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Reversing Effects of Altered Enzyme May Fight Brain Tumor Growth

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An international team of scientists from the Moores Cancer Center at the University of California, San Diego, the University of North Carolina and several institutions in China have explained how a gene alteration can lead to the development of a type of brain cancer, and they have identified a compound that could staunch the cancer's growth.

The researchers, led by Kun-Liang Guan, PhD, professor of pharmacology at the UC San Diego School of Medicine, have shown that when a mutated enzyme fails to do its job, the development of tumor-feeding blood vessels increases, allowing more nutrients and oxygen to fuel cancer growth. They have also shown in the laboratory that they could reverse the mutant enzyme's effects, effectively blocking this process, called angiogenesis, and provide a potential future treatment strategy against some types of brain tumors. They reported their findings in the current issue of the journal Science.

According to Guan, researchers have known that a mutation in the gene encoding the enzyme, isocitrate dehydrogenase (IDH1), contributed to certain brain tumors called low grade gliomas and secondary glioblastomas, but no one understood how. Guan, Yue Xiong, PhD, at the University of North Carolina and their co-investigators have now shown that this is because alterations in a specific gene, IDH1, impairs the body's ability to keep a tumor growth-promoting protein, HIF-1 alpha, in check.

The IDH1 enzyme works to produce a compound called alpha-KG, which is required for HIF-1 breakdown. Without that control, HIF-1 can run amok, promoting angiogenesis and tumor growth. The team was able to reverse this HIF-1 alpha effect by adding a modified form of alpha-KG to brain tumor cells in culture.

"This suggests a direction to exploit cell permeable alpha-KG for potential treatment of brain cancer patients with an IDH1 mutation," Guan said.

He added that IDH1 appears to function as a tumor suppressor gene that when altered - and turned off - can contribute to tumor formation through the HIF-1 pathway. But Guan noted, "IDH1 is not your usual suspect as a cancer gene."

He explained that the alteration in IDH1 is a substitution of an amino acid in one copy of the gene without losing the other normal copy (every gene in normal human cells has two copies), which is different from most tumor suppressor genes. Most either have genetic material that is deleted or truncated - not a single amino acid substitution.

Guan, Xiong and their group are hopeful about their findings. Understanding mechanisms behind the development of such brain tumors is critical to clinical advances, Guan said. "Because of their ability to reverse HIF-1 levels, drugs mimicking alpha-KG may be worth exploring as possible therapies for these types of gliomas."

Other co-authors include: Shimin Zhao, Yan Lin, Wei Xu, Wenqing Jiang, Zhengyu Zha, Pu Wang, Wei Yu, Qunying Lei, Fudan University, Shanghai, China; Zhiqiang Li, Lingling Gong, Wuhan University, Wuhan, China;

Yingjie Peng, Jianping Ding, Chinese Academy of Sciences, Shanghai. Guan and Xiong both have appointments at Fudan University.

The Moores UCSD Cancer Center is one of the nation's 41 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 www.cancer.ucsd.edu.

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