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Altering gut microbiome to enhance therapeutic efficacy in resistant colon cancer by natural agents

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Tumor recurrence and/or metastasis, a common phenomenon in all malignancies, is observed in nearly 50% of patients with colorectal cancer (CRC). This, we believe could in part be due to enrichment of chemotherapy-resistant cancer stem cells (CSCs), accompanied by dysfunction of the gut microbiota (dysbiosis), resulting in alterations in microbial metabolites and by-products in the gut and tumor, some of which may be responsible for the recurrence of CRC. Thus, development of preventive/therapeutic strategies that simultaneously targets the growth potential of CSCs as well as impact the tumor promoting microbiome population should be effective in reducing the risk of relapse and metastasis. We have examined the effectiveness of the combination of ETO-curcumin (ETO-cur; curcumin complexed with essential turmeric oil) and TRF, tocotrienol-rich fraction of a palm oil in inhibiting the growth of SCID mice xenograft of chemo-resistant (CR) colon cancer cells and whether this inhibition could be attributed to alterations in gut and tumor microbiome and their metabolites. Indeed, feeding (oral gavage) of ETO-cur (5 mg/kg) together with TRF (2 mg/kg) or the vehicle (control) in SCID mice, initiated after about 20 days of inoculation of CR colon cancer cells in SCID mice, which continued for 45 days resulted in a marked inhibition of growth of colon tumor that became apparent after 15 days of treatment. At 40 and 45 days, differences in tumor growth between the two groups were statistically significant. At this point, the growth of the tumor in ETO-cur/TRF fed mice began to plateau. This inhibition of growth was not only associated with a significant down-regulation of β-catenin and TNF-α in the tumor but also with alterations in gut microbiota. The latter is evidenced by overlap 340 bacterial species between the control and ETO-cur/TFR-treated SCID mice and 216 and 120 species being different in ETO-cur and TRF treated mice, respectively. A marked increase in anti-inflammatory *Lactobacilaceae* and *Bifidobacteriaceae* and reduction in pro-inflammatory *Akkermansia* spp. was observed in feces from ETO-cur/TRF treated SCID mice, compared to controls. Although the precise nature of bacterial participation in inhibition of growth of colon tumor remains unresolved, we have observed a significant reduction in the expression of 7-α-dehydroxylase in fecal and tumor cells from ETO-cur + TRF treated SCID mice, compared to the control. This suggests that the conversion of bile acids to carcinogens and tumor promoters, catalyzed by 7-α-dehydroxylase is suppressed by the combinatorial treatment of ETO-cur and TRF. Since secondary bile acids in the gut, specifically deoxycholic acid (DCA) and lithocholic acid (LCA) are known for their co-carcinogenic activity and to induce CSCs in the colon, we postulate that the decreased levels of luminal DCA and/or LCA by the combinatorial treatment of ETO-cur and TRF may have contributed to the prevention of growth of colon tumors.

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