation. Moreover, an intricate network of interactions, which encompass metabolic, immune, and neuroendocrine crosstalk between them, controls the symbiotic connection between the liver and the GM (2). The gut-liver axis has been associated with the pathogenesis of numerous chronic liver diseases, comprising liver cirrhosis, chronic hepatitis B/C (CHB and CHC), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and the hepatocellular carcinoma (HCC) (8), that is the third most common cause of cancer-related mortality worldwide (9).

To date, numerous data from animal models and human studies suggest a GM role in the HCC development. In particular, intestinal dysbiosis was found in patients with liver cirrhosis and HCC and in mice after diethylnitrosamine (DEN) administration.

As well reported by Wan and El-Nezami (10), there are three potential mechanisms through which the gut-liver axis can favour the HCC pathogenesis:

(I) Via leaky gut, endotoxemia and toll-like receptor (TLR). Above all, high circulating lipopolysaccharide (LPS) levels were shown in both HCC animal models and patients with HCC. These enlarged values are likely attributed to increased intestinal permeability and so the amplified bacterial translocation.

(II) Via dysbiosis and bacterial metabolite production. It is explicative a recent study where dietary or genetic obesity modifies the GM, increasing the deoxycholic acid (DCA) levels. DCA is a bacterial metabolite that causes DNA damage and stimulate the production of various inflammatory and tumour-promoting factors in the liver, thereby endorsing HCC development in a mouse model (after exposure to chemical carcinogen).

(III) Via immunomodulation. It is postulated that the

high amount of intestinal IL-17 may involve in the HCC development.

So, notified the importance of the link with the GM and owing to a lack of pharmacological preventive strategies and limited chemotherapeutic options for the HCC treatment, the authors suggest that the therapeutic GM modulation by probiotics might represent an innovative approach to prevent the HCC progression. In addition, they analysed and discussed the various mechanisms by which the probiotics can have anti-cancer effects. The probiotics can show anti-cancer effect, directly modulating the microbiota, but they can exert also indirect actions through different pathways, such as immune modulation, anti-inflammatory and anti-pathogenic activities, improving the intestinal barrier function and so decreasing the bacterial translocation, as well as reducing tumor formation and metastasis.

Regarding the anti-HCC probiotics' functions, the authors focusing on the major four:

(I) Binding/adsorption of carcinogens. Animal studies have demonstrated that both AFB1 toxicity and bioavailability are reduced after administration of probiotics.

(II) Improvement of intestinal barrier function. The probiotics could remodel the GM composition, suppressing the outgrowth of Gram-negative bacteria and improving the intestinal barrier, preventing translocation of endotoxins. In this way, the cancer-related inflammation was decreased in the liver.

(III) Modulation of short-chain fatty acids (SCFA) production. Some probiotics' strains (e.g., *Bifidobacteria* and *Lactobacilli*) can modify the GM composition, chancing the production of SCFA and favouring the production of SCFA that may reduce the risk of developing cancer, including HCC.

(IV) Regulation of Th17 response. The probiotics can cause shifts in the GM composition toward specific beneficial bacteria, for example, *Prevotella* and *Oscillibacter*. These bacteria are famous to secrete anti-inflammatory metabolites, which are able to contrast the Th17 polarization, favouring the differentiation of regulatory T cells (Tregs) in the intestinal mucosa.

In conclusion, after these premises and having argued the anti-cancer role of probiotics, Wan and El-Nezami declared that the GM manipulation may represent an innovative, safe and low-cost strategy to prevent or treat HCC. In addition, they specified that more basic studies as well as human clinical trials in GM evaluation and correctly selected useful bacterial strains are required to gain the acceptance of the broader medical community and to consider the possibility to use probiotics as an alternative (or supportive, suggest me) anti-cancer treatment.

In summary, I agree with the authors and I firmly convinced that the GM modulation might have important applications for future treatments in the oncological field. In fact, as previously reported (11) the multifaceted rapport between the GM and human beings do concern not only empirical aspects, but require the necessity to adopt novel concepts/perspectives in order to be appropriately applied, especially in their therapeutic implementation.

Nevertheless, the probiotics are one of the different approaches to modulate the GM and given the complexity of the microbiota ecosystem, it is hard to think that one or few bacterial strains can resolutely change the composition of the microbiota (unless there are definite deficiencies of specific strains). Therefore, I believe that the probiotics may be essentially used in preventive/supportive manner while other approaches could be more effective in editing the microbiota, such as antibiotics, but especially bacteriophages and fecal microbiota transplantation (FMT). Currently the FMT is used for the treatment of *Clostridioides difficile* infection (CDI) but there are clinical trials for different diseases, including one of my group regarding patients with amyotrophic lateral sclerosis (ALS) (12).

About the phage therapy, a recent study demonstrated in a mouse model that phage predation not only directly impacts susceptible bacteria, but also leads to cascading effects on other bacterial species via interbacterial interactions, changing the gut metabolome (13). These data suggest the potential impact of gut phages on the host, with implications for their therapeutic use to precisely edit the microbiome. In addition, some types of CRISPR-Cas systems could be used to modify the genome of gut microorganisms and bacteriophages, to specifically eliminate members of the microbiome or to control gene expression, modulating the production of metabolites/proteins. In conclusion, these tools offer stimulating opportunities to explore the intricate interplay between GM members and our bodies, and open novel roads for the development of drugs targeting the microbiome (14).

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Footnote

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