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Metabolism may keep cancer cells in check

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Researchers have found that a long-known tumor suppressor, whose mechanism of holding cell growth in check has remained murky for over 40 years, works in part by keeping the cell's energy metabolism behaving in grown-up fashion.

The finding, by scientists at the University of Illinois at Chicago and Universitat Pompeu Fabra in Barcelona is reported in the journal *Genes and Development*.

Tumor suppressors are protein molecules that serve as natural "brakes" on cell proliferation to prevent the formation of malignant tumors. Understanding how these protective proteins work may be a key to developing targeted cancer treatments.

The granddaddy of tumor suppressors is RB, named for the childhood cancer of the retina in which it was first discovered. The gene for retinoblastoma susceptibility was the first tumor-suppressor gene, or "anti-oncogene," identified in humans, and it was the first to be successfully "knocked out" of laboratory mice, which went on to develop tumors. The gene encodes a protein, pRb, that is a master regulatory molecule inside the cell, affecting cell growth, replication, differentiation into specialized tissues, interaction with neighboring cells, and timely cell die-off. Scientists now think the pRb protein is weakened or diminished in the majority of human cancers.

Most people studying pRb have—understandably—focused on its roles in cell growth and division. In the new study, the researchers discovered

that pRb prevents tumors by restricting the activity of a molecule called KDM5A, which regulates the burning of fuel in the mitochondria, the sub-cellular engines that power healthy cells. Cancer cells, being in many respects more primitive, rely instead on their ability to ferment sugars for energy.

KDM5A is an enzyme that works epigenetically. It modifies specific proteins associated with DNA that change the activity of genes without changing the DNA sequences. Epigenetic modifications to histones, one type of protein around which DNA is wound, can trigger the activation of a large number of genes simultaneously.

The more immature a cancer cell is—or the less "differentiated" it is from progenitor cells—the more aggressive its tumors tend to be. The researchers found that if they restored mitochondrial oxidation in pRb-deficient cells, they became more mature and less likely to divide.

"If we can replace the mutated pRb with a small-molecule KDM5A inhibitor, or bypass the need for pRb by restoring its metabolic effects, we may be able to reduce tumor aggressiveness," said Elizaveta Benevolenskaya, associate professor of biochemistry and molecular genetics in the UIC College of Medicine and lead author of the paper. "We are excited that the link of KDM5A inhibition to healthy mitochondria may have implications in developing restorative, differentiation-based therapies."

The researchers were able to suppress the activity of KDM5A in tissue culture experiments using several different human cancer cell lines that lack pRb. In each case, the cells switched to normal metabolism and stopped dividing. They saw the same effect when they caused the cells to overproduce mitochondria.

The study "identifies metabolism as a major cause of abnormal function

in pRb-deficient cancers," said co-author Jalees Rehman, UIC associate professor of medicine and pharmacology. "We suspect that tumors may be especially vulnerable to metabolic therapies that can be applied in conjunction with traditional chemotherapy."

Provided by University of Illinois at Chicago