Blocking tumor-associated macrophages decreased glioblastoma's growth, extended survival in mice

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An experimental drug that targets macrophages, a type of immune cells, in the microenvironment surrounding the lethal brain tumor glioblastoma multiforme decreased the cancer's growth and extended survival of laboratory mice with the cancer, scientists will report on Tuesday Dec. 17, at the American Society for Cell Biology (ASCB) annual meeting in New Orleans.

The rates of apoptosis, or programmed cell death, were higher in the mice treated with the experimental agent than in the untreated animals that also had high-grade glioblastomas, said Johanna Joyce, Ph.D., of the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City. As a result, the drug-treated laboratory mice survived many months longer than the untreated animals with the same cancer.

The experimental drug blocks cell receptors for colony-stimulating factor-1 (CSF-1R), which is essential to the differentiation and survival of tumor-associated macrophages and microglia (TAMS), which are the brain's front-line immune defense cells. The microenvironment that surrounds brain tumors contains many macrophages with this receptor.

Glioblastoma multiforme (GBM) is the most common and the most deadly adult primary brain tumor, with an average survival of just 14 months following diagnosis. Even with aggressive treatment by surgery, radiation and chemotherapy, most therapeutic approaches targeting the glioma cells in GBM fail.

Faced with this bleak picture, Dr. Joyce and colleagues MSKCC looked for an alternative strategy and turned to the cancer's cellular neighbors, the non-tumor cells that are part of the glioma microenvironment. In particular, they zeroed in on tumor-associated macrophages and TAMs.

When Dr. Joyce's lab used an inhibitor of the CSF-1 receptor (CSF-1R) to target TAMs in a mouse model of GBM, the treated mice survived many months longer than the control cohort. Their established, high-grade gliomas regressed in proliferation and malignancy, even though the glioma cells themselves were not the targets of the CSF-1R treatment.

With the TAMs blockaded by CSF-1 inhibitors, it was the tumor cells that showed increased rates of apoptosis. The TAMs were not even depleted in the treated mice, despite the drug blockade of their growth factor. Instead the TAMs survived by responding to growth factors secreted by the gliomas, including GM-CSF and IFN-?, according to Dr. Joyce.

The MSKCC researchers also found that tumor spheres, freshly isolated from glioma patients in the surgery department at MSKCC, responded to the drug when implanted in animals. The CSF-1R blockade slowed intracranial growth in the patient-derived glioma xenografts.

Because GBM is the most common glioma, its genome was the first to be sequenced for the Cancer Genome Atlas, which parsed GBM into four genetic subtypes: proneural, neural, classical and mesenchymal. The mice used in Dr. Joyce's lab experiments model the proneural GBM subtype. All forms of GBM have a 2- to 3-person per 100,000 incidence rate in the U.S. and Europe, according to the National Brain Tumor Society. Because of its highly invasive phenotype, GBM is almost impossible to resect completely in surgery. Drug and radiation treatments are the standard follow-ups.

Dr. Joyce says that these new results, which were first reported only two months ago in *Nature Medicine*, http://www.ncbi.nlm.nih.gov/pubmed/24056773, are encouraging for planned clinical trials of CSF-1R inhibitors in combination with radiation therapy in glioma patients.

"We are optimistic that CSF-1R inhibitors may provide a more effective therapy than current treatments for the disease management of glioma patients," Dr. Joyce said.

More information: Author will present, "CSF-1R inhibition alters macrophage polarization and blocks glioma progression," Tuesday, Dec. 17, during the 3:50 to 4:10 p.m. mini-symposium titled, "Tumor Microenvironment as a Driver and Target in Cancer Progression."

Provided by American Society for Cell Biology