Medical Xpress

Study identifies enzyme that helps tumors evade the immune system

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Northwestern Medicine scientists in the Sonabend laboratory have identified an enzyme which aids tumors in evading the immune system. Credit: Northwestern University

Northwestern Medicine scientists have identified an enzyme which aids

tumors in evading the immune system, findings that could provide future directions for tumor treatment, according to a study published in *Nature Communications*.

The enzyme, a kinase produced by the gene Chek2, helps glioma tumor cells evade CD8 T-cells in mice, the study authors found. Responsible for attacking viruses and other immune system targets, CD8 T-cells have been previously identified as a cell type susceptible to dysfunction and exhaustion in the presence of tumors.

Gliomas, tumors found in the brain and spinal cord, are the most common type of central nervous system primary cancer in adults, according to the National Institutes of Health, and patients with malignant gliomas such as glioblastoma often have a low chance of long-term survival.

That's because gliomas have a complicated relationship with the immune system, according to the study authors, and tumors employ a variety of tactics to suppress and evade it.

"This kinase is involved in the DNA damage response, and it's interesting because there are other kinases that are related to the same pathway that didn't have such a strong activity in evasion of T-cells," said Adam Sonabend MD, associate professor of Neurological Surgery and senior author of the study. "But there was something very particular about this. As part of this study, we evaluated the human glioblastoma datasets and realized that when tumors had a lot of this gene, the T-cells in these tumors and the tumors themselves looked different than when there was very little amount of the gene."

In the current study, investigators performed an in vivo kinome knockout CRISPR screen and found that mice with gliomas lacking the Chek2 kinase had higher rates of response to immunotherapy compared

to mice with the kinase.

"We did a comparison of wild-type mice to mice with CD8 knockout, which lack CD8 T-cells, and hoped it would tell us what kinases are responsible for evading CD8 T-cell recognition. We found that there is a kinase, called Chek2, or checkpoint kinase 2, which is the one that escapes recognition from CD8 T-cells. This means if that kinase is present in the tumor cells, the T-cells will not be able to recognize and attack it," said Crismita Dmello, Ph.D., a postdoctoral fellow in the Sonabend laboratory and first author of the study. "So, if we inhibit this kinase on the tumor cells, we can make the tumor more immunogenic. The CD8 T-cells would be able to attack it."

Moving forward, Sonabend and his collaborators hope to further validate their findings in clinical trials.

"Most people study gliomas and try to understand how the microenvironment is modulating the potential response to immunotherapy because these tumors are not very responsive to immunotherapy," said Sonabend, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

"Here, we focus on the tumor's intrinsic biology, and ask 'What are some things that might be different within tumor cells across patients that make some patients do better than others?' And so, the significance is that we found a target that can be drugged with two different drugs that are already in clinical trials that penetrate the blood-brain barrier. There is a relatively straightforward path for translation of this project into a clinical trial to test this hypothesis."

More information: Crismita Dmello et al, Checkpoint kinase 1/2 inhibition potentiates anti-tumoral immune response and sensitizes gliomas to immune checkpoint blockade, *Nature Communications*

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