Medical Xpress

Double-therapy approach effectively inhibited brain cancer recurrence

August 24 2010

Researchers from the University of Massachusetts Medical School have identified a novel approach of combining chemotherapy with a targeted therapy to decrease the recurrence of glioblastoma multiforme, the most common and aggressive brain tumor.

"Glioblastomas are horrendous tumors, and new therapies are desperately needed," said lead researcher Alonzo H. Ross, Ph.D., professor of biochemistry and molecular pharmacology at the University of Massachusetts Medical School.

"We found that this double therapy of combining temozolomide with a Notch inhibitor was highly effective at treating tumor cells in culture and in mice," he added.

Results of this study are published in the September issue of *Cancer Research*, a journal of the American Association for Cancer Research.

Despite treatment with surgery, radiotherapy and chemotherapy, glioblastoma prognosis and survival rates are poor. This may in part be due to the fact that some cells within the tumor — cancer stem cells — are more resistant to these therapies, eventually allowing the tumor to recur, according to Ross.

"We're both very successful and unsuccessful with cancer therapy; in most cases we can substantially diminish the tumor mass. The problem is that it comes back with vengeance, and is even more resistant and

difficult to treat," he said.

Temozolomide is one chemotherapeutic agent that helps patients with glioblastomas live longer; two-year survival rates increase from approximately 10 percent with radiation alone to 25 percent when temozolomide is combined with radiation, according to Ross. Likewise, data have indicated that the Notch signaling pathway is often over-expressed in glioma tissue and tumor cells.

Ross and colleagues evaluated this double-therapy approach of combining temozolomide with a Notch inhibitor in cell culture and in immunodeficient mice to determine if this combination therapy enhances therapy to reduce tumor recurrence.

In both models, the researchers saw that the combination of temozolomide with the Notch inhibitor much more effectively reduced tumor growth and recurrence compared to either agent alone. Either drug used individually only transiently slowed tumor growth.

"Temozolomide is a chemotherapy drug of choice for glioblastomas, and the results of our preclinical study represent a potential promising new approach to combat an extremely difficult tumor," Ross said. "The effect of the two together is very dramatic."

Patrick M. O'Connor, Ph.D., chief scientific officer of Selexagen Therapeutics and editorial board member for *Cancer Research*, believes this study provides preclinical proof-of-concept evidence that the Notch pathway confers a survival advantage to glioma cells treated with temozolamide.

"These results help lay the groundwork for future clinical research and are yet another stepping stone towards a future era dominated by 'precision therapeutics' designed to specifically target the underlying

molecular drivers of cancer growth and spread," said O'Connor.

The researchers are currently investigating the mechanism of action for cell death and hope to move these findings into the clinic.

Provided by American Association for Cancer Research