Customized Drug to Kill Brain Cancer Cells

Researchers created a new type of cancer drug that causes lethal DNA damage in the cells of brain tumors called glioblastomas.

August 30, 2022 By National Institutes of Health

A type of tumor called glioblastoma is the most common brain cancer in adults. It's also one of the most lethal tumor types overall. Only about 5% of people with glioblastoma will be alive five years after diagnosis.

When DNA gets damaged, cells use specialized molecular pathways to fix it. But about half of glioblastomas have low levels of a protein that's important for DNA repair called O6-methylguanine methyl transferase (MGMT). Loss of MGMT makes these tumors sensitive to a combination of radiation therapy and a DNA-damaging drug called temozolomide (TMZ). However, tumor cells often quickly develop resistance to TMZ. This resistance is driven by mutations in the genes that control another DNA-repair pathway known as the mismatch repair pathway.

An NIH-funded research team led by Drs. Ranjit Bindra and Seth Herzon from Yale University have been looking for new ways to turn glioblastoma's loss of MGMT into a vulnerability. They created a new type of drug, similar in structure to TMZ, that was designed to selectively kill cells that lack MGMT while sparing normal cells.

The new drugs, like TMZ, create a type of DNA damage that can be quickly repaired by MGMT. But if a cell lacks MGMT, the drugs then cause a further type of DNA damage, known as an interstrand cross-link, that kills cancer cells regardless of whether the mismatch repair pathway is altered. Healthy cells should be able to use MGMT to repair the early damage and remain unaffected.

The team reasoned that this approach could specifically kill TMZ-resistant glioblastoma cells while sparing normal cells. They tested their experimental compounds in human glioblastoma cells and then in mouse models of brain cancer. The study results were published on July 29, 2022, in Science.

In the laboratory, the compounds selectively killed cells that lacked MGMT. The most potent of the compounds, called KL-50, killed MGMT-deficient cells regardless of how well the mismatch repair pathway worked. But the compound was not toxic to normal human cells.

Further experiments showed that KL-50 was working as expected, producing interstrand cross-links in cells that lacked MGMT. Other types of DNA damage didn't seem to affect how or whether KL-50 killed cells.

The researchers then tested KL-50 in mice with human glioblastoma cells implanted in their brains. While TMZ had no effect, KL-50 effectively suppressed tumor growth, whether given orally or as an injection. At all but the highest doses tested, no toxicity was observed, indicating that normal cells weren't being damaged by KL-50.

More work in animals is needed before this concept can be tested in people. But many cancer types bypass specific types of DNA repair to resist treatment, so similar drugs may have the potential to improve the treatment of other types of tumors as well. The researchers have founded a company called Modifi Bio that aims to conduct clinical trials of these new compounds.

"These molecules are particularly promising as therapeutics because of their ability to directly modify the DNA of cancer cells, which we believe will not only be effective in fighting cancer but will also allow us to overcome key resistance mechanisms," Herzon says.

This announcement was originally published August 23, 2022, on the National Institutes of Health website.
