

1328 THE USE OF FECAL FILTRATE TRANSPLANT TO ENHANCE RESPONSE TO IMMUNE CHECKPOINT BLOCKADE

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Background Treatment with immunotherapy has revolutionized cancer care. Nevertheless, strategies to enhance response remain an urgent need to overcome resistance to treatment. Our group and others have shown that distinct microbial signatures are associated with favorable response to ICB. Furthermore, recent trials have demonstrated that patients with ICB refractory cancer benefit from fecal microbiota transplantation (FMT) of stool samples from patients with beneficial response to ICB. However, the clinical application of FMT is limited by the rigorousness of screening criteria and needed volume of fecal material. The aim of our study is to identify the active components in FMT material that enhance response to ICB to develop microbiome-based strategies to improve cancer response to ICB. We hypothesized that microbial derivatives within the stool (filtrate) can induce immunomodulation and enhance response to ICB.

Methods We prepared filtrates from stool samples from melanoma patients who were complete responders (CR) and those who did not benefit from ICB (non-responder, NR). Filtrates were prepared via centrifugation and filtration of stool suspensions to remove bacteria, human cells, and debris. Eight-Twelve-week female germ-free C57BL6 mice received oral gavage of NR or CR FMT or NR or CR filtrate every other day (3 doses total). After a five-day period for engraftment, mice received subcutaneous injection of BP melanoma tumor cells, and were subsequently treated with anti-PD-L1 (3 doses total). Tumor measurement was conducted using a caliper. At endpoint, tumors and colon samples were collected for digital spatial profiling. To characterize the components of filtrates, we analyzed the proteome of the filtrates through mass spectrometry.

Results Treatment of mice with both CR FMT and CR filtrate significantly improved response to anti-PD-L1 treatment, suggesting that microbial derivatives might be sufficient for inducing a response to ICB. In contrast, treatment with NR FMT and NR filtrate was associated with poor response, though responses were worse with NR FMT. Proteomic analysis of filtrates from CR donors demonstrated an enrichment of immunoglobulins and bacterial proteins from 4 major bacterial species compared to NR filtrate, suggesting a role for the microbiome in inducing a B cell response. Digital spatial profiling of tumor and colon samples are currently underway, as well as further characterization of the fecal filtrate to determine putative therapeutic targets to improve ICB response.

Conclusions Together, these studies suggest that acellular components of FMT may confer improved response to ICB, though further studies are needed to derive optimal therapeutic targets and to gain mechanistic insights.

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Ethics Approval All patients whose samples were used for in vivo and in vitro studies, provided voluntary informed consent to research procedures, including biospecimen collection, under Institutional Review Board (IRB) approved protocols. Animal studies were approved by the Institutional Animal

Care and Use Committee (IACUC) at The UT MD Anderson Cancer Center.

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