Editorial

Gut microbiome-immune crosstalk affects progression of cancer

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The intestinal microbiota is increasingly recognized as a major modulator of health and disease (1). The dramatic explosion of genetic tools and metagenomic techniques in the last decade allowed to characterize the composition of the microbiome from several areas of the body. In addition, this knowledge increasingly enables scientists to link composition and changes with human health and more importantly with various disorders far beyond the gastrointestinal tract (2,3). It is currently believed that the gastrointestinal tract inhabits as much bacteria as cells composing the human body (4). Prototypic examples for an altered microbiome structure are derived from complex diseases such as inflammatory bowel disease, metabolic disorders such as type 2 diabetes, chronic liver diseases and various cancers (5-9). Most information on the gut microbiome so far is rather descriptive and whether there exist direct pathogenetic correlations with human disease is mostly unknown. The interaction between the epithelial surface and its microbial ecosystems could have a major impact on local and systemic immunity and might directly influence the evolution and progression of various cancers in and outside the gastrointestinal tract.

Sethi and colleagues recently reported that the gut microbiota is able to promote tumor growth in rodents by affecting immune responses (10). In their studies, they assessed the role of antibiotic therapy on the evolution of various cancers in mice. Mouse cancers were induced either by subcutaneous injection of KPC pancreatic cancer cells derived from tumors developed in $Kras^{G12D/+}$, $Trp53^{R172H/+}$ or $Pten^{fl/fl}$ mice, by subcutaneous injection of melanoma cells from Tyr-CreER, $Braf^{V600E/+}$ or $Pten^{fl/fl}$ mice or by splenic injection of pancreatic carcinoma cells, melanoma cells or MC38 colon cancer cells to induce liver metastasis. The oral antibiotic combination with vancomycin, neomycin, metronidazole, ampicillin and amphotericin B resulted in a substantial decrease in subcutaneous tumor growth in models of pancreatic cancer and melanoma. Furthermore, this treatment intervention also decreased liver metastases in pancreatic and colon cancer and in melanoma. Importantly, when experiments where performed using Rag1 knockout mice which lack both T and B cells the tumor-suppressing effect of oral antibiotics was no more visible clearly suggesting that the effect of the gut microbiota on tumor formation needs presence of certain immune cells. Further experiments in this study demonstrated that an increase in Th1 ($IFN^+CD4^+CD3^+$) and Tc1 ($IFN^+CD8^+CD3^+$) cells in the tumor microenvironment was crucial for a tumor-suppressive effect of oral antibiotics. In addition, neutralization of IL-17a with a specific antibody abrogated the tumor-attenuating effect of oral antibiotics. This part of the study reveals that various cytokines and especially T cell immunity seems to link the effect of the intestinal microbiota on certain cancers also distant from the gastrointestinal tract. When assessing the gut microbiome after administration of oral antibiotics, the authors observed that especially *Proteobacteria* were increased in feces of mice and also a gut microbiome signature could be detected in liver metastases. *Proteobacteria* are in general considered pro-inflammatory and might be able to drive immune responses characterized by increased IFN expression (11).

In summary, this study nicely links the gut microbiome with immunity and various cancers and suggests that interference at the gut microbiome level might constitute an attractive treatment strategy in human cancers.

Indeed, it has been assumed from several recent microbiome studies that functional properties of the intestinal microbiome refer mainly to metabolic and immune functions. This is expected as the gastrointestinal tract is involved in nutrient digestion and metabolic processes throughout the body and shapes intra- and extra-intestinal immunity (12). Several lines of evidence from the past years have revealed exciting interactions between the intestinal microbiota and cancer (13). Microbes can affect cancer development by many mechanisms, either by production of toxic metabolites, acting oncogenic or regulating immune processes thereby affecting host antitumor immune responses. Early studies proving such interactions demonstrated that certain anticancer drugs showed impaired efficacy in germ-free mice as well as in mice treated with certain antibiotics (14,15). Mechanisms behind are currently not well understood but might involve a fine-tuned interaction with various immune pathways including certain cytokines, specialized lymphocytes and dendritic cells. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade results in the damage of intestinal epithelial cells involving intraepithelial lymphocytes and this was accompanied by an increase in certain bacteria such as *Bacteroides fragilis* thereby activating IL-12-producing dendritic cells and T helper 1 immune responses (15). The most exciting findings in this field probably refer to the fact that checkpoint inhibitors, now used in the treatment of many human cancers, are obviously able to interfere with the gut microbiome. A first piece of evidence was generated by the demonstration that therapeutic efficacy of programmed cell death 1 protein (PD-1/PD-L1) blockade in mice was paralleled by the presence of certain *Bifidobacteria* species which have been demonstrated to activate antigen-presenting cells (16). The most compelling evidence for a key role of the intestinal microbiome in various cancers undergoing checkpoint immunotherapies came from recently published clinical studies (17,18). In a first report, Routy and colleagues demonstrated that primary resistance to immune checkpoint inhibitor therapy was influenced by an abnormal gut microbiome composition. Fecal microbiota transplantation (FMT) from cancer patients responding to such therapies into germ free mice enhanced efficacy of these drugs. The authors could identify *Akkermansia muciniphila* as a crucial commensal bacterium. Non-responders to immune therapies were characterized by low abundance of *Akkermansia muciniphila* and response to tumor therapy could be improved by oral administration of this bacterium (17). *Akkermansia mucinipila* constitutes 3–5% of the human gut microbiota and has demonstrated so far mainly metabolically beneficial and anti-inflammatory effects (19,20). In a second study from the US authors studied oral and gut microbiome of 112 melanoma patients undergoing anti-PD1 immunotherapy. Analysis showed that responders exhibited a higher alpha diversity and an increased concentration of *Ruminococcaceae* bacteria (18). These results are fascinating as they propose a totally unexpected but obviously relevant role of the gut microbiome in systemic immunotherapies.

So what could be the role of antibiotics in patients undergoing cancer therapies? Would they act detrimental or beneficial when administered close to certain anti-cancer treatments? This might, as discussed before be highly dependent on underlying disease and might also be species specific. As outlined in their article (10), in the used preclinical model use of antibiotics was beneficial regarding tumor promotion. Several lines of evidence in humans, however, suggest that the situation might be different. Some studies in humans with various cancers such as metastatic kidney, lung or bladder cancers showed a detrimental role for antibiotics when administered around the administration of monoclonal antibodies targeting PD1/PDL-1 (18). This retrospective data, however, suggested that controlled prospective large human trials are needed to understand how antibiotic usage affects efficacy of certain immunotherapeutic cancer strategies. The box is now open and we can only speculate how important antibiotic modulation of the gut microbiota is in cancer medicine. The findings on *Akkermansia muciniphila*, however, certainly reveal that future studies using administration of designed probiotics (e.g., by using *Akkermansia muciniphila*) or certain FMT strategies could be of relevance to enhance efficacy of cancer drugs especially targeting the immune system. Recent evidence also suggests that the intestinal microbiome is also linked to the pharmacological effects of various chemotherapies including 5-fluorouracil, cyclophosphamide, irinotecan, oxaliplatin, gemcitabine, and others. The gut microbiome affects these agents through key mechanisms such as immunomodulation, metabolism or enzymatic degradation activity (21).

Evidence is increasing that the intestinal microbiota composition affects tumor evolution of various origins far beyond the intestine. This is exciting and reflects likely

a complex interaction of various members of this highly complex bacterial world with various immune pathways. The overall net effect of this bacterial world is currently unclear i.e., whether the intestinal microbiota and its manipulation results in deleterious or beneficial effects on affected patients. The study by Sehti and colleagues offers that manipulation of the intestinal microbiota by antibiotics might be beneficial, although this report is entirely preclinical. Furthermore, it has to be stated that human and mouse microbiome differ substantially. Despite these important preclinical findings, only careful and respective powered clinical trials will allow to understand whether interference at the microbiome level will result in clinical benefit for cancer patients. A new fascinating interaction between microbes and host has entered cancer medicine and manipulation of this intriguing world could evolve as important strategy in the future treatment of many cancers.

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Footnote

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

References

1. Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. N Engl J Med 2016;375:2369-79.
2. Gilbert JA, Blaser MJ, Caporaso JG, et al. Current understanding of the human microbiome. Nat Med 2018;24:392-400.
3. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. Gut 2016;65:330-9.
4. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol 2016;14:e1002533.
5. Zuo T, Kamm MA, Colombel JF, et al. Urbanization and the gut microbiota in health and inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2018. [Epub ahead of print].
6. Sonnenburg JL, Backhed F. Diet-microbiota interactions as moderators of human metabolism. Nature 2016;535:56-64.
7. Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. Gut. 2016;65:2035-44.
8. Tilg H, Adolph TE, Gerner RR, et al. The Intestinal Microbiota in Colorectal Cancer. Cancer Cell 2018;33:954-64.
9. Zitvogel L, Ma Y, Raoult D, et al. The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies. Science 2018;359:1366-70.
10. Sethi V, Kurtom S, Tarique M, et al. Gut Microbiota Promotes Tumor Growth in Mice by Modulating Immune Response. Gastroenterology 2018. [Epub ahead of print].
11. Mukhopadhya I, Hansen R, El-Omar EM, et al. IBD-what role do Proteobacteria play? Nat Rev Gastroenterol Hepatol 2012;9:219-30.
12. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science 2012;336:1268-73.
13. Dzutsev A, Badger JH, Perez-Chanona E, et al. Microbes and Cancer. Annu Rev Immunol 2017;35:199-228.
14. Iida N, Dzutsev A, Stewart CA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 2013;342:967-70.
15. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 2013;342:971-6.
16. Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015;350:1084-9.
17. 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.
18. Gopalakrishnan V, Spencer CN Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97-103.
19. Plovier H, Everard A, Druart C, et al. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med 2017;23:107-13.
20. Grander C, Adolph TE, Wieser V, et al. Recovery of ethanol-induced Akkermansia muciniphila depletion ameliorates alcoholic liver disease. Gut 2018;67:891-901.
21. Alexander JL, Wilson ID, Teare J, et al. Gut microbiota modulation of chemotherapy efficacy and toxicity. Nat Rev Gastroenterol Hepatol 2017;14:356-65.

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