Editorial

The gut microbiome, antitumor immunity, and liver cancer

Kosuke Mima[1,2], **Hideo Baba**[2]

[1]Department of Surgery, National Hospital Organization Kumamoto Medical Center, Kumamoto, Japan; [2]Department of Gastroenterological Surgery, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan

Correspondence to: Hideo Baba, MD, PhD, FACS. Department of Gastroenterological Surgery, Graduate School of Medical Science Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan. Email: hdobaba@kumamoto-u.ac.jp.

Comment on: Ma C, Han M, Heinrich B, *et al.* Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science 2018;360. doi: 10.1126/science.aan5931.

Submitted Oct 13, 2018. Accepted for publication Nov 08, 2018.
doi: 10.21037/hbsn.2018.11.09
View this article at: http://dx.doi.org/10.21037/hbsn.2018.11.09

Primary liver cancer is one of the leading causes of cancer deaths globally (1). Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and the major risk factors for HCC include hepatitis B and C, alcohol consumption, non-alcoholic fatty liver disease, and liver cirrhosis (2). The liver is the common site of metastasis from breast, lung, and colorectal cancer, and malignant melanoma (3).

Accumulating evidence demonstrates that the human gut microbiota can influence metabolism, inflammation, immune response, and disease conditions, including cancer (4). The liver is exposed to components and metabolites from the gut microbiota via the hepatic portal vein, and is enriched in immune cells, such as T cells, B cells, and macrophages (5). In a mouse model of diethylnitrosamine-induced HCC, lipopolysaccharide from the gut microbiota can promote liver tumor progression through the activation of NFKB (6). In a mouse model of obesity-induced HCC, the gut microbiota provoke the senescence-associated secretory phenotype in hepatic stellate cells and promote liver tumor development (7). However, roles of the gut microbiota in host immunity against primary and secondary liver tumors are poorly understood.

Ma and colleagues demonstrate that in multiple mouse models, *Clostridium* species can inhibit the accumulation of hepatic natural killer T (NKT) cells, and suppress antitumor immune response against both primary and secondary liver tumors (8). Using mouse models of primary liver tumor and secondary liver tumors from lymphoid or melanoma tumor cell lines, Ma *et al.* found that antibiotic treatment altered the gut microbiome and reduced tumor growth and liver metastases. They analyzed immune cell subsets in the mouse models and found the accumulation of NKT cells that express CXCR6 in the liver. Further investigation showed that CXCL16 expression on liver sinusoidal endothelial cells contributed to the accumulation of hepatic NKT cells.

Bile acids have been synthesized in the liver and involved in dietary fat absorption. Ma *et al.* showed that primary bile acids, which have been metabolized to secondary bile acids by gut bacteria, increased CXCL16 expression on liver sinusoidal endothelial cells. Antibiotic treatment decreased secondary bile acids and increased CXCL16 expression on liver sinusoidal endothelial cells. Colonization with a commensal *Clostridium* species, which are Gram-positive bacteria and involved in the conversion of primary to secondary bile acids, decreased hepatic NKT cells and increased liver tumor metastases. In nontumor liver tissue specimens from liver cancer patients, primary bile acid levels were correlated with CXCL16 expression, whereas secondary bile acid levels were inversely correlated with CXCL16 expression.

The data from Ma *et al.* may open new opportunities to target the gut microbiota for the prevention and treatment of primary and metastatic liver tumors. Accumulating evidence demonstrates that the composition of the human gut microbiota can be influenced by several factors, including diet, antibiotics, lifestyle, and probiotics (9). Hence, future studies are needed to examine the potential influence of these factors on the immunosurveillance of liver tumors.

Therapeutic monoclonal antibodies that block CTLA4,

PDCD1 [programmed cell death 1 (PD-1)], and CD274 [programmed cell death 1 ligand 1 (PD-L1)] protein have been shown to potentiate antitumor T cell responses and improve survival in patients with non-small-cell lung cancer, melanoma, head and neck squamous carcinoma, renal cell carcinoma, lymphoma, and bladder cancer (10). Nivolumab, a monoclonal antibody that blocks PDCD1 protein, may be effective in HCC (11). Experimental evidence from animal models demonstrates that intestinal microbes, such as *Bacteroides* species, *Bifidobacteria* species, and *Akkermansia muciniphila*, can potentiate anticancer effect of T-cell-based immunotherapies (12-15). In light of the data from Ma *et al.*, it would be intriguing for future studies to examine the influence of the gut microbiota on efficacy of the T-cell-based immunotherapies for liver cancer. Considering the complex relationship between the gut microbiome, immune cells, and tumor cells in human liver, future analyses of human liver tissue specimens are required for clinical application.

Acknowledgements

Funding: K Mima is supported by grants from Takeda Science Foundation, KANAE Foundation for the Promotion of Medical Science, YOKOYAMA Foundation for Clinical Pharmacology, the Uehara Memorial Foundation, and JSPS KAKENHI (Grant Number 17H05094).

Footnote

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

References

1. Torre LA, Siegel RL, Ward EM, et al. Global Cancer Incidence and Mortality Rates and Trends--An Update. Cancer Epidemiol Biomarkers Prev 2016;25:16-27.
2. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2016;2:16018.
3. Ananthakrishnan A, Gogineni V, Saeian K. Epidemiology of primary and secondary liver cancers. Semin Intervent Radiol 2006;23:47-63.
4. Zitvogel L, Ma Y, Raoult D, et al. The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies. Science 2018;359:1366-70.
5. Szabo G. Gut-liver axis in alcoholic liver disease. Gastroenterology 2015;148:30-6.
6. Dapito DH, Mencin A, Gwak GY, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell 2012;21:504-16.
7. Yoshimoto S, Loo TM, Atarashi K, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 2013;499:97-101.
8. Ma C, Han M, Heinrich B, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science 2018;360. doi: 10.1126/science.aan5931.
9. Gilbert JA, Blaser MJ, Caporaso JG, et al. Current understanding of the human microbiome. Nat Med 2018;24:392-400.
10. Sharma P, Hu-Lieskovan S, Wargo JA, et al. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell 2017;168:707-23.
11. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
12. Vetizou M, Pitt JM, Daillere R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015;350:1079-84.
13. Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015;350:1084-9.
14. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359:91-7.
15. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 2018;359:104-8.

Cite this article as: Mima K, Baba H. The gut microbiome, antitumor immunity, and liver cancer. HepatoBiliary Surg Nutr 2019;8(1):67-68. doi: 10.21037/hbsn.2018.11.09

