New immunotherapy target discovered for malignant brain tumors

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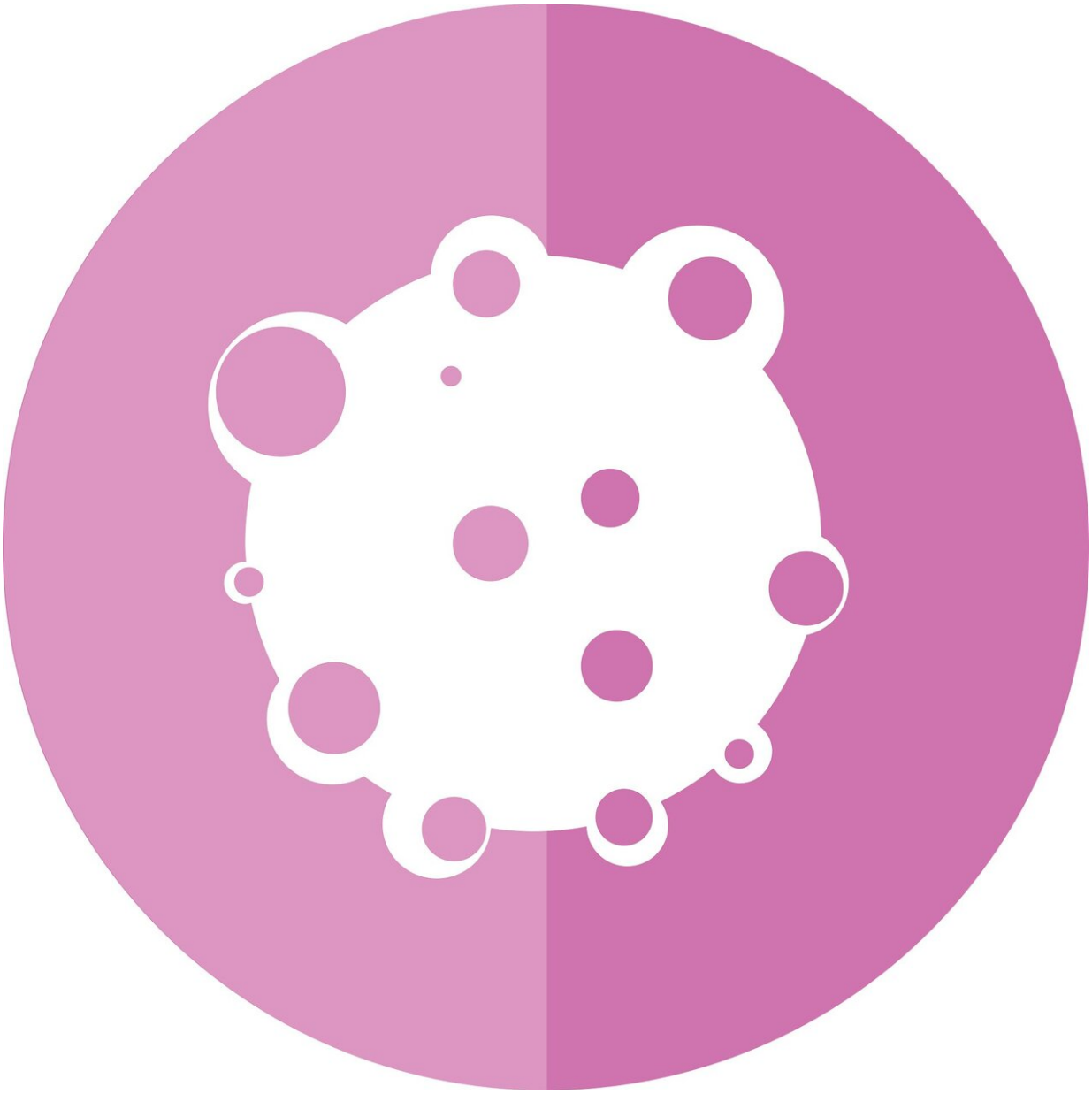

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Scientists say they have discovered a potential new target for immunotherapy of malignant brain tumors, which so far have resisted the ground-breaking cancer treatment based on harnessing the body's immune system. The discovery, reported in the journal *Cell*, emerged from laboratory experiments and has no immediate implications for treating patients.

Scientists from Dana-Farber Cancer Institute, Massachusetts General Hospital, and the Broad Institute of MIT and Harvard said the target they identified is a molecule that suppresses the cancer-fighting activity of immune T cells, the white blood cells that seek out and destroy virus-infected cells and tumor cells.

The scientists said the molecule, called CD161, is an inhibitory receptor that they found on T cells isolated from fresh samples of brain tumors called diffuse gliomas. Gliomas include glioblastoma, the most aggressive and incurable type of brain tumor. The CD161 receptor is activated by a molecule called CLEC2D on tumor cells and immune-suppressing cells in the brain, according to the researchers. Activation of CD161 weakens the T cell response against tumor cells.

To determine if blocking the CD161 pathway could restore the T cells' ability to attack the glioma cells, the researchers disabled it in two ways: they knocked out the gene called KLRB1 that codes for CD161, and they used antibodies to block the CD161-CLEC2D pathway. In an animal model of gliomas, this strategy strongly enhanced the killing of tumor cells by T cells, and improved survival of the animals. The researchers were also encouraged because blocking the inhibitory pathway appeared to reduce T-cell exhaustion—a loss of cell-killing

function in T cells that has been a been a major hurdle in immunotherapy.

In addition, "we showed that this pathway is also relevant in a number of other major human cancer types," including melanoma, lung, colon, and liver cancer, said Kai Wucherpfennig, MD, Ph.D., director of the Center for Cancer Immunotherapy Research at Dana-Farber. He is corresponding author of the report along with Mario Suva, MD, Ph.D., of Massachusetts General Hospital; Aviv Regev, Ph.D., of the Broad Institute, and David Reardon, MD, clinical director of the Center for Neuro-Oncology at Dana-Farber.

Many cancer patients are now being treated with immunotherapy drugs that disable "immune checkpoints"—molecular brakes exploited by cancer cells to suppress the body's defensive response by T cells against tumors. Disabling these checkpoints unleashes the immune system to attack cancer cells. One of the most frequently targeted checkpoints is PD-1. However, recent trials of drugs that target PD-1 in glioblastomas have failed to benefit patients. In the current study, the researchers found that fewer T cells from gliomas contained PD-1 than CD161. As a result, they said, "CD161 may represent an attractive target, as it is a cell surface molecule expressed by both CD8 and CD4 T cell subsets [the two types of T cells involved in response against tumor cells] and a larger fraction of T cells express CD161 than the PD-1 protein."

Prior to the current study, the researchers said little was known about the expression of genes and the molecular circuits of immune T cells that infiltrate glioma tumors, but fail to halt their growth. To open a window on these T cell circuits, the investigators took advantage of new technologies for reading out the genetic information in single cells—a method called single-cell RNA-seq. They applied RNA-seq to glioma-infiltrating T cells from fresh tumor samples from 31 patients and created an "atlas" of pathways that regulate T cell function. In analyzing

the RNA-seq data, the researchers identified the CD161 protein, encoded by the KLRB1 gene, as a potential inhibitory receptor. They then used CRISPR/Cas9 gene-editing technology to inactivate the KLRB1 gene in T cells and showed that CD161 inhibits the tumor cell-killing function of T cells.

"Our comprehensive atlas of T cell expression programs across the major classes of diffuse gliomas thus identifies the CD161-CLEC2D pathway as a potential target for immunotherapy of diffuse gliomas and other human cancers," the authors of the report said.

This strategy was tested in two different animal models created by implanting "gliomaspheres"—3-dimensional clusters of tumor cells from human patients—into rodents, which developed aggressive tumors that invaded the brain. The scientists subsequently injected T cells with the KLRB1 gene edited out into the cerebrospinal fluid of some of the animals, and T cells that hadn't had the KLRB1 gene deleted. Transfer of the gene-edited T cells slowed the growth of the tumors and "conferred a significant survival benefit," in both of the animal models of gliomas, the scientists said.

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