Transplant drug could boost the power of brain tumor treatments

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Every day, organ transplant patients around the world take a drug called rapamycin to keep their immune systems from rejecting their new kidneys and hearts. New research suggests that the same drug could help brain tumor patients by boosting the effect of new immune-based therapies.

In experiments in animals, researchers from the University of Michigan Medical School showed that adding rapamycin to an immunotherapy approach strengthened the immune response against brain tumor cells.

What's more, the drug also increased the immune system's "memory" cells so that they could attack the tumor if it ever reared its head again. The mice and rats in the study that received rapamycin lived longer than those that didn't.

Now, the U-M team plans to add rapamycin to clinical gene therapy and immunotherapy trials to improve the treatment of brain tumors. They currently have a trial under way at the U-M Health System which tests a two-part gene therapy approach in patients with brain tumors called gliomas in an effort to get the immune system to attack the tumor. In future clinical trials, adding rapamycin could increase the therapeutic response.

The new findings, published online in the journal *Molecular Cancer Therapeutics*, show that combining rapamycin with a gene therapy approach enhanced the animals' ability to summon immune cells called CD8+ T cells to kill tumor cells directly. Due to this cytotoxic effect, the tumors shrank and the animals lived longer.

But the addition of rapamycin to immunotherapy even for a short while also allowed the rodents to develop tumor-specific memory CD8+ T cells that remember the specific "signature" of the glioma tumor cells and attacked them swiftly when a tumor was introduced into the brain again.

"We had some indication that rapamycin would enhance the cytotoxic T cell effect, from previous experiments in both animals and humans showing that the drug produced modest effects by itself," says Maria Castro, Ph.D., senior author of the new paper. Past clinical trials of rapamycin in brain tumors have failed.

"But in combination with immunotherapy, it became a dramatic effect, and enhanced the efficacy of memory T cells too. This highlights the versatility of the immunotherapy approach to glioma." Castro is the R.C. Schneider Collegiate Professor of neurosurgery and a professor of cell and developmental biology at U-M.

Rapamycin is an FDA-approved drug that produces few side effects in transplant patients and others who take it to modify their immune response. So in the future, Castro and her colleagues plan to propose new clinical trials that will add rapamycin to immune gene therapy trials like those already ongoing at UMHS.

She notes that other researchers currently studying immunotherapies for glioma and other brain tumors should also consider doing the same. "This could be a universal mechanism for enhancing efficacy of immunotherapies in glioma," she says.

Rapamycin inhibits a specific molecule in cells, called mTOR. As part of the research, Castro and her colleagues determined that brain tumor cells use the mTOR pathway to hamper the immune response of patients.

This allows the tumor to trick the immune system, so it can continue growing without alerting the body's T cells that a foreign entity is present. Inhibiting mTOR with rapamycin, then, uncloaks the cells and makes them vulnerable to attack.

Castro notes that if the drug proves useful in human patients, it could also be used for long-term

prevention of recurrence in patients who have had the bulk of their tumor removed. "This tumor always comes back," she says.

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