Novel form of immunotherapy could revolutionize cancer treatment

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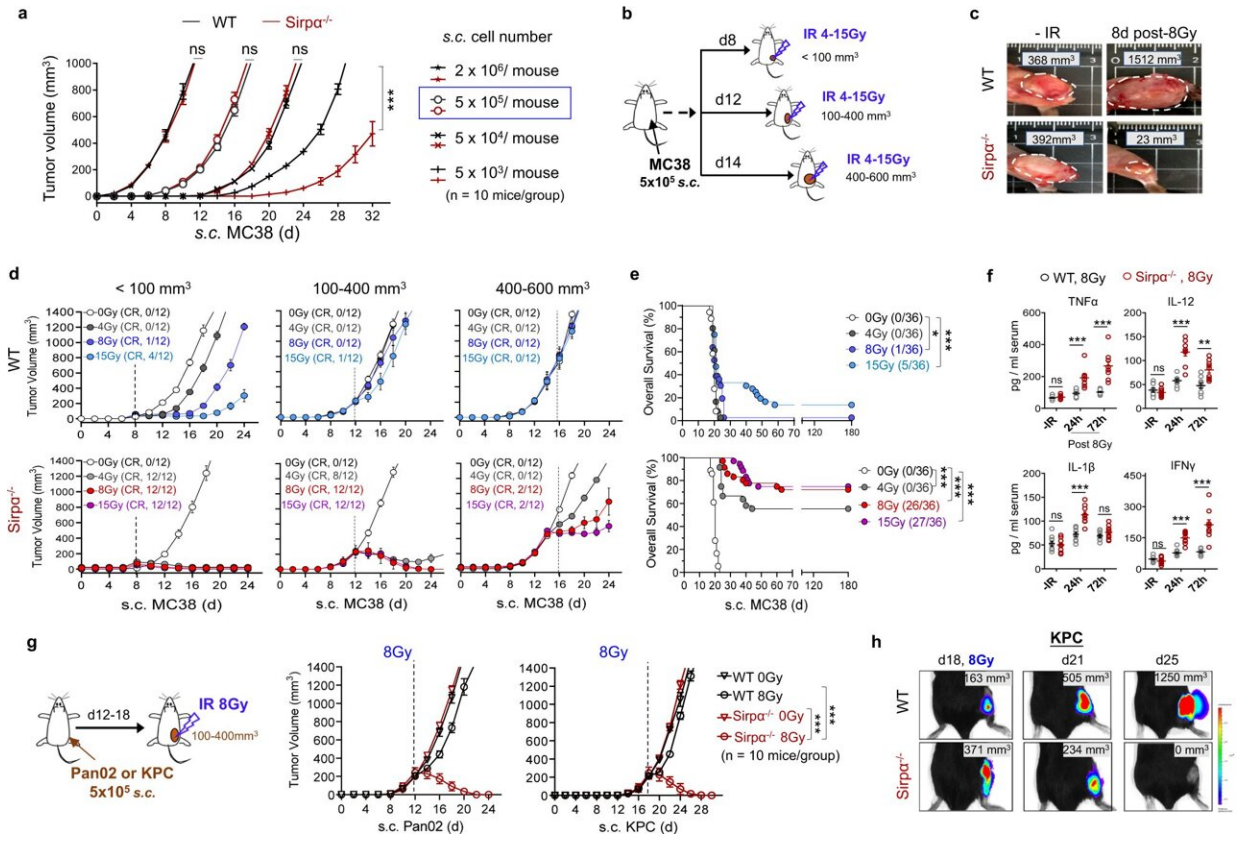

Fig. 1: Local RT eliminates late-stage MC38 tumors in Sirpα−/− mice but not WT mice. From: Intratumoral SIRPα-deficient macrophages activate tumor antigen-specific cytotoxic T cells under radiotherapy

A novel form of macrophage-based immunotherapy is effective at

treating a broad spectrum of cancers, including those at advanced stages, according to a groundbreaking study led by Georgia State immunology professor Yuan Liu.

Liu's treatment works by leveraging macrophages, specialized white blood cells involved in the detection and elimination of cancer cells and other pathogens. Macrophages also activate T-cells which then attack and destroy cancer cells. Under normal conditions, this system works well to limit the growth of abnormal cells. However, cancer cells are tricky. Macrophages are vulnerable to cancer cells masquerading as healthy cells by co-opting mechanisms normal cells rely on that evade immune surveillance and detection. These mechanisms can profoundly increase cancer's ability to grow and resist traditional treatment.

This new immunotherapy alters macrophages by knocking out Signal-regulatory protein α (SIRPα), a receptor whose primary function is to prevent macrophages from engulfing and destroying healthy cells. Cancer cells often exploit SIRPα by expressing a marker (CD47) that disguises them as normal cells. In the animal study, published in *Nature Communications*, Liu and her team found that Sirpα-deficient macrophages initiate a robust immune response against cancer by triggering inflammation and activating tumor-specific T-cells.

The immune system is built to fight off invaders and aberrant cell growths like cancer. But cancer can also suppress and subvert the natural immune response by making it difficult for the body to recognize cancer cells as abnormal. While immunotherapy, which helps recruit the immune system to attack cancer cells, has revolutionized the treatment of tumors, the therapies only work for a limited number of patients.

"Scientists recognize that tumor-specific T-cells are the best weapon we have against cancer, but immunosuppression prevents them from doing their job," Liu said. "Our treatment uses macrophages like a general to

call up an army of T-cell soldiers to kill cancer."

The study demonstrates the treatment is effective—and does not destroy large amounts of healthy cells—when delivered locally to the tumor site in conjunction with radiation therapy (RT), one of the cornerstone treatments for cancer.

"To kill the cancer without harming the patient, you need to localize the effects," Liu said. "We developed a method that is very effective while minimizing the global adverse effects."

The researchers found that local RT cured colorectal cancer and two types of pancreatic cancer in SIRPα-deficient mice with advanced tumors. The findings are significant, given that colorectal and pancreatic cancers are often treatment-resistant with high mortality rates.

The mice in the study developed inflammatory immune responses, and in most cases the tumors stopped growing immediately after irradiation. Within four to 12 days, mice with small and medium tumors had cleared the cancer completely, without apparent long-term adverse effects, and the animals remained tumor-free for the remainder of the study. In general, mice that were cured of their cancer exhibited similar longevity (about 18 months) as healthy mice.

The treatment also prevented one of the major negative effects of RT—its tendency to drive a strong wound-healing response that can result in the regrowth of cancer, as the local immune response is suppressed to promote new tissue growth and repair at the site of the RT. This mechanism, however, was absent post-RT in the SIRPα-deficient mice.

The mice exhibited long-lasting immunity to the cancer, which Koby Kidder, a Ph.D. student at Georgia State and co-author of the study, said

is the result of an immune response robust enough to control the tumor cells throughout the body. Even when the cured mice were injected with new cancer cells, these cells failed to form tumors, suggesting the animals had acquired long-term immunity that prevented tumor recurrence.

"The reason we achieved such a high degree of efficacy is that we directly used the macrophage to mobilize other cells within the body," Kidder said. "The mounting of a consummate anti-tumor immune response in concert with removing immunosuppressive factors (cells and cytokines) from the tumor microenvironment drastically affected the immune response. By removing SIRPα and combining it with radiotherapy, we elicited such a robust response it essentially cured the cancer."

The study demonstrates SIRPα is a master controller of immunity inside the tumor microenvironment, directing post-RT wound healing, strengthening immunosuppression, conferring treatment resistance and allowing the cancer to progress. In the absence of SIRPα, however, antitumor immune responses are significantly enhanced.

The treatment has the potential to become a "pan-cancer therapy," meaning it could be used to cure a broad spectrum of cancers, including those at advanced stages with metastasis. The study provides strong proof-of-concept for developing Sirpα-negative macrophage-based cell therapies, Liu said.

The cell therapy approach has already been tested against the entire NCI-60 cancer panel—made up of 60 various human tumor cell lines representing leukemia, melanoma, lung, colon, brain, ovary, breast, prostate and kidney cancers—and has been found to be effective. The researchers are applying for approval of the therapy as an investigational new drug by the U.S. Food & Drug Administration and hope to begin

human clinical trials in 2022.

Liu has received grants from the National Cancer Institute, the Georgia Research Alliance and Biolocity to support this research.

"Currently, the treatments using immune therapy only benefit a small percentage of patients," Liu said. "This therapy has already proven effective in the laboratory and could be the key to fighting all types of cancer. This is basically a battlefield in the body, and if we are able to activate the proper delivery signals, our bodies win."

More information: Zhen Bian et al, Intratumoral SIRPα-deficient macrophages activate tumor antigen-specific cytotoxic T cells under radiotherapy, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23442-z

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