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Novel combination therapy shuts down escape route, killing glioblastoma tumor cells

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Glioblastoma, the most common and lethal form of brain tumor in adults, is challenging to treat because the tumors rapidly become resistant to therapy. As cancer researchers are learning more about the causes of tumor cell growth and drug resistance, they are discovering molecular pathways that might lead to new targeted therapies to potentially treat this deadly cancer.

Scientists at the Ludwig Institute for Cancer Research in San Diego worked collaboratively across the laboratories of Drs. Paul Mischel, Web Cavenee and Frank Furnari to investigate one such molecular pathway called the mammalian target of rapamycin or mTOR. This signaling pathway is hyperactivated in close to 90 percent of glioblastomas and plays a critical role in regulating tumor growth and survival. Therapies that inhibit mTOR signaling are under investigation as drug development targets, but results to date have been disappointing: mTOR inhibitors halt the growth but fail to kill the tumor cells.

A study published this week in the Proceedings of the National Academy of Sciences uncovers an unexpected but important molecular mechanism of mTOR inhibitor resistance and identifies a novel drug combination that reverses this resistance.

The story begins with a closer look at a gene-encoded protein called promyleocytic leukemia gene or PML. The study investigators explored the role of PML in causing resistance to mTOR inhibitor treatment. They found that when glioblastoma patients are treated with drugs that

target the mTOR pathway, the levels of PML rise dramatically. Further, they showed that PML upregulation made the tumor cells resistant to mTOR inhibitors, and that if they suppressed the ability of the tumor cells to upregulate the PML protein, the tumor cells died in response to the mTOR inhibitor therapy.

"When we looked at cells in in vivo models and patients treated in the clinic, it became clear that the glioblastoma cells massively regulated PML enabling them to escape the effects of mTOR inhibitor therapy," reported senior author Paul Mischel, MD, Ludwig Institute member based at the University of California at San Diego.

"Our team hypothesized that if we could use a pharmacological approach to get rid of PML and combine it with an mTOR inhibitor, it could change the response from halting growth to cell death. The question was how?" added Mischel.

Previous research had shown that the use of low-dose arsenic could cause degradation of the PML protein in patients with leukemia. The team hypothesized that if arsenic could degrade PML, it may reverse resistance to mTOR inhibitors. The combination of mTOR and low-dose arsenic in mice indeed showed a synergistic effect, with massive tumor cell death along with very significant shrinkage of the tumor in mice with no ill side effects.

"Current therapy upregulates PML, turning off the mTOR signaling pathway. The tumor cells hide, waiting for the target signal to return," said Mischel. "When low-dose arsenic is added, not only does it stop the cell from returning, it shuts down the escape route killing the tumor cell."

These results present the first clinical evidence that mTOR inhibition promotes PML upregulation in mice and patients, and that it mediates

drug resistance. The clinical relevance was confirmed when researchers looked at before- and after-treatment tissue samples from patients treated with mTOR inhibitors, confirming that PML goes up significantly in post treatment of mTOR inhibitors.

"These data suggest a new approach for potential treatment of glioblastoma," said Mischel. "We are moving forward to test that possibility in people."

Post-doctoral students Akio Iwanami and Beatrice Gini from the Mischel lab as well as Ciro Zanca from the Furnari/Cavenee lab, also contributed significantly to this paper.

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