Tumor microbiome linked to immunotherapy success in sarcoma patients

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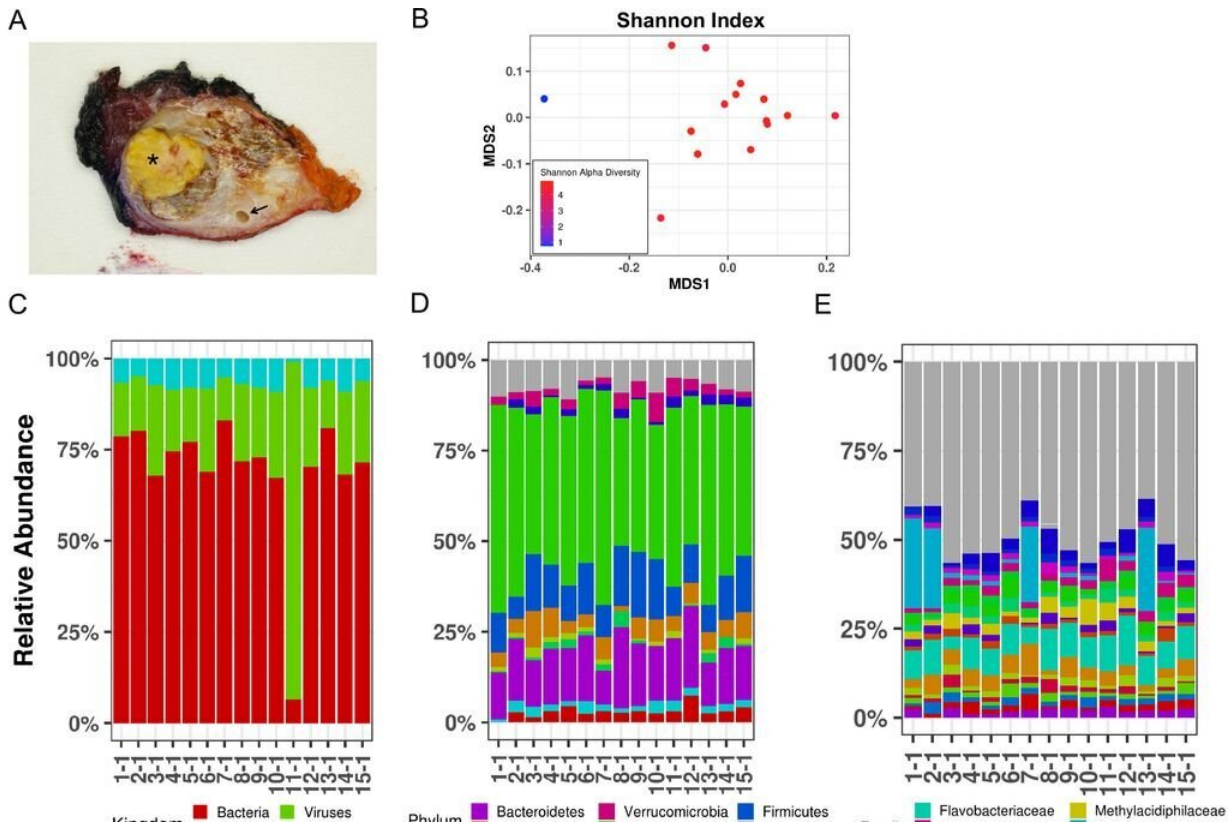

Soft tissue sarcomas intratumoral microbiome at diagnosis may link with prognosis. (A) Representative gross examination of extremity synovial sarcoma specimen; asterisk demonstrates tumor necrosis and arrow identifies an encased major artery. (B) Multidimensional scaling (MDS) plot based on mathematical distance of taxonomic divergence for pre-RT intratumoral microbiome by alpha diversity. MDS plot demonstrates notable biodiversity for all pre-RT tumor samples with the exception of one patient with low intratumoral biodiversity (blue). (C–E) Relative abundances for pre-RT intratumoral microbiome by

individual patients at the (C) kingdom, (D) phylum, and (E) family levels. Relative abundance describes the per cent composition of a specific organism relative to the total organism number. (F) MDS plot for pre-RT intratumoral microbiome by patient deaths. (G) MDS plot for pre-RT intratumoral microbiome by progression to metastases. (H) Kaplan-Meier estimates for overall survival (OS) and metastasis-free survival (MFS). (I–J) MDS plots for pre-RT intratumoral microbiome by (I) histology, (J) tumor size, and (K) tumor location. RT, radiotherapy. Credit: *Journal for ImmunoTherapy of Cancer* (2023). DOI: 10.1136/jitc-2021-004285

In a new study, UC Davis Comprehensive Cancer Center researchers have uncovered a link between a patient's microbiome and their immune system that can potentially be used to improve the treatment of soft tissue sarcoma. This type of cancer is found in connective tissues like muscle, fat and nerves.

Findings from the study were published in the *Journal for Immunotherapy of Cancer*.

"The study's data show new lines of research in the paradigm-shifting concept that the microbiome of a patient and their immune system can interact and shape one another, as well as be potentially engineered to improve patient outcomes," said Robert Canter, the lead author of the study and chief of the Division of Surgical Oncology.

The gut microbiome is made of microorganisms in the digestive tract that include bacteria, fungi and viruses. Microbial communities have also been found in other parts of the body, including the mouth, lungs and skin. And now the study shows they are also found in tumor cells.

"We found that soft tissue sarcomas harbor a quantifiable amount of microbiome within the tumor environment. Most importantly, we found

that the amount of microbiome at diagnosis may be linked with the patient's prognosis," Canter added.

Although the levels of microbes are low, the study findings are significant because many tumors, especially sarcomas, were believed to be sterile.

Viruses within the microbiome may attract cancer-fighting cells

The UC Davis researchers also uncovered how the microbiome within a sarcoma tumor plays a role in attracting specific types of immune cells like cancer-fighting natural killer cells. Canter said that's important because the higher the rate of natural killer cell infiltration in a tumor, the greater the chance that the sarcoma won't spread to other parts of the body. Natural killer cells are a prime target for improving the effectiveness of immunotherapy.

The team found that viruses within the microbiome of a tumor appear to impact the amount of natural killer cells found in sarcomas and, for that reason, affect survival rates. Specifically, the study found a strong positive correlation between the presence of Respirovirus, a genre of viruses known for causing respiratory illnesses, and the presence of natural killer cells in the tumor. Canter and his colleagues are now considering ways to create viruses to attract more cancer-killing immune cells.

"It has become clear that the microbiome in the gut and other parts of the body has a major impact on human health and disease. Amazingly, it shapes the immune system throughout the body and, because of its interaction with the immune system, we now know it also has a big role in how the body responds to cancer and cancer treatments like

immunotherapy," Canter said.

Cross-campus collaboration

The authors obtained tumor and stool samples from 15 adult patients with non-metastatic soft tissue sarcoma, which was studied for a median of 24 months. Analysis revealed that most of the tumors were advanced stage III (87%) and affected a patient's limb (67%).

Tissue samples were sent to the university's Genome Center in Davis for sequencing and to the Flow Cytometry Shared Resource Laboratory on the UC Davis medical campus in Sacramento for immune profiling. Patients were monitored for two years as part of their cancer treatment follow-up.

Canter said past research has shown the existence of microbiome inside tumors across several cancer types, including breast, lung, pancreas and melanoma. For that reason, he said further research into the connection between microbiome and the immune system in other cancer types is warranted.

More information: Lauren M Perry et al, Human soft tissue sarcomas harbor an intratumoral viral microbiome which is linked with natural killer cell infiltrate and prognosis, *Journal for ImmunoTherapy of Cancer* (2023). DOI: 10.1136/jitc-2021-004285

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