Colorectal cancer (CRC) cells have intimate associations with the bacterial microbiota. Bacterial members of the intratumoral microbiota exhibit metabolic activity in CRC and, together with malignant cells, interact with the chemotherapeutic agents. In this study, the authors from the United States investigated the complex interactions between CRC microbiota and the chemotherapeutic agents.

A growing body of evidence demonstrated that the microbiota composition plays a significant role (both directly and indirectly) in the chemotherapeutic efficacy of numerous drugs in various cancers. *Fusobacterium nucleatum* (*Fn*) is a dominant bacterial species found in CRC tissue. Numerous studies have demonstrated that *Fn* is associated with cancer recurrence and outcomes, contributing to tumorigenesis, accelerated cancer growth, resistance to chemotherapy, disease recurrence, metastasis, and reduced survival. Post-chemotherapeutic studies revealed the persistence of *Fn* in distant CRC metastases. Furthermore, a high load of *Fn* in primary CRC tissue positively correlated with a higher risk of disease recurrence.

The same research group has demonstrated before that treatment of *Fn*-positive human CRC xenografts with the antibiotic metronidazole in mice significantly reduced tumor growth and cancer cell proliferation. These results showed that *Fn* targeting may be a therapeutic option for a subset of patients with CRC.

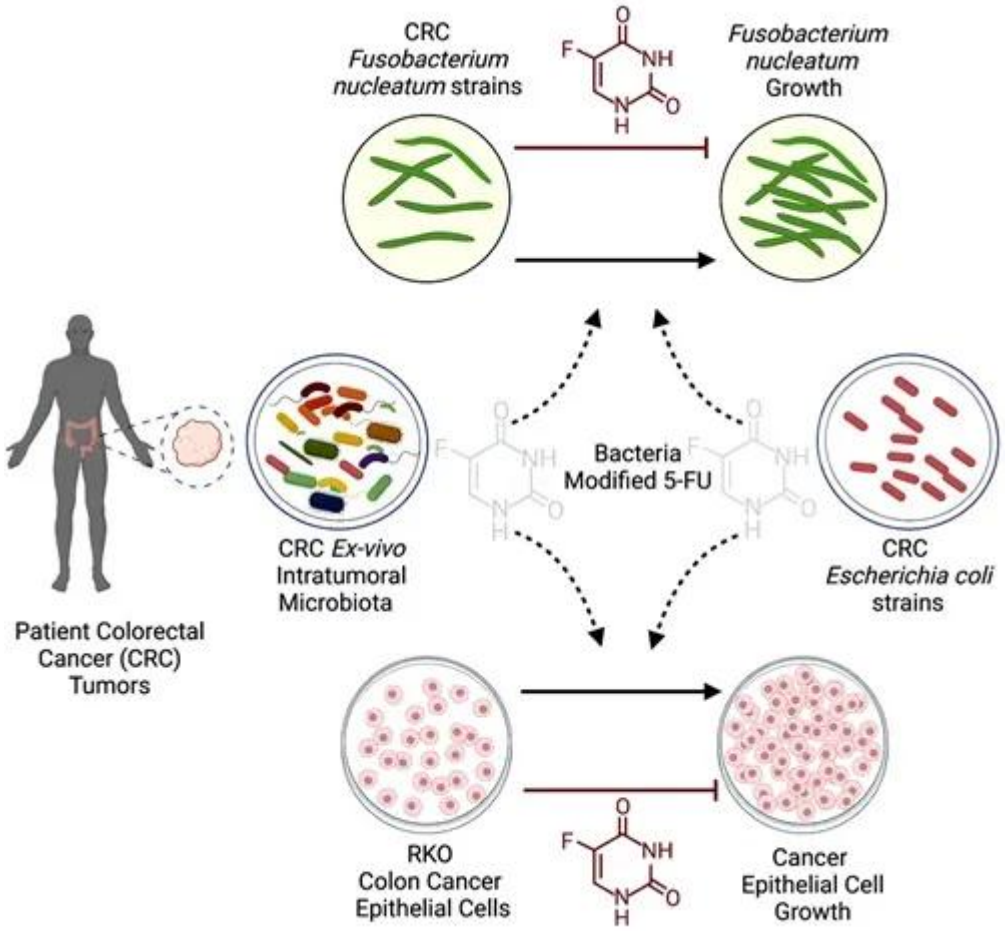
About the study

The researchers screened a random selection of 1,846 small molecules from the Broad Institute's "Bioactive Compound" library. They identified 34 compounds that inhibit *Fn* growth, and approximately half (56%) are well-known antimicrobial compounds, but, 15% of inhibitors are classified as antineoplastic agents.

The scientists then monitored *Fn* growth in the presence of 24 chemotherapeutic agents. The mainstay CRC chemotherapeutic drug tegafur and its active metabolite, 5-fluorouracil (5-FU), have been identified as potent inhibitors of *Fn* CRC strain growth. Capecitabine, another prodrug of 5-FU, did not affect *Fn* growth *in vitro* under these conditions. The authors speculated that the difference in inhibition of *Fn* growth *in vitro* between 5-FU prodrugs might be due to different enzymatic pathways required for prodrug activation.

The authors then investigated the sensitivity of CRC *Fn* clinical isolates to 5-FU. They assessed the half-maximal inhibitory concentration (IC50) of 5-FU in 14 strains of *Fn* obtained from CRC tumor tissue (n= 11), the oral cavity (n= 2), and inflamed irritable bowel disease tissue (n= 1). The results showed that 5-FU exhibited potent growth inhibition properties on CRC *Fn* isolates.

They also assessed the sensitivity of other dominant CRC-associated bacterial species that frequently co-occur with *Fn* to 5-FU. Since the members of the intratumoral microbiota like *Escherichia coli*, *Bacteroides fragilis*, *Bifidobacterium breve*, and *Parvimonas micra* were resistant to physiologically relevant concentrations of 5-FU (2.5–10μM), the authors speculated that these strains might have mechanisms capable of detoxifying 5-FU. To investigate this possibility, they inoculated 5-FU with *Escherichia coli* and *Fn,* the most prevalent bacterial subspecies in CRC. They found that *Fn* was protected from 5-FU toxicity, with a viability of 74% after 48 hours.



Original illustration from the article by LaCourse KD. Cell Reports 2022.

The researchers then explored whether *E.coli* can alter the chemotherapeutic efficacy of 5-FU towards CRC cells. They cultured a human CRC epithelial cell line sensitive to 5-FU with 5-FU previously exposed to *E.coli* and monitored cell growth over 72 h. Remarkably, prior exposure of 5-FU to *E.coli* completely abrogated toxicity of 5-FU against human CRC epithelial cells. These findings revealed that depletion of 5-FU, mediated by bacteria, reduced the efficacy of 5-FU against human CRC cells.

Certain members of the microbiota are capable of metabolizing and detoxifying 5-FU. To investigate whether exposure to 5-FU alters the CRC microbiota structure and facilitates the expansion of 5-FU-resistant bacterial species, researchers performed the metagenomic analysis of treatment-naive CRC tissue from six patients. The results showed that exposure

to 5-FU altered the relative abundance of community members and enabled the expansion of 5-FU-resistant bacterial species. It suggests that some bacterial community members can resist 5-FU toxicity and potentially decrease drug bioavailability.

Conclusion

This study showed that bacterial community members fit into three categories concerning a first-line CRC chemotherapeutic agent, 5-FU: highly sensitive, resistant, and resistant and depleting. These findings support the hypothesis that in some patients with CRC, certain bacterial species are capable of metabolizing and detoxifying 5-FU. The reduced efficacy of 5-FU would protect tumor-supporting bacteria such as *Fn* and resident cancer cells from the drug's toxicity, and promote CRC recurrence. The authors emphasized a need for further clinical studies on the co-occurrence of bacterial species like *E. coli,* which can modify 5-FU and intratumoral *Fn.*

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