Natural antioxidant helps improve immune-based therapies by modulating T-cells

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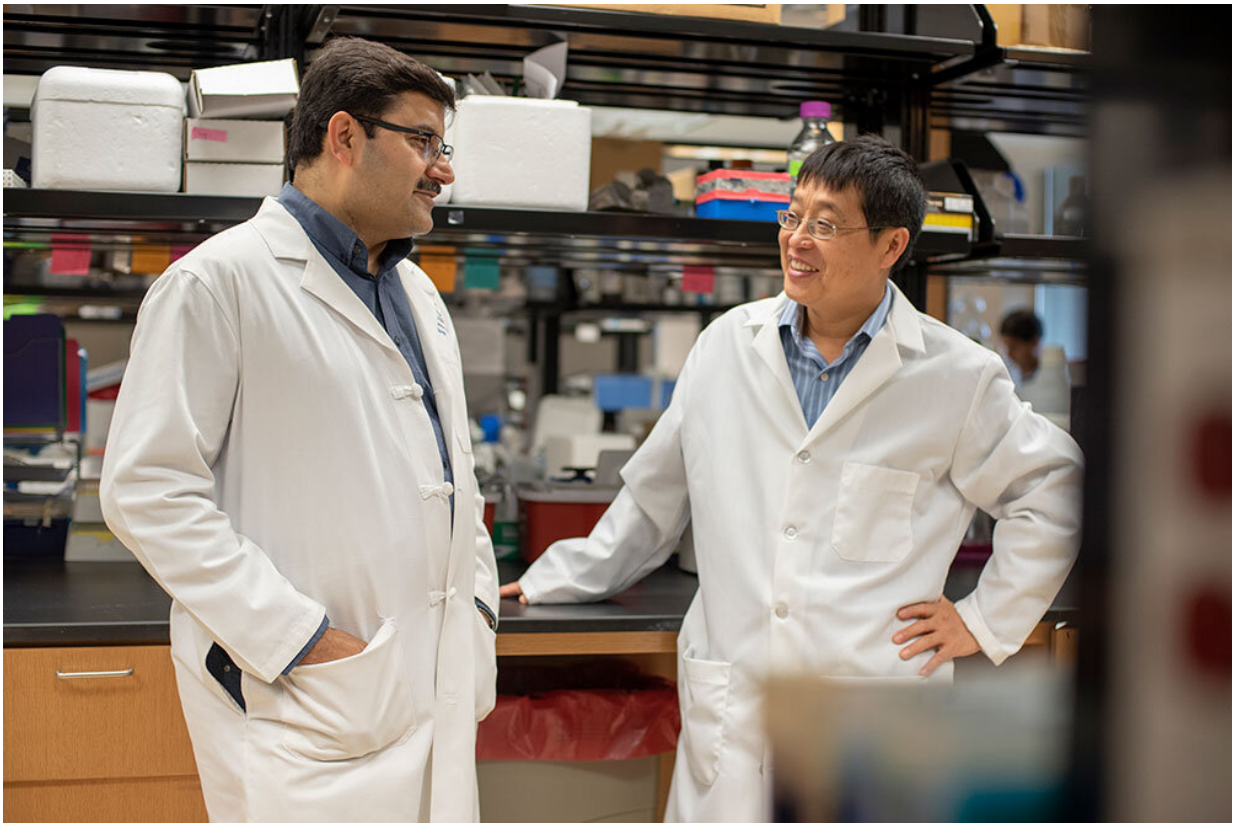

Long-time Medical University of South Carolina collaborators Dr. Shikhar Mehrotra (left) and Dr. Xue-Zhong Yu (right) author papers showing that a natural antioxidant can modulate T cell activity in cancer immunotherapy and graft-vs.-host disease, respectively. Credit: Emma Vought, Medical University of South Carolina

Shikhar Mehrotra, Ph.D. and Xue-Zhong Yu, M.D., National Institutes of Health-funded researchers at the Medical University of South Carolina (MUSC), have discovered a way to improve immune-based treatments, such as adoptive T-cell therapy (ACT) and hematopoietic stem cell transplantation (HSCT), by modulating T-cells with thioredoxin, a powerful, naturally occurring antioxidant molecule.

ACT is a cancer immunotherapy in which the patient's own immune cells (T-cells) are engineered to recognize cancer cell-specific markers. First, the patient's blood is collected, then T-cells are removed and genetically modified to attack cancer cells. Finally, the modified T-cells are re-administered to the patient.

ACT is currently used for patients with leukemia and lymphoma. However, a major downside to the treatment is that the re-administered T cells do not live long, leading to relapse.

HSCT is a classic immune-based treatment that requires a donor to supply stem cells, which are then administered to the patient to help them produce more immune cells to fight blood-related diseases, including blood cancers. A severe side effect of HSCT is graft-versus-host disease (GVHD), which occurs when the donor T-cells attack the recipient's healthy tissues instead of diseased cells.

Though they study different models, Mehrotra and Yu are long-time collaborators. Both are dedicated to understanding T-cell function.

"Our collaboration is a common interest in the biology of T-cells and how to manipulate them to benefit different disease conditions," Yu explains.

Mehrotra is an associate professor in the College of Medicine and co-scientific director of the Center for Cellular Therapy at MUSC Hollings

Cancer Center. He and his team recently published a study in the *Journal of Biological Chemistry* that showed that thioredoxin extends the life of adoptive T-cells by neutralizing toxic reactive oxygen molecules (ROS).

Tumor environments have high concentrations of ROS. Without antioxidants such as thioredoxin, ROS will damage the cell and eventually cause cell death.

"Treating anti-tumor T cells with recombinant thioredoxin before adoptive transfer not only imparted high anti-oxidant capacity," explained Mehrotra.

"It also metabolically programmed these cells to withstand nutrient competition with the tumor—which resulted in better tumor control."

The team at MUSC used a strain of mice that overexpress thioredoxin and performed a standard ACT procedure. They observed increased T-cell viability and antitumor activity from mice overexpressing thioredoxin.

They confirmed the findings by engineering human T-cells to overexpress thioredoxin and again observed prolonged T-cell lifespan at the site of the tumor. The results suggest that treating human T-cells with thioredoxin before administration will increase cell viability and improve the anti-tumor effect of ACT in patients.

Yu is a professor in the College of Medicine and S.C. SmartState Endowed Chair in Cancer Stem Cell Biology and Therapy. Yu and his team at MUSC study the development of graft-versus-host disease (GVHD) in recipients of HSCT.

Using a mouse model, Yu's lab tested the effect of thioredoxin on donor T-cells, and the results were published in the *Journal of Clinical*

Investigation. Like Mehrotra's study with adoptive T-cells, Yu's study found that thioredoxin's antioxidant effect decreased toxic ROS in donor T-cells, made them less reactive to the patient's healthy tissues, and thereby prevented development of GVHD.

"Thioredoxin is a natural product with no toxicity. We can use it to fine tune T-cell activation in a way that will reduce graft-vs-host disease but maintain anti-tumor effect," Yu reports on the new finding.

Mehrotra and Yu plan to continue to work closely to develop this new advancement in T-cell immune therapy.

The next step for both projects is to induce human tumors into mice and test the effect of thioredoxin-treated T-cells in both ACT and HSCT models. This will determine if it can be moved to clinic to be tested on patients.

More information: M. Hanief Sofi et al, Thioredoxin-1 confines T cell alloresponse and pathogenicity in graft-versus-host disease, *Journal of Clinical Investigation* (2019). DOI: 10.1172/JCI122899

Paramita Chakraborty et al. Thioredoxin-1 improves the immunometabolic phenotype of antitumor T cells, *Journal of Biological Chemistry* (2019). DOI: 10.1074/jbc.RA118.006753

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