Selectively stopping glutathione sensitizes brain tumors to chemotherapy

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Brain cancer cells are particularly resistant to chemotherapy — toxins enter the cells, but before the toxins can kill, cancer cells quickly pump them back outside. In fact, brain cancer cells are even better than healthy cells at cleaning themselves. This means that when hit with chemotherapy, healthy cells tend to die before brain cancer cells. Especially in the brain, killing healthy cells is bad.

Researchers at the University of Colorado Cancer Center have discovered a way to turn off the pumps — only in brain cancer cells and not in their healthy neighbors. Promising early testing provides hope for the nearly 45,000 people diagnosed with brain cancer in the United States every year, who are currently expected to survive less than 12 months after diagnosis.

The key is a chemical called glutathione (GSH). The GSH pathway allows both healthy and cancerous cells to pump out toxins. The more GSH a cell makes, the more efficiently it can cleanse itself. Brain cancer cells may literally coat themselves with GSH, allowing them to pump out and thus survive doses of chemotherapy that quickly kill healthy brain cells. (This GSH pathway is the focus of a recent CU Cancer Center paper published in the journal *Biochemical Pharmacology*.)

But this same mechanism that makes brain cancer cells especially hearty may in fact be the key to their demise.

The idea is this: stop a cell's ability to make GSH and you stop its ability

to detoxify — thus sensitizing the cell to even a low dose of chemotherapy. It's tricky to target GSH directly, but clinical trials are already underway for a drug that breaks a link in the chain that leads to GSH. The link is an enzyme called glutamate cysteine ligase (GCL), which cells need in order to make GSH.

No GCL means no GSH, means a cell is doomed to stew in chemotherapy rather than pumping it out.

Unfortunately, the drug in clinical trials stops ALL cells — healthy and cancerous — from making GSH. And by so doing, it sensitizes both healthy and cancerous cells to chemotherapy. Killing everything more effectively does little good. (The same could be accomplished simply by giving a higher dose of chemotherapy.)

So here is the trick and the promise. "If we can selectively keep brain tumor cells from making GSH we can sensitize these tumors to chemotherapy, which may allow doctors to kill more tumor cells with a safe dose of chemotherapeutics," says Christopher Franklin, PhD, investigator at the CU Cancer Center and assistant professor of molecular toxicology at the Skaggs School of Pharmacy and Pharmaceutical Sciences.

Franklin is working with Philip Reigan, PhD, investigator at the CU Cancer Center and assistant professor of medicinal chemistry at the Skaggs School of Pharmacy and Pharmaceutical Sciences to do just that — targeting cancer cells' GSH while leaving the pathway unharmed in healthy cells.

To do it, they're using an exciting class of medicines called prodrugs. By itself a prodrug doesn't do anything — it floats harmlessly through the body. Only, when it comes in contact with another target chemical the prodrug releases a little payload.

In this case, the prodrug payload is the drug that stops cells from making GSH. And the chemical that tells the prodrug to release its payload is an enzyme specific to brain cancer cells. This means that only when near brain cancer cells does the prodrug stop cells' ability to make GSH. Given along with chemotherapy, the prodrug should turn the table on brain cancer cells, making them die sooner than healthy neighbors.

"The current standard of care adds only about three months to the life expectancy of a patient diagnosed with glioblastoma multiforme," Reigan says. "The promise of prodrugs that selectively target tumor cells is not only exciting, but it's desperately needed for the treatment of brain tumors."

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