Spiking immunotherapy with a bacterial cocktail brings T cells back to the fight

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https://doi.org/10.1016/j.xcrm.2021.100430

A recent study by Montalban-Arques et al.1 in Cell Host & Microbe shows that augmenting the function of the gut microbiota reduces tumor burden. Four Clostridiales species blocked tumor growth as efficient as chemotherapy or immunotherapy in colorectal cancer and melanoma.

Recent studies have highlighted the important role that gut microbiota play in both the prevention and treatment of several cancer types, including colorectal cancer (CRC). However, an outstanding need in the field of cancer treatment is improving response to immunotherapy, especially for metastatic CRC: ~97% are refractory to immunotherapy because of being proficient for mismatch repair (pMMR) and microsatellite stable (MSI-L). Unfortunately, these tumors also have low immunogenicity; either the CD8+ T cells are activated but cannot enter the tumor environment or the tumor is in an “immune desert” and no longer recognized by the cytotoxic T cells. Thus, identifying a new approach that may augment standard chemotherapeutic or immunotherapeutic treatments would be of great benefit in this population.

Montalban-Arques et al.1 in Cell Host & Microbe initially observed that azoxymethane and dextran sodium sulfate (AOM/DSS) induced significantly different tumor burdens in genetically identical (C57BL/6J) animals from separate vendors (Figure 1). Using 16S rRNA sequencing of gut microbiota, they identified a mixture of four Clostridiales species (CC4), Roseburia intestinalis, Eubacterium hallii, Faecalibacterium prausnitzii, and Anaerostipes caccae, based on the reduced presence of a marker of butyrate production, butyryl-CoA transferase. To provide clinical support for use of this mixture of Clostridiales species, Montalban-Arques et al.1 found that, from stool samples (285 CRC cases and 290 tumor-free controls), the order Clostridiales, namely R. intestinalis, E. hallii, and F. prausnitzii, was depleted in CRC, especially late stage. Furthermore, all four strains produce butyrate through different pathways,2 which led to the hypothesis that butyrate was a potentially protective mechanism; however, targeted butyrate pathway analysis showed no consistency with either CRC patients or healthy controls. Additionally, oral supplementation of the mice with sodium butyrate had no mitigating effect on the CRC tumors compared to placebo, thus diminishing the role of butyrate in the treatment effect mechanism.

To test whether this cocktail could mitigate tumor formation in the AOM/DSS model, they provided CC4 as an oral gavage once after each of the three DSS treatments. They discovered that CC4 treatment not only acts to reduce tumor formation but does so by enhancing the amount of IFN-γ, CD8+ T cells and natural killer (NK) cells in the CRC tumor and by decreasing PD-L1 macrophages, which is consistent with findings by Tanoue et al.1 When they provided the CC4 cocktail prophylactically, prior to ortho- or heterotopic cancer cell injections, they also found reduced tumor development not only in chemical or heterotopic models of CRC but also in other cancer models: breast, lung, and skin. The CC4 treatment also induced a marked decrease in colonic inflammation while preserving microbial diversity, compared to control and P. stomatis-treated mice. This is also a similar finding to that of Tanoue et al.,3 who observed that an 11-strain cocktail mitigated colitis in the same colon carcinoma (MC-38) model. Interestingly, individual CC4 strains, R. intestinalis and A. caccae, were also able to impede tumor development in CRC as a standalone treatment.

Next, they sought to determine whether the CC4 mix may be as effective or enhance immunotherapy. They pretreated with CC4 prior to MC-38 or B16 (melanoma) injections and followed with oral gavage of CC4 along with anti-PD-1 (immune checkpoint inhibitor) or IgG control and found that CC4 was more effective than anti-PD-1 alone in reducing tumors, although B16 tumors did not respond to anti-PD-1 treatment in contrast to other studies.4 This lower tumor development was accompanied by an increase in IFN-γ, granzyme B, and TNF-α, as well as an increase in perforin frequencies within the CD8+ population in the CC4-treated model. Importantly, when used with the chemotherapeutic agent 5-fluorouracil (5-FU), which is a standard option in CRC treatment (stage II-IV), CC4 was found to be as effective as 5-FU. Lastly, it has recently been shown that tumor mutation burden, which is higher in dMMR/MSI-H tumors, is a predictive marker for immunotherapy response;5 however, the effect of CC4 treatment was independent of mutation burden, indicating that this therapy may also be applicable to pMMR/MSI-L tumors with lower mutation burdens. It is intriguing to put into context with the recent findings by Fluckiger et al.,6 which also found that E. hirae improves long-term benefit of anti-PD1 therapy. Specifically, it was the bacteriophage of E. hirae, tail-length tape measure protein (TMP), that was found to be an antigen for MHC class 1 cells, which was capable of activating CD8+ T cells because of its “molecular mimicry” to the tumor antigen proteasome subunit beta type-4 (PSMB4). Putting this together with the previous findings of improved immunotherapy response
among patients showing higher bacterial diversity suggests that the more diversity in microbial and/or bacteriophage antigens present increases the potential to mimic a tumor antigen and recruit more activated CD8+ T cells to the tumor site, although many other yet undiscovered mechanisms are likely at play.

This work is supported and preceded by seminal findings illustrating a common theme: specific strains of bacteria or combinations thereof are effective in increasing the immunogenicity of several tumor types, mainly through activation and/or recruitment of immune cells (CD103+ dendritic cells and CD4+, CD8+ T cells), and, therefore, the efficacy of immunotherapy. The work presented herein builds on these original findings by demonstrating this microbiome-enhanced immune response across multiple tumor types and in both neo- and adjuvant treatment conditions. Together, these findings set the stage for human trials and additional research into understanding the full repertoire of mechanisms that allow certain microbial communities or strains to bring the immune system back into the fight.

DECLARATION OF INTEREST

The authors declare no competing interests.

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