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Gut Microbiota Promotes Tumor Growth in Mice by Modulating Immune Response

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We studied the effects of gut microbiome depletion by oral antibiotics on tumor growth in subcutaneous and liver metastases models of pancreatic cancer, colon cancer, and melanoma. Gut microbiome depletion significantly reduced tumor burden in all the models tested. However, depletion of gut microbiome did not reduce tumor growth in Rag1-knockout mice, which lack mature T and B cells. Flow cytometry analyses demonstrated that gut microbiome depletion led to significant increase in interferon gamma–producing T cells with corresponding decrease in interleukin 17A and interleukin 10–producing T cells. Our results suggest that gut microbiome modulation could emerge as a novel immunotherapeutic strategy.

Keywords: Gut Bacteria; Immune Regulation; Tumor Promotion; Metastases.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Gut microbiome has been implicated in the etiopathology of various disease-states like colitis, metabolic syndrome, ischemic stroke etc. but its role in cancer modulation is obscure.

NEW FINDINGS

Depletion of gut microbiome in mice using oral antibiotics attenuated cancer and metastases burden in multiple models, and activated an antineoplastic immune phenotype in the tumor microenvironment.

LIMITATIONS

It is unclear if dysbiosis in general or some specific gut microbe is responsible for the effects observed.

IMPACT

This study suggests manipulation of the gut microbiome may be an anti-cancer therapeutic strategy.

There are more resident microbes in the human body than there are "human" cells, and most of these microbes occupy an ambiguous niche in the gut. The gut microbiota, forming a unique metagenome, is dynamic and changes with a person's nutrition state, geography, and even age. A growing body of evidence hints toward a co-evolved relationship between gut microbes and our immune system.[1] In fact, some inflammatory diseases, like colitis, are characterized by a transition in the gut microbiome, which changes from a "eubiotic" to a "dysbiotic" state, with interesting therapeutic implications.[2] Although several epidemiological studies associate dysbiosis with cancer, the exact role of gut bacteria in the pathogenesis of cancer is still unclear.

We evaluated the impact of gut microbiome depletion on tumor growth in multiple mouse models. Gut microbiome was depleted in age and sex-matched C57BL/6J mice with a broad-spectrum cocktail of oral antibiotics (vancomycin, neomycin, metronidazole, ampicillin and amphotericin B) using a well-established protocol[3] (Figure 1*A*). Mice, with or without gut microbiome depletion, were used to establish cancer models by subcutaneous injection of KPC pancreatic cancer cells derived from tumors forming in *Kras*$^{G12D/+}$; *Trp53*$^{R172H/+}$; *Pdx-1cre* mice[4]; or melanoma cells derived from tumors forming in *Tyr-CreER; Braf*$^{V600E/+}$; *Pten*$^{fl/fl}$ mice,[5] and by splenic injection of KPC cells; B16-F10 melanoma cells; or MC38 colon cancer cells to induce liver metastases.

Our results show that gut microbiome depletion led to a significant decrease in subcutaneous tumor burden in pancreatic cancer and melanoma models (Figure 1*B* and *C*). There was also a significant decrease in liver metastases burden in pancreatic cancer, colon cancer, and melanoma models (Figures 1*D* and *E*, and Supplementary Figure 1*A*). Interestingly, the tumor-suppressing effect of gut microbiome depletion was abolished when the subcutaneous experiments were carried out in *Rag1* knockout mice

§Authors share co-senior authorship.

Abbreviations used in this paper: IFN, interferon; IL, interleukin; Th, T-helper cell; TME, tumor microenvironment.

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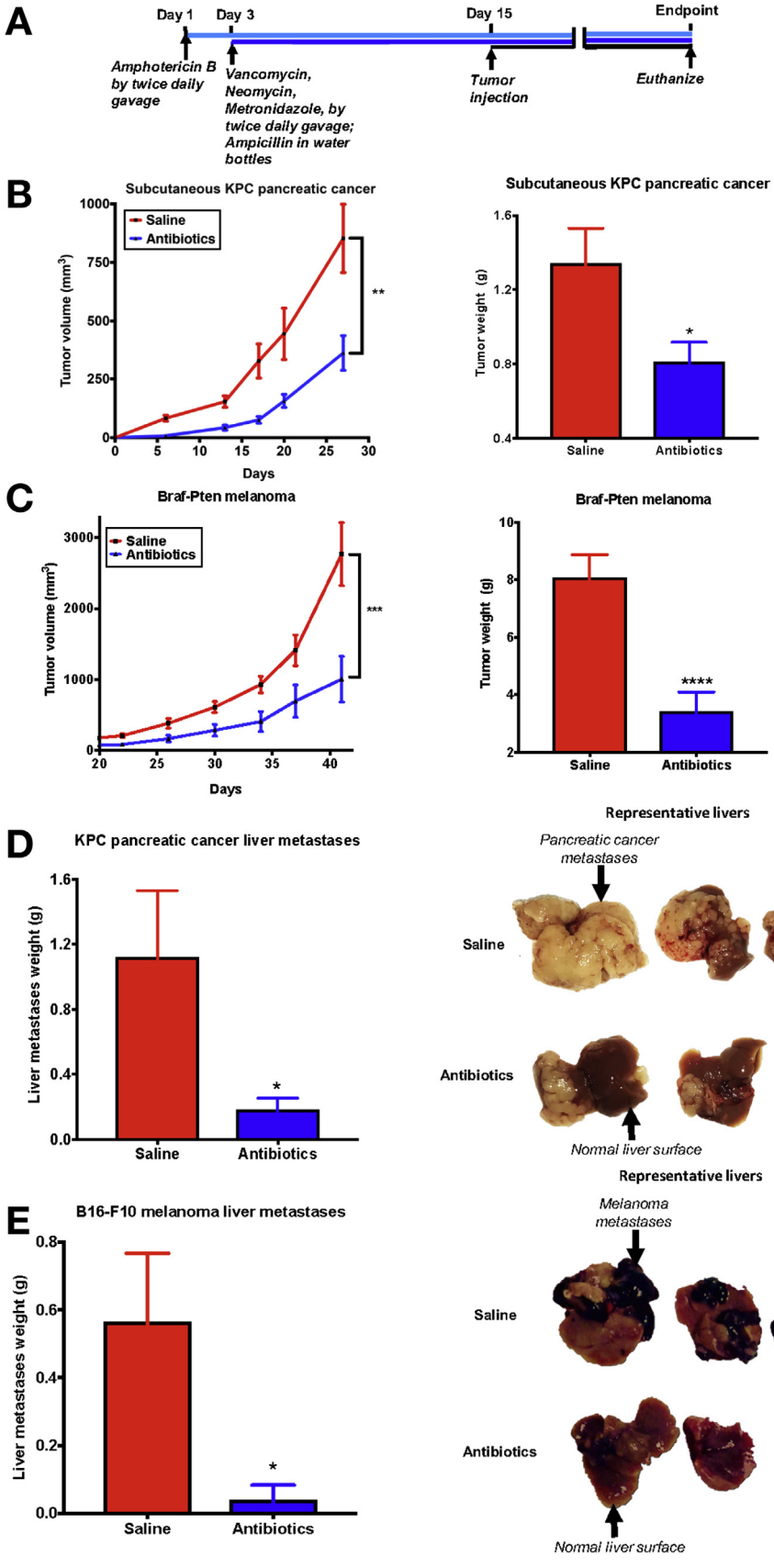

Figure 1. Depletion of gut microbiome decreases tumor burden in multiple models of cancer. (*A*) schematic of the experiments; (*B*) and (*C*) saline and antibiotics-gavaged C57BL/6J mice were subcutaneously implanted with (*B*) KPC pancreatic cancer cells (n = 13 for saline; n = 7 for antibiotics) or (*C*) Braf-Pten melanoma cells (n = 14 for saline; n = 15 for antibiotics). Experiments were repeated 4 independent times with similar results. Results from 1 experiment are shown. X-axis label in (*B*) and (*C*) tumor kinetics represents days after tumor injection. (*D*) and (*E*) saline and antibiotics-gavaged mice were injected intrasplenically with (*D*) KPC cells (n = 9 for saline; n = 7 for antibiotics) or (*E*) B16-F10 melanoma cells (n = 10 for saline; n = 9 for antibiotics) (unpaired Student *t* test with Welch's correction was used. Data are shown as mean ± SEM. $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .005$; $^{****}P < .0005$.