Molecular battle in cancer cells offers clues for treatment

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CHAPEL HILL, N.C. Scientists around the world have been hot on the trail of a genetic mutation closely associated with some brain cancers and leukemia since the mutation's discovery in 2008. The hunt is now yielding fruit. In the Jan. 18, 2011 issue of *Cancer Cell*, researchers reveal how the mutation contributes to cancer development and suggest potential ways to counter its effects.

About 75 percent of people with low-grade brain tumors and 20 percent of people with acute myeloid leukemia have a mutated version of a gene known as IDH. IDH helps cells metabolize, or eat, food. "We now know that IDH represents the most frequently mutated metabolic gene in human cancer. And that changes the landscape of cancer research in metabolism quite a lot," said Yue Xiong, PhD, William R. Kenan Jr. professor of biochemistry and biophysics at the UNC Lineberger Comprehensive Cancer Center.

Xiong and collaborators at UNC, the University of California San Diego, and the Shanghai Medical College of Fudan University in China discovered that the IDH mutation sets off a battle inside cells between two metabolites, small molecules produced by metabolic enzymes. On the good side?the side that leads to normal cell growth?is a molecule called ?-KG. On the bad side?the side that leads to cancer?is a molecule called 2-HG.

The researchers discovered that cells with the IDH mutation produce less ?-KG and more 2-HG than normal cells. 2-HG then outcompetes ?-KG, disabling a whole family of enzymes that depend on ?-KG to do their jobs in the cell. Normal cell functions break down, contributing to the development of cancer.

Two of the affected enzymes are also involved in controlling gene expression, so if 2-HG wins the battle, it can also activate other genes that lead to cancer growth.

Bolstering ?-KG to help fight 2-HG could offer a new treatment option for patients with the mutation. "?-KG is a natural product of the body. So we know we can survive it, we know it's not toxic. That gives us a window of opportunity," said Xiong.

"In terms of future therapeutic interventions for IDH-mutated tumors, there are two directions we could go," Xiong said. "One is developing a drug that inhibits the ability of the mutant enzyme from producing 2-HG. Another is to somehow provide ?-KG back to the patients with mutated IDH to battle 2-HG."

Such therapies would help only those cancer patients with IDH mutations. "We no longer believe there will be a single silver bullet, a drug to treat and cure all types of cancers," Xiong said. "Instead, we are looking into the therapeutic treatment of individual types of cancer. Therefore, a specific agent that is targeting a very specific event such as tumor with mutated IDH now becomes much more valuable."

In 2010, more than 13,000 people died from brain and other nervous system cancers, and more than 20,000 died from leukemia. A drug that helps even a portion of patients with these cancers can still affect a lot of people, said Xiong.

SOURCE [2]

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