MedicalXpress

Targeting cholesterol to fight deadly brain cancers

September 15 2011

Blocking the uptake of large amounts of cholesterol into brain cancer cells could provide a new strategy to battle glioblastoma, one of the most deadly malignancies, researchers at UCLA's Jonsson Comprehensive Cancer Center have found.

The study, done in cells lines, mouse models and analysis of tissue from brain cancer patients, uncovered a novel mechanism by which the most commonly activated oncogene, the mutated epidermal growth factor receptor (EGFR), overcomes normal cell regulatory mechanisms to feed large amounts of cholesterol to the brain cancer cells, said Dr. Paul Mischel, a professor of pathology and laboratory medicine and molecular and medical pharmacology, a Jonsson Cancer Center researcher and senior author of the study.

The study appears Sept. 15 in *Cancer Discovery*, the newest peer-reviewed journal of the American Association for Cancer Research. It shows that EGFRvIII, common in glioblastoma, promotes the import of cholesterol into cancer cells by up-regulating its cellular receptor, the LDL receptor, promoting rapid tumor growth and survival.

There are at least three ways by which cells normally tightly control their cholesterol levels - synthesis, import and efflux, or pumping out the cholesterol, Mischel said.

"Our study found that the mutant EGFR hijacks this system, enabling cancer cells to import large amounts of cholesterol through the LDL

receptor," Mischel said. "This study identifies the LDL receptor as a key regulator of cancer cell growth and survival, and as a potential drug target."

Mischel and his colleagues hypothesized that targeting the LDL receptor for destruction could result in strong anti-tumor activity against glioblastoma. They showed that a drug that activates the nuclear Liver X Receptor, a critical regulator of intracellular cholesterol that ensures appropriately balanced levels, degraded the LDL receptor in tumor cells bearing EGFR mutations, potently killing the cancerous tumors in mice.

About 45 percent of glioblastoma patients have cancers driven by mutated EGFR, so the findings have the potential to help almost half of those diagnosed with this aggressive malignancy. EGFR also is mutated in a number of other cancers, indicating that these findings may have relevance for other malignancies.

"This study suggests a potential therapeutic strategy to treat glioblastoma, and potentially a broader range of cancer types," Mischel said.

In a previous study, Mischel showed that inhibiting fatty acid synthesis in brain cancer cells may offer an additional option to treat those with mutated EGFR. Rapidly dividing cancer cells also require these fatty acids to form new membranes and provide energy for the cells. Mischel and his team found the same cell signaling pathway is at work in fatty acid synthesis and the import of cholesterol into cancer cells.

"That was a surprise here, this ghastly trick of the cancer cells," Mischel said. "The same mutation is coordinately regulating both the cholesterol and fatty acid synthesis mechanisms."

Going forward, Mischel and his colleagues will do more preclinical

studies that could lead to clinical trials of drugs that activate the Liver X receptor.

Glioblastoma is the most common brain malignancy and one of the most lethal of all cancers, killing most of those diagnosed within 12 to 15 months despite aggressive treatment. It is also one of the most chemotherapy- and radiation-resistant cancers. New treatments are desperately needed, Mischel said.

"This study uncovers a novel and potentially therapeutically targetable tumor cell growth and survival pathway, which could result in more effective treatments for patients," he said.

Mischel's findings are the result of a collaboration with Dr. Peter Tontonoz, a Howard Hughes Medical Institute investigator and a professor of pathology and laboratory medicine at UCLA, Dr. Timothy Cloughesy, professor of neurology and director of neuro oncology at UCLA's Jonsson Comprehensive Cancer Center, and Dr. Deliang Guo, an assistant professor of radiation oncology at the Ohio State University Comprehensive Cancer Center.

Provided by University of California - Los Angeles