Scientists discover mechanism that promotes lung cancer growth and survival

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A multi-institutional research study has uncovered a new mechanism that may lead to unique treatments for lung cancer, one of the leading causes of death worldwide.

The study recently published in the journal Genes *& Development* was a collaboration between Sanford-Burnham Medical Research Institute, Virginia Commonwealth University (VCU) Massey Cancer Center and the VCU Institute of Molecular Medicine, the University of California, San Diego, the University of Minnesota and St. Jude Children's Research Hospital. The scientists discovered that the protein Bax Inhibitor-1 (BI-1) protects lung cancer cells and promotes tumor growth by regulating autophagy, a complex process initiated under stressful conditions that breaks down a cell's own components to provide nutrients needed for survival.

"Cancer cells are remarkably adaptive and depend on a variety of mechanisms to ensure their survival and continued growth when challenged by their environment," says John C. Reed, M.D., Ph.D., professor and CEO of Sanford-Burnham. "By reducing levels of BI-1, it appears we were able to modulate intracellular signals and starve lung cancer cells of the energy needed to carry out one of their most important survival mechanisms, autophagy."

The researchers showed that BI-1 appeared to be linked to levels of calcium, which aids in signal transduction. Suppressing BI-1 reduced calcium levels in the endoplasmic reticulum, the interconnected network

of sacs and tubules that manufacture, process and transport a variety of compounds for use inside and outside of cells. Lowering BI-1 levels led to reduced mitochondrial activity, oxygen consumption and adenosine triphosphate (ATP) levels. ATP is often called the "molecular unit of currency" due to the important role it plays in transporting chemical energy needed for metabolism.

The researchers' laboratory findings were confirmed by animal models that showed BI-1 suppression reduced human lung cancer tumor growth.

"These studies are the first to show that BI-1 may play an important survival role in cells under circumstances where oxygen and nutrient deprivation are encountered, such as the conditions that arise in advanced tumors or when cells are stressed by chemotherapy treatments," says Paul B. Fisher, M.Ph., Ph.D., Thelma Newmeyer Corman Endowed Chair in Cancer Research and program co-leader of Cancer Molecular Genetics at VCU Massey Cancer Center, chairman of VCU's Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine. "We are excited by our findings because they uncover a new pathway that may be an effective target for future therapies to treat advanced lung cancer."

Next, the scientists hope to apply their findings to screen for potential drugs that can reduce BI-1-mediated protective autophagy in cancer cells.

More information: The full manuscript of this study is available online at: genesdev.cshlp.org/content/26/10/1041.full

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