'Oncometabolite' linked with widespread alterations in gene expression

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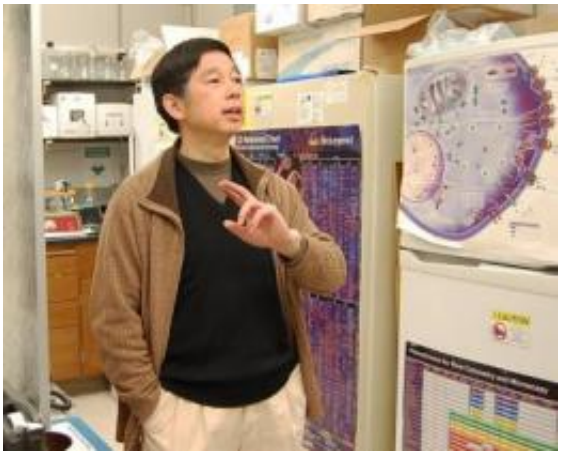

This is Yue Xiong, Ph.D., of the University of North Carolina at Chapel Hill. Credit: UNC Medical Center News Office

A new study finds that a metabolite commonly elevated in brain cancer and leukemia may promote tumorigenesis by altering the expression of a large number of genes. New research, published by Cell Press in the January 18th issue of the journal *Cancer Cell*, enhances the understanding of the link between metabolic deregulation and cancer and may help to guide development of new targeted cancer therapies.

More than 75% of low grade gliomas and secondary glioblastoma multiforme (GBM), and about 20% of acute myeloid leukemia (AML), exhibit mutations in genes for isocitrate dehydrogenase (IDH1 and

IDH2). The tumor-derived mutations in IDH1 and IDH2 lead to loss of normal production of α-ketoglutarate (α-KG), which is required for over 60 enzymes known as dioxygenases, and a gain in the production of 2-hydroxygulatrate (2-HG), which is found at very low levels in normal cells.

"Although 2-HG has been proposed to be an 'oncometabolite', its mechanism of action is not known," explains senior study author, Dr. Yue Xiong from the University of North Carolina at Chapel Hill. "Previous work demonstrated that 2-HG and α-KG are structurally similar, suggesting that 2-HG might interfere with the ability of α-KG to bind to and activate dioxygenases." Dr. Xiong, co-authors Dr. Kun-Liang Guan from the University of California at San Diego and Dr. Shi-min Zhao from Fudan University in Shanghai, and their colleagues designed a series of experiments to uncover how 2-HG contributes to cancer and determine the functional relationship between α-KG reduction and 2-HG elevation.

The researchers discovered that 2-HG functioned as a competitive inhibitor of multiple α-KG-dependent dioxygenases. Some of these dioxygenases regulate methylation of histones, a group of proteins that contribute to the structural organization of chromatin, and methylation of DNA. Alteration of histone and DNA methylation is likely to have a substantial impact on regulation of gene expression and, quite possibly, promote tumor growth. The researchers also showed that a cell-permeable derivative of α-KG reversed the effects of 2-HG inhibition.

"Our findings support the notion that although D-2-HG may not play a significant role in the regulation of α-KG-dependent dioxygenases in normal cells because of its low level, it could play an important role under pathological conditions in tumor cells expressing mutated IDH1 or IDH2", concludes Dr. Xiong. "We also suggest that drugs mimicking α-KG merit exploration as a therapy for tumors that harbor an IDH1 or

IDH2 mutation, either alone or in combination with inhibitors to reduce the 2-HG production."

Provided by Cell Press