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Scientists identify genes critical to protecting ovarian cancer from the immune system

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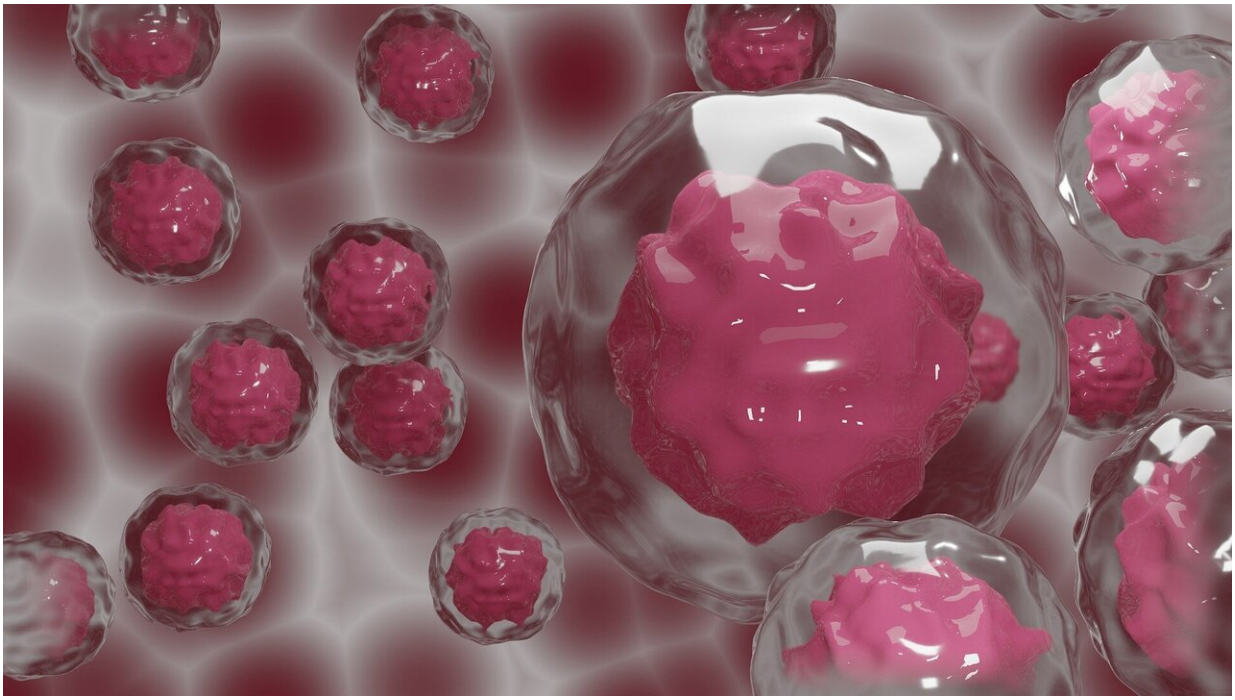

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Immunotherapies have shown striking clinical benefit in the treatment of many cancers, especially when used in combination with chemotherapy. However, some cancers respond poorly to immunotherapy, and ovarian cancer is among the most resistant. Now a new study by scientists at The Wistar Institute, a biomedical research leader in cancer, immunology, infectious disease, and vaccine development, identifies two genes that

play a critical role in protecting ovarian cancer from the immune system.

The findings, published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research, could be a step forward in developing new treatments aimed at making ovarian cancer, and other types of cancer, more vulnerable to immunotherapy.

"Ovarian cancer has a relatively poor response to immunotherapy compared to other types of cancer, like melanoma and non-small cell lung cancer," says Rugang Zhang, Ph.D., deputy director of the Cancer Center, Christopher M. Davis Endowed Professor and program leader in the Immunology, Microenvironment & Metastasis Program, at The Wistar Institute. "However, we still want to take advantage of immunotherapy, so in order to do that, we have to identify a new strategy."

For the study, the researchers used CRISPR screening, a tool that allows scientists to scan through a large group of genes and determine which ones perform a specific function. In a screen of genes taken from mouse ovarian cancer cells, they identified genes encoding a complex called SETDB1-TRIM28 as playing a critical role in suppressing the immune system.

They then went on to review genetic data from human ovarian cancer patients and found that these genes were negatively correlated with immune profiles. That suggests patients who had more of these genes tended to respond poorly to immunotherapy.

Notably, the complex identified in the study is over-expressed in many types of cancers, especially ovarian cancer, where it's prevalent in as many as 25% of patients. The findings could lead to the development of new treatments that target the complex and boost the effectiveness of immunotherapies against resistant cancers, including ovarian cancer.

First author Jianhuang Lin, Ph.D., a postdoctoral fellow in the Zhang Laboratory, noted that drugs already exist that broadly target the type of enzyme that interacts with the immune-suppressing complex. These drugs could be modified to specifically target SETDB1-TRIM28.

"There are a number of histone methyltransferase inhibitors in development, however none are currently being advanced against this particular target," he said. "Because our discovery is brand new, it holds promise for creating new combination immunotherapies for ovarian cancer."

In addition to ovarian cancer, new treatments could benefit patients with other cancers in which these genes are over-expressed.

Next, the Zhang lab is moving on to exploring how to best target this newly discovered complex to boost anti-tumor immunity.

More information: SETDB1-TRIM28 complex suppresses antitumor immunity, *Cancer Immunology Research*, 2021. DOI: 10.1158/2326-6066.CIR-21-0754

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