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Scientists link 'oncometabolite' to onset of acute myeloid leukemia

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A team of international scientists led by principal investigator Dr. Tak Mak at the Princess Margaret Cancer Centre, University Health Network, has identified a causative link between the product of a mutated metabolic enzyme and the onset of acute myeloid leukemia (AML), one of the most common types of leukemia in adults.

Called an "oncometabolite" for its role in cancer metabolism, the metabolite2-hydroxyglutarate (2HG) is a by-product of a gene mutation of an enzyme known as isocitrate dehydrogenase (IDH).

Says Dr. Tak Mak of the findings published today in Nature: "For the first time, we have demonstrated how a metabolite can cause cancer. This sets the stage for developing inhibitors to block the mutation and prevent the production of this disease-initiating enzyme." The research team included scientists at Weill Cornell Medical College, New York City, and Agios Pharmaceuticals, Cambridge, Massachusetts.

Dr. Mak, Director, The Campbell Family Institute for Breast Cancer Research at Princess Margaret Hospital, is an internationally acclaimed immunologist renowned for his 1984 discovery of cloning the human T-cell receptor. He is also Professor, University of Toronto, in the Departments of Medical Biophysics and Immunology.

The connection between cancer and metabolism has fascinated scientists at Agios and Dr. Mak, who were the first to identify the oncometabolite in research published in *Nature* (2009) and *The* Journal of Experimental

Medicine (2010). The IDH gene mutation was initially discovered in brain cancers in 2008 by American scientists at Johns Hopkins in Baltimore and subsequently also linked to leukemia.

In the lab, Dr. Mak's team genetically engineered a mouse model with the mutation in its blood system to mimic human AML. They discovered that the gene mutation launches the perfect storm for the oncometabolite to trigger the blood system to increase the stem cells pool and reduce mature blood cells in the bone marrow. The resulting condition creates a situation with similarities to myelodysplastic syndrome - one of the precursors to this type of leukemia.

"This is one of the most common mutations in AML," says Dr. Mak. "We also found that it is the common mutation in about 40% of a specific type of lymphoma." The mutation is also known to be involved in about 70-90% of low-grade brain cancers (glioblastomas gliomas) and a variety of other cancers.

Dr. Mak's interest in the blood system began as a young researcher three decades ago with Drs. Ernest McCulloch and James Till, the acclaimed "fathers of stem cell science" at Ontario Cancer Institute, the research arm of Princess Margaret Hospital, whose 1961 discovery of stem cells launched the new field.

Provided by University Health Network