Drug's impact on amino acid transporter may offer non-small cell lung cancer patients new hope

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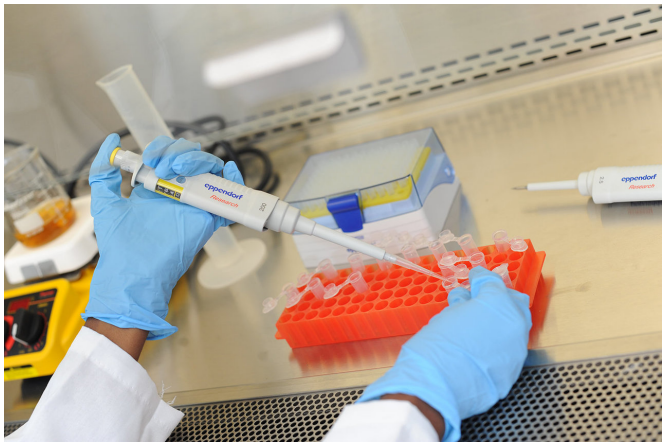

An amino acid transporter named xCT may affect the growth and progression of non-small cell lung cancer. Credit: Georgia State University

An amino acid transporter named xCT may affect the growth and progression of non-small cell lung cancer, a discovery that may predict the five-year survival rate of patients suffering from this cancer, now at 16 percent, researchers at Georgia State University and Vanderbilt University Medical Center have concluded.

The team, led by Xiangming Ji of Georgia State and Pierre Massion of Vanderbilt University Medical Center, published their findings in the current issue of *Oncogene*.

xCT is an amino acid transporter, which carries the amino acid cystine into the cells and exports glutamate, a chemical that nerve cells use to send signals to other cells. It provides the key building blocks for glutathione (GSH) synthesis, which feeds cancer cell function and growth. The researchers used sulfasalazine, an anti-inflammatory drug often used to treat Crohn's disease, rheumatoid arthritis and related diseases, to reduce tumor formation by inhibiting the function of xCT.

Previous studies published in cancer research journals show sulfasalazine's ability to affect xCT in other forms of cancer, including breast, bladder and small cell lung cancer.

Researchers first examined xCT protein expression in non-small cell lung cancer cell lines and found larger quantities in the non-small cell lung cancer cells compared to normal lung tissue.

By analyzing protein expression of patients from Vanderbilt-Ingram Cancer Center, the researchers found patients with higher xCT expression have a lower five-year cancer survival rate. On the positive side, the data show xCT as a therapeutic targeting candidate.

Ji and Massion tested the cancer cells in the laboratory and in mice, discovering that targeting xCT genetically or therapeutically could reduce the tumor formation in vitro (in cell culture) and in vivo (in living organisms). They also found only cells with elevated xCT expression were more sensitive to glutamine withdrawal. The results show strong evidence that lowering xCT may improve survival rates for individuals with non-small cell lung cancer.

"In conclusion, our results demonstrate that xCT is a major regulator of metabolic reprogramming with overarching effects on glucose metabolism, glutamine dependency and intracellular GSH/GSSG redox balance. All these metabolic effects contribute to lung cancer development," Ji said.

The expression of xCT is correlated with a poor prognosis in non-small cell lung cancer and

represents a new opportunity to therapeutically target this biomarker in molecularly strati?ed non-small cell lung cancer patients. Further studies are needed to better understand the unwanted communication between xCT and other tumor-associated cell signaling pathways such as MYC, KRAS and NOTCH in the formation of lung cancer tumors.

More information: Xiangming Ji et al. xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression, *Oncogene* (2018). DOI: 10.1038/s41388-018-0307-z

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