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Targeting an 'Energy Crisis' in the Treatment of Non-Small Cell Lung Cancer

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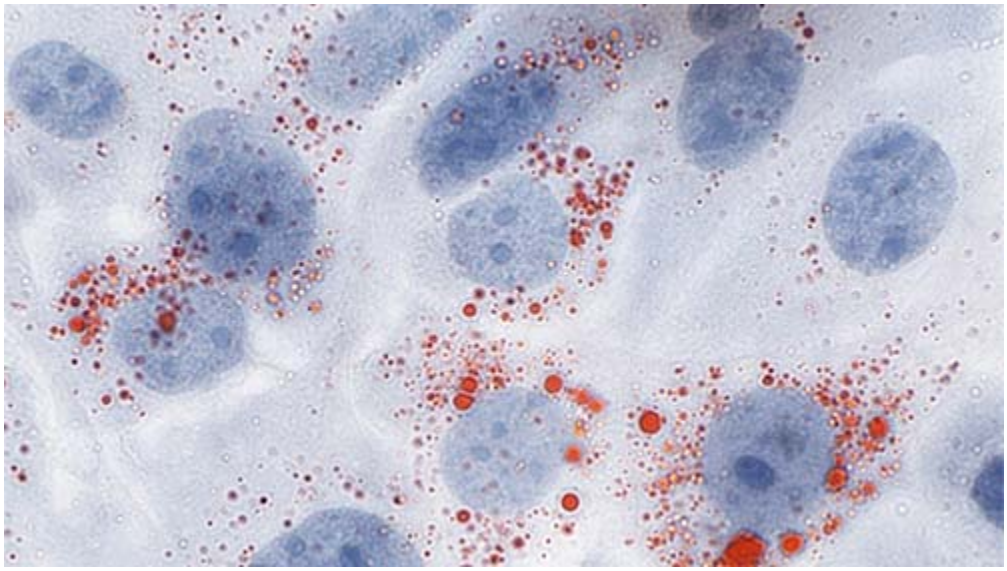

New Brunswick, N.J. – An energy crisis usually isn't viewed as a positive situation, but when it comes to stopping a common form of lung cancer, it's considered a good thing. Research from investigators at Rutgers Cancer Institute of New Jersey examined a potential approach to cancer therapy that disrupts a cancer cell's 'fuel supply' by targeting a cellular survival mechanism known as autophagy. **'Jessie' Yanxiang Guo, PhD**, a resident researcher in the Cancer Metabolism and Growth Program at Rutgers Cancer Institute and an assistant professor of medicine at Rutgers Robert Wood Johnson Medical School, is the senior author of the work published in the January 28 online edition of *Genes & Development* (doi:10.1101/gad.320481.118). She shares more about the research, which focused on lung cancers driven by mutations known as *LKB1* and *KRAS*:

Q: Why is this topic important to explore?

A: Between 85 to 90 percent of lung cancers are non-small cell lung cancer, and response to standard treatment for this disease is generally poor. Driver mutations are molecular alterations in tumors that play a significant role in tumor progression and growth. In recent years, discovery of a number of these mutations found in non-small cell lung cancer has led to significant treatment advances. However, patients harboring co-mutations in the tumor suppressor *LKB1* and the oncogene *KRAS*, which are two of the most common mutations in non-small cell lung cancer, develop more aggressive tumors, show a high frequency of cancer spread and have limited treatment options.

We know cancer cells activated by the Ras protein family require a process known as autophagy for cell maintenance, metabolic stress tolerance and tumor development. When Ras proteins are 'switched on,' they have the ability to turn on other proteins that can activate genes responsible for cell growth and survival. In addition, loss of tumor suppressor LKB1 facilitates tumor growth and spread under energetically unfavorable conditions. In this work, we wanted to know if autophagy compromises for LKB1 loss to support Ras-driven lung tumor growth and understand the underlying mechanism. Thus, we would be able to see if targeting this process could lead to potential therapeutic strategies for LKB1-deficient Ras-driven lung cancers that have limited treatment options so far.

Q: How did your team approach the work and what did you learn?

A: Sufficient energy production is essential for tumor growth. As an energy sensor and metabolic switch, LKB1 plays an important role in maintaining cellular energy homeostasis. Autophagy is activated in order to recycle cellular components for

energy production when extracellular nutrients are limited in order to help keep cells alive. Therefore, we hypothesize that loss of LKB1 promotes cell growth but also results in broad defects in metabolic control in response to nutrient deprivation and other types of metabolic stress, a property that may be further compromised by loss of autophagy. Using laboratory models for *LKB1*-deficient *KRAS*-mutant non-small cell lung cancer, we found that autophagy ablation reduced the frequency of tumor initiation and tumor growth in *Lkb1*-deficient lung tumors, and extended the life span of laboratory models. We also found that lack of autophagy impacts lipid metabolism-mediated energy production needed for the development of *LKB1*-deficient *KRAS*-mutant lung cancer. Most importantly, compared to our previous work that loss of autophagy impaired p53-deficient Kras-driven lung tumors, the extent of tumor growth inhibition by loss of autophagy in *Lkb1*-deficient *Kras*-mutant lung tumors was much more dramatic.

Q: What is the implication of this finding?

A: This finding suggests that blocking autophagy, and in essence cutting of the fuel supply to cancer cells causing an energy crisis and breakdown of function, could be a potential therapeutic strategy for KRAS-driven lung cancers, particularly in treating LKB1-deficient KRAS-driven non-small cell lung cancer. Future research should focus on translating this pioneering scientific finding to the clinic through early-phase clinical trials in order to improve lung cancer treatment.

Along with Dr. Guo, other authors on this work are Vrushank Bhatt, Khoosheh Khayati, Zhixian Sherrie Hu, Amy Lee, and Wali Kamran, all Rutgers Cancer Institute; and Xiaoyang Su, Rutgers Cancer Institute and Rutgers Robert Wood Johnson Medical School.

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