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Precision dietary supplementation based on personal gut microbiota

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Abstract

Over the past decade, many studies have revealed the importance of the gut microbiome in disease development and treatment, including in cancer. Because both host genetics and the gut microbiome can influence host phenotype and treatment outcome, there is an urgent need to develop precision medicine and personalize dietary supplementation based on an individual's microbiome.

In a new study in *Cell*, Singh et al. published their unexpected findings that long-term (6 months) supplementation of the soluble fibre inulin (7.5% by mass) improved the metabolic syndrome in 40% of Toll-like receptor 5 (TLR5)-deficient mice, but many of those same mice later developed icteric hepatocellular carcinoma (HCC; 40% penetrance in male and 20% in female mice)[1]. In addition, HCC was also found in other lines of mice that have innate immune deficiency, such as those lacking TLR4. When fed a high-fat diet supplemented with inulin, but not the insoluble fibre cellulose, 10% of wild-type mice developed small well-differentiated tumours with foci of inflammation and fibrosis. Moreover, inulin-induced HCC in TLR5-deficient mice could be mitigated by depletion of butyrate-producing bacteria, inhibiting gut fermentation and preventing bile acid recycling; however, these mice were not protected by cross-fostering using wild-type mice. Furthermore, supplementation of drinking water with butyrate, a product of bacterial fermentation of inulin, for 9 months at a dose of 100 mM led to hepatic inflammation and fibrosis in 54% of TLR5-knockout mice but without evidence of liver tumours[1]. Thus, these unexpected findings suggest that there is potential risk in long-term consumption of inulin and butyrate, particularly when TLR5 is missing.

A large body of literature has revealed the health benefits of fibres and short-chain fatty acids (SCFAs)[2] in a diverse range of conditions (FIG. 1). The paper published by Singh et al. cautions that these dietary supplements might have carcinogenic effects, especially in immunocompromised conditions, suggesting individual variability in responding to dietary supplementation. The data also implied that improving metabolism was not enough to prevent liver carcinogenesis in TLR5-deficient mice or high-fat-diet-fed wild-type mice. By

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Competing interests

The authors declare no competing interests.

contrast, another study by Weltkunat et al. published in 2017 showed that, despite long-term feeding (7.5 months) of inulin (7%) or SCFAs, liver tumours did not develop in wild-type mice. This study also found that inulin and SCFAs, but not guar gum, improved metabolic health in mice fed a high-fat diet[3]. Similarly, our group did not observe pro-inflammatory or tumorigenic effects of inulin in wild-type male C57BL/6 mice fed a Western diet. In addition, inulin supplementation (6%) for 5 months reversed Western diet-induced hepatic steatosis and restored neuroplasticity, which was reduced owing to Western diet consumption (unpublished data). Because steatosis and inflammation are risk factors for liver carcinogenesis, the underlying mechanism by which inulin can treat steatosis and improve the metabolic syndrome but promote liver tumorigenesis is of interest and requires further study.

The finding that inulin did not induce liver tumours in TLR5-deficient mice purchased directly from Jackson Laboratory in the study by Singh et al. is also very interesting; HCC was only found in the TLR5-deficient mice receiving inulin that were bred independently in three universities[1]. Thus, environment had a substantial effect on liver carcinogenesis. Emerging evidence has revealed that the gut microbiota is a major environmental aetiological factor for carcinogenesis that occurs within and outside the digestive tract. Similarly, the growth of subcutaneous B16.SIY melanoma in C57BL/6 mice obtained from Jackson Laboratory was less aggressive than the same cancer growing in mice obtained from Taconic Farms, and co-housed mice acquired the phenotype of mice from Jackson Laboratory[4]. The authors of this study concluded that such a phenotypic difference is immune-mediated controlled by microorganisms. Furthermore, the same study showed that commensal *Bifidobacterium* modulates the efficacy of anti-programmed cell death 1 ligand 1 (PD-L1) therapy[4]. Thus, it seems that gut microbiome is more important than host genetic composition in precision medicine. Taken together, these findings indicate that gut microorganisms contribute to liver carcinogenesis and modulate the success of cancer treatment.

Bile acids derived from hepatic cholesterol not only serve as digestive surfactants but also regulate inflammation and lipid and sugar metabolism. The recognition of these important roles was spurred by identification of bile acid receptors, including farnesoid X receptor (FXR; mainly found in the liver and intestine) and G-protein-coupled bile acid receptor (ubiquitously expressed)[5]. Primary and secondary bile acids are produced by hepatic and microbial enzymes, respectively. Hence, diet, hepatic enzymes and the gut microbiota influence the production of various bile acids, which in turn affects systemic host health. In the study by Singh et al., inulin-induced HCC was associated with early cholestasis with elevated serum primary and secondary bile acids, butyrate levels and Proteobacteria, suggesting their roles in contributing to liver carcinogenesis[1]. FXR-knockout mice, which have elevated secondary bile acid levels and increased Proteobacteria abundance, also develop spontaneous steatosis, steatohepatitis and liver carcinogenesis[6]. Thus, using different models, both studies suggest that dysregulated bile acid synthesis accompanied by dysbiosis is an aetiology of liver carcinogenesis. However, reduced levels of butyrate and butyrate-generating bacteria were found in mice with steatosis and steatohepatitis induced by Western diet consumption and/ or FXR knockout[7]. Moreover, butyrate supplementation reverses cancer-prone steatohepatitis in Western-diet-fed FXR-knockout mice[7]. In another

study, butyrate induced colon carcinogenesis in mice, but was independent from microbial-driven inflammation, probably through increased stem cell production[8]. Thus, the inflammatory and proliferative effect of butyrate in the liver and intestine might depend on the animal model used and warrants additional study to address this apparent paradox. In summary, these conflicting findings again stress the importance of personalized dietary supplementation.

The beneficial or adverse effects of any endobiotics or xenobiotics are dependent on dose, duration, and host genetics. The important role of gut microorganisms in regulating detoxification, metabolism, and immunity becomes apparent when all variables are controlled in animal experiments. Thus, colonization of commensal microorganisms in early life probably has a large effect on disease risk, and it is crucial to have a healthy, balanced diet during pregnancy. Of course, bacterial colonization is also probably influenced by the host genetic makeup, such as levels of TLR5, highlighting the importance of gene–gut microbiome interactions.

Although SCFAs, especially butyrate, have been extensively studied, there are still many unclear issues. As one of the most abundant bacterial metabolites, the interactions of SCFAs with other nutrients or xenobiotics and the influence of host genes on their effects would be particularly interesting and important to investigate. Given that histone deacetylase (HDAC) inhibitors have emerged as promising therapeutic targets in HCC, the HDAC-inhibitory properties of propionate and butyrate might be useful for liver cancer treatment in combination with other drugs[9].

Despite rigorous studies, it is alarming that mice bred in different institutions can generate different outcomes, which is the case in the study by Singh et al. This challenging issue needs to be addressed for microbiome research. Additionally, the composition of the gut microbiota varies by sex, similar to the incidence of liver diseases in humans and many mouse models[10]. Including both sexes in studies is key to understanding why females are protected from metabolic disease and liver cancer. Furthermore, human relevance in microbiota research needs to be considered and addressed like any other animal research.

In summary, owing to the importance of the gut microbiota in human health, there is an urgent need to develop precision dietary supplementation and personalized medicine based on an individual’s microbiome in addition to genetic makeup to effectively prevent and treat disease.

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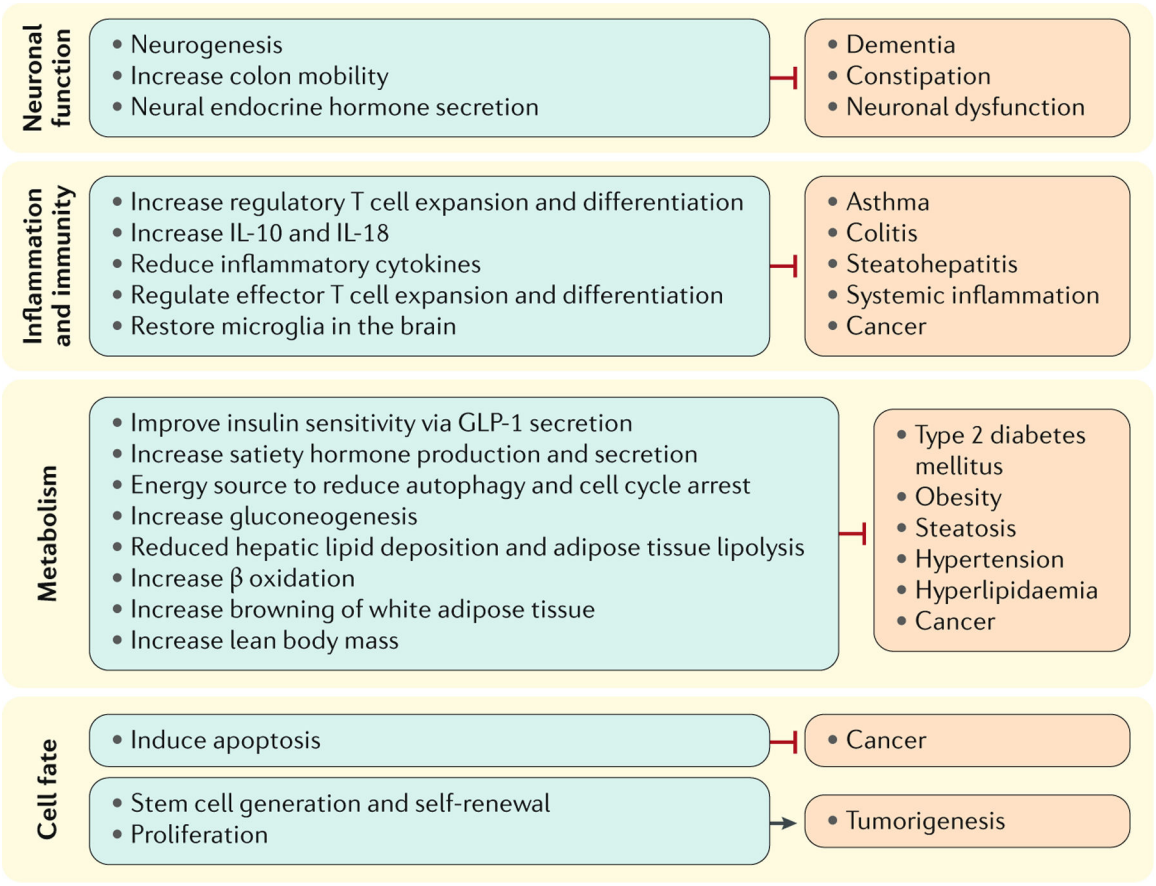

Fig. 1 |. The effect of short-chain fatty acids in health and disease.

Short-chain fatty acids, which are produced through the fermentation of dietary fibres by the gut microbiota, have effects on many disease processes. GLP-1, glucagon-like peptide 1.