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Researchers find protein promotes cancer, suppresses anti-tumor immunity

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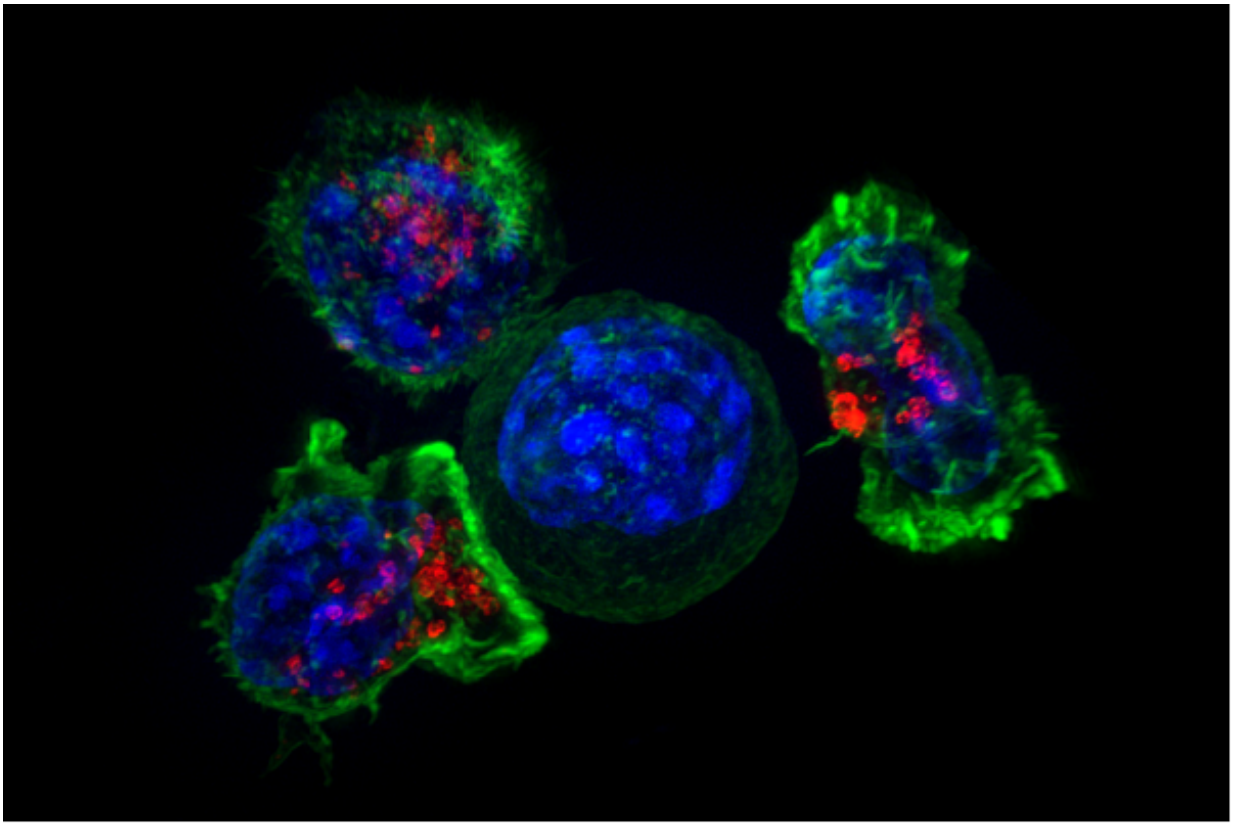

Killer T cells surround a cancer cell. Credit: NIH

Researchers at The University of Texas MD Anderson Cancer Center have found that a protein involved in immune response to microbes also can fuel cancer development and suppress immune response to the

disease.

Working in mouse models of lung cancer, the team found TANK-binding kinase 1 (TBK1) and its adaptor protein TBK-binding protein 1 (TBKBP1) contribute to tumorigenesis when they are activated by growth factors rather than by innate immune mechanisms. Their findings are reported today in *Nature Cell Biology*.

"Our work also provides the first evidence that TBK1 functions in cancer cells to mediate immunosuppression, suggesting that targeting TBK1 will both inhibit tumor growth and promote antitumor immunity," says senior author Shao-Cong Sun, Ph.D., professor of Immunology.

Recent research indicated that TBK1, which normally mediates induction of type 1 interferon in response to viruses or bacteria, also promotes the survival and reproduction of KRAS-dependent cancer cells. Sun and colleagues set out to identify TBK1's impact on cancer cells and its role in cancer development *in vivo*.

They first found that knocking out TBK1 in a mouse model designed to spontaneously develop lung cancer driven by KRAS mutations sharply reduced the number and size of tumors. Knockdown in a human lung cancer line promoted programmed cell death and suppressed tumor growth.

In a series of experiments, the researchers showed that TBK1 and TBKBP1 form a growth factor signaling axis that activates mTORC1 to promote tumor development. The pathway consists of TBKBP1 recruiting TBK1 to protein kinase C-theta (PKCθ), through a scaffold protein called CARD10, enabling PKCθ to activate TBK1.

Amlexanox inhibits TBK1, shrinks tumors

To test the protein's therapeutic potential, they treated mice with KRAS-driven lung cancer with amlexanox, a drug approved by the Food and Drug Administration as a paste to treat certain oral ulcers. The drug was recently identified as a TBK1 inhibitor. Mice injected with amlexanox had a steep reduction in the number and size of lung tumors.

KRAS-driven cancer is resistant to immune response, but the researchers found amlexanox sensitized tumors to blockade of the CTLA-4 checkpoint on immune T cells.

Knocking down TBK1 in the KRAS-driven mouse model increased the frequency of effector CD4 helper T cells and CD8 cell-killing T cells in the lungs of the mice. A similar experiment in another mouse model also reduced the frequency of immune-suppressing myeloid-derived suppressor cells.

Additional experiments implicated TBK1 in promotion of glycolysis—a sugar-burning metabolic process that also suppresses the immune system—and the increased presence of PD-L1, a protein on tumor cells that turns off attacking T cells by connecting with the PD-1 protein on their cell surface.

Treatment with amlexanox and anti-CTLA-4 immunotherapy stimulated immune response and reduced tumor size and frequency in the mouse models.

"We're continuing to examine the signaling function of TBK1 in different types of immune cells using animal models and to assess the therapeutic potential of TBK1 using preclinical cancer models," Sun says.

While amlexanox has been tested in a clinical trial for treatment of type 2 diabetes and obesity, there are no clinical trials open to test the drug

against cancer. Sun says his team continues preclinical research necessary to lay the groundwork for clinical trials, including research to determine whether amlexanox might work against other cancer types.

More information: Lele Zhu et al, TBKBP1 and TBK1 form a growth factor signalling axis mediating immunosuppression and tumourigenesis, *Nature Cell Biology* (2019). DOI: 10.1038/s41556-019-0429-8

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