Study shows how certain cancers neutralize T cells to subvert the immune system and help tumors grow

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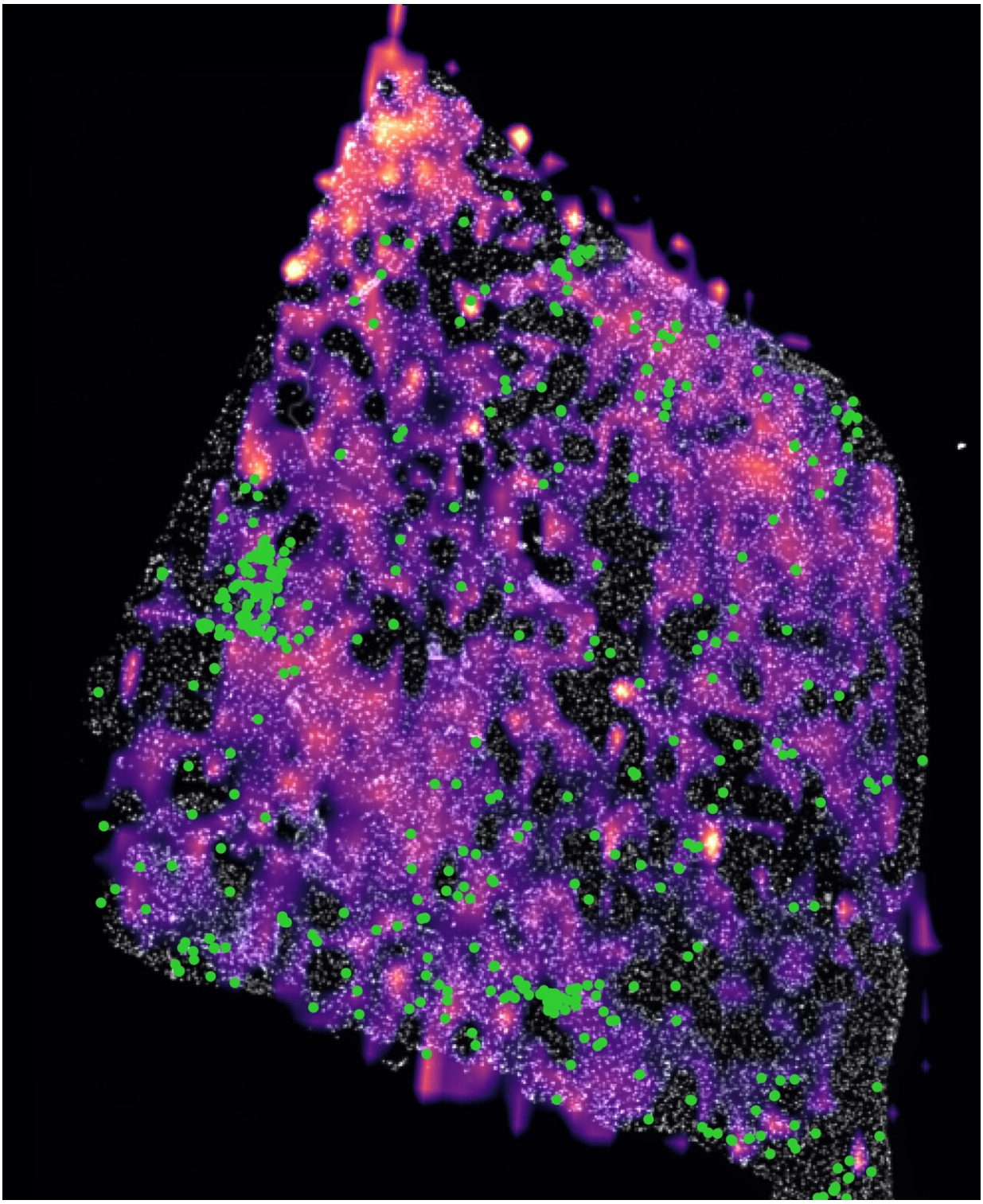

An IDH-mutant human glioma tumor, showing clusters of CD8+ T cells in green, and a gradient of purple to pink representing low to high D-2HG concentrations. CD8+ T cells were more abundant in areas with less D-2HG, and

less abundant in regions with more D-2HG, suggesting that D-2HG has an effect on the immune cells. Credit: Gregory Baker, HMS

When cancer arises in the body, it starts with tumor cells that rapidly grow and divide and eventually spread. But what enables these nascent tumor cells to dodge the body's immune system, which is built to identify and fend off an attack from such defective cells? The answer to this question, which long mystified scientists, may be the key to unlocking more effective cancer treatments—therapies that disable tumors' subversive maneuvers and allow the immune system to do its job.

Now, a team led by researchers at Harvard Medical School has identified a way that tumor cells can turn off the immune system, allowing the tumor to grow unchecked. The research, conducted primarily in mice and published Sept. 29 in *Science*, shows that tumor cells with a particular mutation release a chemical, a metabolite, that weakens nearby immune cells, rendering them less capable of killing cancer cells.

The findings reveal critical details of how tumors deactivate the immune system and highlight the role of tumor metabolites in this process. The results also point to the essential role that the area around the tumor—the tumor microenvironment—plays in cancer growth.

If elucidated through further research, the results could eventually help scientists develop better, more targeted therapies to treat cancers whose growth is fueled by this mechanism.

"Our study highlights an immune component in this type of cancer that wasn't fully appreciated before," said senior author Marcia Haigis, professor of cell biology in the Blavatnik Institute at HMS. "We now

know that a metabolite produced by tumor cells can impact nearby immune cells to make the surrounding environment less hostile for the cancer."

Fueling cancer

For the past 15 years, the Haigis lab has been studying the mechanisms that fuel cancer, including tumor metabolites that help cancer cells survive and grow. The research led Haigis and colleagues to the immune system, which works to suppress tumor growth by dispatching immune cells into the tumor microenvironment to kill tumor cells. But how exactly do tumor and immune cells interact? Why do certain tumors survive the immune attack, while others do not?

"We became really interested in understanding how metabolites mediate the cross talk between tumor cells and immune cells," Haigis said.

The scientists decided to focus their work on tumors with a mutation in a gene called isocitrate dehydrogenase, or *IDH*. *IDH* mutations occur in around 3.5 percent of cancers, including solid cancers such as gliomas and blood cancers such as acute myeloid leukemia. In fact, approximately 80 percent of low-grade gliomas and secondary glioblastomas have an *IDH* mutation. Tumor cells that harbor this mutation secrete D-2-hydroxyglutarate (D-2HG), a metabolite not normally found at high levels in the human body.

Previous studies have shown that D-2HG aids the growth of tumor cells by altering their genetic pathways to permanently transform them into a more aggressive, rapidly dividing state. However, very little research has investigated how D-2HG affects other cells in the tumor microenvironment, including CD8+ T cells—immune cells that release proteins called granzymes and other immune chemicals called cytokines to kill cancer cells.

"We had an incomplete picture because much of the focus has been on understanding how this metabolite directly affects cancer cells, whereas its impact on the surrounding cells has been less explored," Haigis explained.

In the new study, graduate student and first author Giulia Notarangelo led a series of experiments in mouse models to elucidate how D-2HG interacts with CD8+ T cells in the tumor microenvironment.

First, the researchers established that CD8+ T cells sense D-2HG in their environment and take it up. Next, they demonstrated that as soon as CD8+ T cells were exposed to a concentration of D-2HG produced by a tumor, the immune cells immediately slowed down their proliferation and lost their ability to kill tumor cells. Specifically, D-2HG deactivated T cells by inhibiting a key metabolic enzyme called lactate dehydrogenase that plays a role in producing cytokines and granzymes, helping T cells proliferate, and maintaining T cells' tumor-killing capacity. When D-2HG was removed, the T cells regained their ability to kill tumor cells, suggesting that the process is reversible.

In another set of experiments, the scientists monitored D-2HG and CD8+ T cells in human glioma tumors with *IDH* mutations. They found that tumor regions with higher D-2HG levels had lower levels of T-cell infiltration, while tumor regions with more T cells had lower D-2HG levels—thus supporting the mouse-model findings.

"What we found is that this metabolite secreted by the tumor hijacks the body's normal defense mechanism and causes it to break down," Haigis said. She emphasized, however, that "this is only one part of the puzzle, and major questions in the field remain."

For example, she hopes future research will delve deeper into D-2HG to identify additional targets and explore how the metabolite affects other

cells—including other immune cells—in the tumor microenvironment.

"The field has initially focused on tumor cell functions of this metabolite, and I think that the door is now open for other studies to look at how it impacts immune cells and the whole microenvironment," Haigis said. Such work, she added, could extend beyond D-2HG to investigate how other metabolites secreted by tumors remodel the tumor microenvironment.

Haigis' lab recently published a paper in *Cell Metabolism* showing that lactate produced by tumor cells similarly reduces the cancer-killing ability of nearby CD8+ T cells.

Haigis is also interested in understanding the importance of this D-2HG–T cell mechanism in patients treated with *IDH* inhibitors—existing drugs that combat tumor growth by blocking *IDH* mutations to reduce D-2HG production.

"We still don't know the therapeutic implication of this research—do *IDH* inhibitors work in part by increasing the activity of the immune system, or do they only act directly on the cancer cells?" Haigis asked.

Haigis emphasized that her research focuses on unraveling the basic biology of how tumor cells use metabolites to suppress the immune system. However, she is hopeful that long-term, scientists may be able to use her findings, along with additional research, to develop therapies that take advantage of the interaction between cancer cells and immune cells.

More information: Giulia Notarangelo et al, Oncometabolite D-2HG alters T cell metabolism to impair CD8+ T cell function, *Science* (2022). DOI: 10.1126/science.abj5104.
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