ORAL ANTIBIOTICS IMPROVE THERAPEUTIC RESPONSE OF TUMORS TO ANTI-PD1 TREATMENT BY MODULATING THE TUMOR MICROENVIRONMENT

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Objectives: Gut dysbiosis and the host immune system play important roles in tumor progression and response to cancer immunotherapy. Here, we investigated how manipulation of the gut microbiota by oral antibiotics affects the outcome of cancer treatment with anti-PD1 and which factors are responsible for this effect.
Methods: The effect of an oral antibiotic mixture (ATB; vancomycin, colistin, streptomycin and metronidazole) or a single antibiotic on anti-PD1 efficacy was tested in MC-38 tumor-bearing conventionally bred C57BL/6 mice. The role of microbiota was tested by colonizing germ-free C57BL/6 mice with an antibiotic-modified microbiota followed by subcutaneous inoculation of MC-38 and anti-PD1 treatment. Microbiota was analyzed by 16S rRNA gene sequencing, cells in mesenteric lymph nodes and tumors were analyzed by flow cytometry and cytokine production in Peyer's patches and colon was analyzed by organ culture and ELISA. Gut permeability was analyzed in vivo by FITC-dextran assay.

Results: Both oral ATB and colistin alone enhanced the efficacy of anti-PD1 on MC-38 adenocarcinomas. Neither antibiotic increased intestinal permeability, but their effects on the gut microbiota and immune system were very different. Unlike ATB, colistin did not appreciably alter alfa-diversity because the decrease in *Enterobacteriaceae* and *Bacilli* was compensated by the increase in *Clostridia*, mainly from the *Lachnospiraceae* family. The ATB decreased the production of IL-33 and IL-6 in Peyer's patches and increased Th1 and Tc1 cells in the tumor microenvironment, whereas colistin mainly increased the production of S100A8 in Peyer's patches and Th17 cells in the tumor microenvironment. Improvement in therapeutic effect was possible to transfer with ATB-modified microbiota, but not with colistin-modified microbiota.

Conclusions: ATB and colistin treatments enhance anti-PD1 efficacy in MC-38 adenocarcinomas by increasing the antitumor response of adaptive immunity in the tumor microenvironment. While colistin must act directly to achieve this effect, it can act indirectly via the microbiota when combined with more antibiotics.
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