Team work shines light on how to improve cancer immunotherapy

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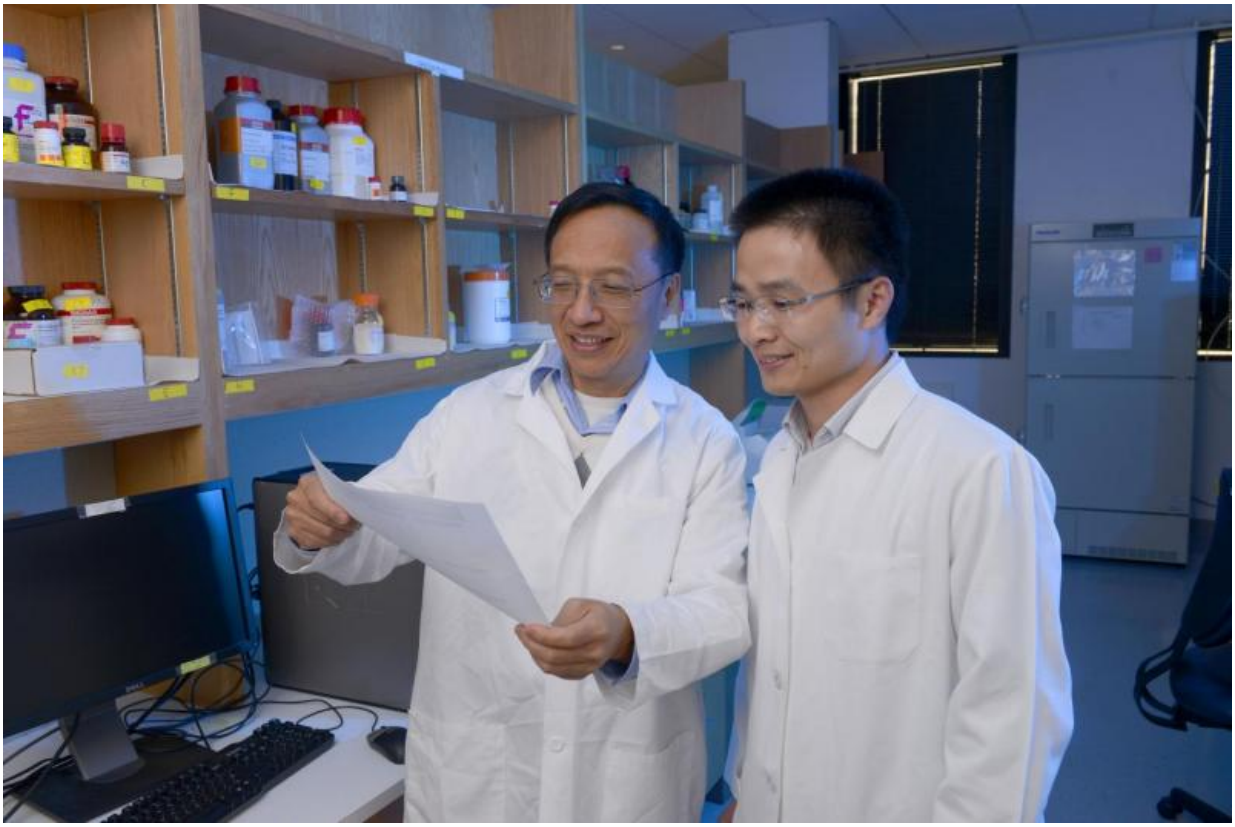

Dr. Yang-Xin Fu (left) and Dr. Haidong Tang. Credit: UT Southwestern Medical Center

UT Southwestern Medical Center researchers today report on a strategy to make a major advance in cancer treatment even better, and a means to

test and refine this new type of immunotherapy.

Tumor cells contain immune checkpoint molecules that make tumors nearly invisible to the immune system. Immune checkpoint blockade therapies are drugs that rev up the body's immune system to fight cancer.

"When the drugs work, they work phenomenally well, providing unprecedented long-term responses. However, the therapies fail to induce responses in the majority of tumors, especially in tumors that contain few killer T cells," said Dr. Haidong Tang, a postdoctoral researcher at UT Southwestern and lead author of the study published in *Cancer Cell*. T cells are central to the immune response.

The first immune checkpoint inhibitor, pembrolizumab, received U.S. Food and Drug Administration approval in September 2014 based on its remarkable effects on melanoma in clinical trials.

"In patients with advanced cancer who have undergone multiple treatments, up to 10 percent have a complete response. A similar number have a partial but significant response, so the disease becomes chronic basically. It's very exciting to the field," said senior author Dr. Yang-Xin Fu, Professor of Pathology and Immunology at UT Southwestern. "The problem is that more than two-thirds don't respond at all, therefore increasing the response rate presents an urgent challenge."

In their study, the researchers first showed that the success of the PD-L1 blockade—the scientific name for one cellular pathway targeted by immune checkpoint blockade therapy—depends on whether the patient's own T cells can infiltrate the tumor, he said.

Earlier studies that analyzed patient tumor samples hinted at that possibility because they found that tumors with more T-cell infiltration responded more vigorously to checkpoint blockade treatment. However,

prior to this study there was no tumor model available to test that hypothesis directly, explained Dr. Fu, who holds the Mary Nell and Ralph B. Rogers Professorship in Immunology.

Using their novel mouse models of tumors with and without T-cell infiltration, the researchers demonstrated that T-cell infiltration indeed is required for this immunotherapy to work: Tumors that contained few active T cells failed to respond to immune checkpoint blockade while tumors containing large numbers of active killer T cells responded well. Then the research team treated highly responsive, T-cell-rich tumor models with a chemical that blocks T-cell infiltration into tumor tissues. Checkpoint blockade therapy quit working, validating their hypothesis, the researchers report.

To address the problem of how to get more T cells into tumors, the researchers used a T-cell recruiting protein called LIGHT fused to an antibody that recognizes a molecule on the surface of cancer cells. The researchers developed the fusion protein when the laboratory was at the University of Chicago's Pritzker School of Medicine.

Experiments indicated that the antibody-LIGHT molecule caused cell signaling, which led to production of chemicals (chemokines) that sounded an alarm and recruited T cells to the tumors. This action overcame tumor resistance to checkpoint blockade therapy and killed tumor cells. "The antibody guides LIGHT to find and target the tumor so the killer T cells can work to reject it," Dr. Fu said.

Using antibody-LIGHT and immune checkpoint blockade therapy together provided a one-two punch to fight tumor cells.

"Our study indicates a strategy—antibody-guided LIGHT—with the potential to increase the response rate to immune checkpoint blockade therapy, and provides a model in which to test this approach," said Dr.

Fu, also a member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern.

The next step will be working to make the team's molecule even stronger, researchers said.

More information: Haidong Tang et al. Facilitating T Cell Infiltration in Tumor Microenvironment Overcomes Resistance to PD-L1 Blockade, *Cancer Cell* (2016). DOI: 10.1016/j.ccell.2016.02.004

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