Altered cell metabolism has role in brain tumor development

January 31 2011

(PhysOrg.com) -- Scientists at Duke Cancer Institute have discovered that genetic mutations found in brain tumors can alter tumor metabolism. This work could help lead to new designs for anti-cancer drugs based on the unique properties of these tumors.

“Malignant glioma appears to be at least two large subclasses of diseases – one that involves mutations in the IDH1 and IDH2 genes and one that doesn’t,” said Hai Yan, M.D., Ph.D., an associate professor in the Duke Department of Pathology who led a collaborative group of researchers to conduct the study. “The IDH mutation can serve as a biomarker to help single out individuals who are likely to have better outcomes and who might then receive a particular type of treatment based on their tumor IDH mutation status."

“What we and other researchers are learning now is that certain changes in cellular metabolism are probably a hallmark of cancer,” Yan said.

The study was published in the journal *Proceedings of the National Academy of Sciences Early Edition* the week of Jan. 31.

Two years ago, work by Yan and his colleagues showed that a mutation that disrupts the isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) genes was common in some types of incurable brain tumors, including astrocytomas, oligodendrogliomas, and glioblastomas. Their work suggested that these tumors require the gene to go awry at some point during cancer development. Though key IDH discoveries have been

made around the world, a reason that IDH gene mutations could have such a profound influence on brain cancer has remained elusive.

In the current study, Yan's group solved the connection to metabolism. The IDH1 and IDH2 genes are known to play an important role in cell metabolism — the conversion of nutrients into energy and into building blocks to manufacture new cells.

The researchers examined concentrations of hundreds of metabolites, including sugar, protein, and fat molecules, in cancer cells that they were able to grow in their laboratory. Technological improvements in the past five years – the science of metabolomics -- have made it possible for scientists to simultaneously look at hundreds or thousands of such metabolites to learn what happened in cells with the mutation.

The technology revealed that more than 100 metabolites had altered concentrations in cells with the defective IDH1 or IDH2 genes compared to cells without the defective genes.

One very common metabolite in the human brain -- N-acetyl-aspartyl-glutamate -- was found to be 50 times less common in cells that had that IDH1 mutation compared to those that did not, said Zach Reitman, a student pursuing combined M.D. and Ph.D. degrees in the Medical Scientist Training Program at Duke. "The fact that defective genes can alter the metabolism of cancer cells could mean that altering cellular metabolism is an important step in brain tumor development."

Ivan Spasojevic, Ph.D., assistant director and manager of the Duke Clinical Pharmacology Laboratory, said, "We devised a brand new method to confirm that some of these changes were also present in patients with brain tumors. This approach gave us confidence that what we saw in metabolomics studies of cancer cells in petri dishes was what was really happening in patients," Spasojevic said.

Tumors were removed as part of the patients' normal treatment course, and the tumor tissue was analyzed with patient consent.

"The study emphasized that cellular metabolism could potentially be an 'Achilles heel' for brain tumors, and it points to several promising avenues for future research into new treatments for brain tumors in particular," said Genglin Jin, Ph.D., a key author and postdoctoral research fellow in Yan's lab.

Provided by Duke University