

Scientists Show How Brain Tumors Outsmart Drugs

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Researchers at the Ludwig Institute for Cancer Research (LICR) at the University of California, San Diego School of Medicine and Moores UCSD Cancer Center have shown one way in which gliomas, a deadly type of brain tumor, can evade drugs aimed at blocking a key cell signaling protein, epidermal growth factor receptor (EGFR), that is crucial for tumor growth. In a related finding, they also proved that a particular EGFR mutation is important not only to initiate the tumor, but for its continued growth or “maintenance” as well.

The findings, which appear during the week of January 18 in an online early edition of the *Proceedings of the National Academy of Sciences*, provide both new insights into the behavior of gliomas as well as potential new drug targets and treatment strategies.

“The results suggest that the expression of EGFR is required for tumors to keep growing, and we’ve shown for the first time that there are mechanisms that the tumor is using to circumvent the need for the receptor,” said Frank Furnari, PhD, associate professor of medicine at the UCSD School of Medicine and associate investigator at the San Diego branch of the LICR, adding that other cancers may use similar tactics. “We need to find out more about the signaling pathways that brain tumors use to get around targeted therapeutics, such as those directed at EGFR.”

In aggressive gliomas, extra copies of the EGFR gene are produced, and half of such tumors also carry an EGFR mutation, which ramps up tumor growth and portends a poor prognosis. Clinical trials of anti-EGFR agents have been disappointing; brain tumors may respond initially, but later become resistant to the drugs. To better understand why, Furnari, Webster Cavenee, PhD, professor of medicine and director of San Diego’s LICR branch, and their group wanted to find out if the mutant EGFR was needed by tumors for their continued growth.

The team – including postdoctoral fellows Akitake Mukasa, MD, PhD, and Jill Wykosky, PhD – created a genetic system in mice in which they could control the expression of mutated EGFR, turning it off and on with the drug tetracycline. They found that the tumors’ growth would stop for a period of time when tetracycline blocked EGFR, much like what is seen in patients who respond to EGFR inhibitors. But the tumors would start to grow again, even without EGFR, meaning something else was driving tumor growth.

The researchers examined individual tumors that had sidestepped or “escaped” the need for mutant EGFR to sustain their growth. In some cases, tumors that would normally have killed mice in 20 days were stable for months with the blocked expression of mutant EGFR. The scientists used microarray technology to test for genes that had not been previously expressed in the tumors but were now overexpressed in tumors that no longer required EGFR. They finally found one, *KLHDC8* which, when inhibited, halted tumor growth.

“That finding makes us think that this gene would be a reasonable target,” Cavenee said. “About half of the individual tumors that didn’t need mutant EGFR to grow expressed that gene and, if we silenced the gene, those tumors did not grow.”

Cavenee thinks this could be a model for the behavior of other tumors. “If the tumors use the same strategy to get around receptor inhibitors, then targeting that alternate pathway plus the receptor up front should give a longer response because it’s hitting the primary event plus the escape route,” he said.

Now the research team is searching for other genes expressed in tumors that can escape EGFR dependence, and looking for biological pathways that might be involved.

Other contributors include: Keith L. Ligon, MD, PhD, Dana-Farber Cancer Institute, and Lynda Chin, MD, Dana-Farber and Brigham and Women’s Hospital.

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The Moores UCSD Cancer Center is one of the nation’s 40 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer. For more information, visit [UCSD Moores Cancer Center](#) [↗](#). The Ludwig Institute for Cancer Research (www.ludwigcancerresearch.org [↗](#)) is an international organization with branches in 10 countries.

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