New treatment strategy may thwart deadly brain tumors

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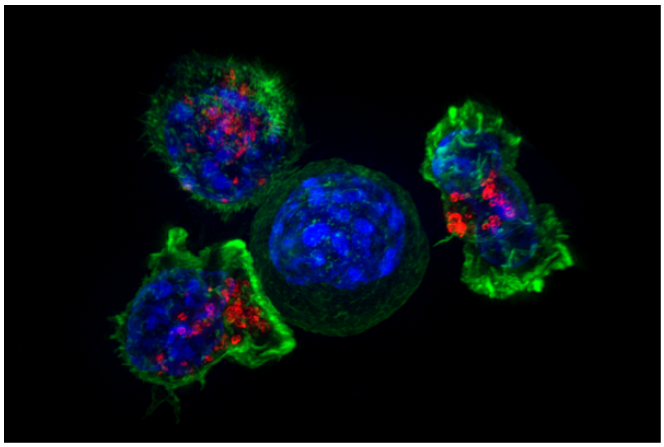

Killer T cells surround a cancer cell. Credit: NIH

Immune checkpoint inhibitors are important medications that boost the immune system's response against certain cancers; however, they tend to be ineffective against glioblastoma, the most deadly primary brain tumor in adults. New research in mice led by investigators at Massachusetts General Hospital (MGH) and the University of Florida reveals a promising strategy that makes glioblastoma susceptible to these medications. The findings, which are published in the *Proceedings of the National Academy of Sciences*, indicate that such combination therapy should be tested in clinical trials of patients with glioblastoma, for whom there is no known cure.

Part of the reason glioblastoma does not respond well to immune checkpoint inhibitors and other immunotherapies is because cells called myeloid-derived suppressor cells (MDSCs) infiltrate the region surrounding glioblastoma tumors, where they contribute to immunosuppression, tumor progression, and treatment resistance. Thus, targeting these cells may augment immunotherapy and improve responses to treatment in affected patients.

A collaborative effort co-led by Jeffrey K. Harrison, Ph.D., of the Department of Pharmacology and Therapeutics at the University of Florida, and Rakesh K. Jain, Ph.D., of the Department of Radiation Oncology at MGH and Harvard Medical School, set out to test this strategy. Using two mouse models of glioblastoma, the team targeted receptors—called chemokine receptors—that are important for allowing MDSCs to infiltrate into the region surrounding glioblastoma tumors. In mice that were bred to lack chemokine receptor 2 (CCR2) and to develop glioblastoma, MDSCs could not carry out such infiltration. Treating these mice with an immune checkpoint inhibitor stimulated a strong anti-cancer immune response and prolonged the animals' survival. In mice with normal CCR2, treatment with a molecule that blocks CCR2 had similar effects.

"The CCR2 antagonist used in this study—called CCX872— has passed phase Ib safety trials in patients with pancreatic tumors, and clinical trials are ongoing to investigate the use of CCR2 inhibitors in several cancers," said Jain. "Thus, the results of this study support targeting CCR2-expressing MDSCs as a means to enhance immunotherapies, and warrant investigation of this combination therapy in clinical trials for patients with glioblastoma."

More information: Joseph A. Flores-Toro el al., "CCR2 inhibition reduces tumor myeloid cells and unmasks a checkpoint inhibitor effect to slow progression of resistant murine gliomas," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1910856117

Provided by Massachusetts General Hospital

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