Hippo 'crosstalk' may be vital to tumor suppression

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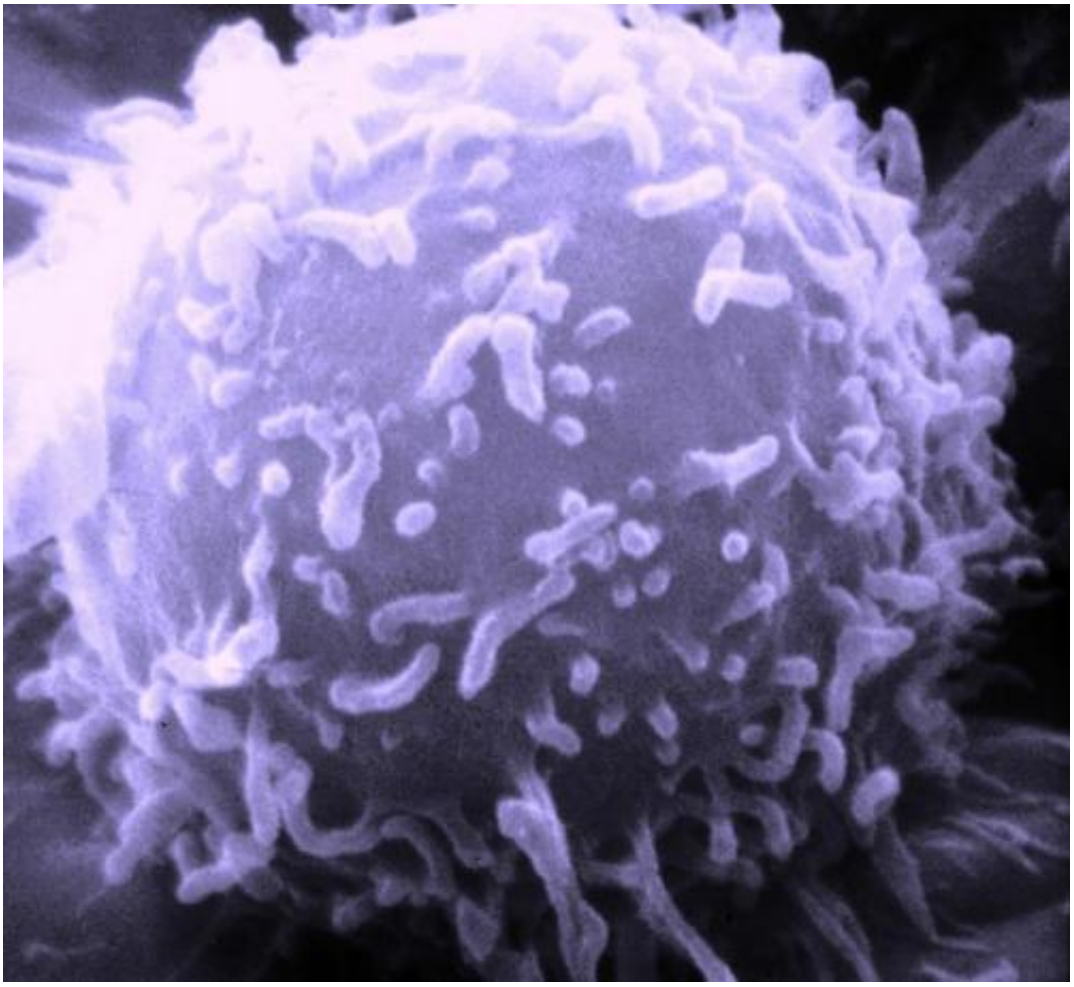

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Think of a waterfall, and you might see why cell-signaling pathways are important to cancer research. As water cascades, it impacts everything downstream. And everything upstream affects the waterfall.

Cell-signaling pathways are similar in that one molecular action results in another, and another, ultimately culminating in a bodily reaction such as breaking down blood sugar for energy, or in the case of cancer, feeding a tumor.

Scientists at The University of Texas MD Anderson Cancer Center have discovered new information about a key pathway known as Hippo, a metaphoric name referencing its link to tissue "overgrowth." The Hippo pathway has been shown to regulate cell death and cell growth, thus playing a role in the development or prevention of tumors. Junjie Chen, Ph.D., chair of Experimental Radiation Oncology, has revealed that the Hippo pathway can be manipulated to regulate the fuel, or glucose, that feeds all cells including those in tumors, thus presenting a potentially new avenue for cancer therapy.

"We have identified crosstalk between glucose metabolism and the Hippo pathway," said Chen, whose study results are published in this week's issue of *Nature Cell Biology*. "This is a previously unknown function of the Hippo pathway in glucose metabolism. It is highly significant because it established a connection between a pathway involved in organ size control and nutrient availability."

In other words, we now know what feeds the Hippo and how. By regulating the body's blood sugar, glucose, Hippo is able to impact a tumor's nutrient source.

How? By a waterfall cascade of cellular events that includes proteins named YAP and AMPK. YAP (yes-associated proteins) have previously been shown to promote cancer progression and metastasis. Chen's team

found that when cells were starved of glucose, the AMPK enzyme was activated, which deactivated YAP. This was achieved, in part, by YAP's regulation of a gene called GLUT3, which is involved in glucose metabolism. The results revealed a new "upstream" role for YAP as a link between the Hippo pathway and the very metabolism that allows cancer to spread.

"The discovery of AMPK's effect on YAP extends our understanding of YAP regulation outside of the Hippo pathway," said Chen. "Our study proposes yet another cancer-related function of YAP. This provides an exciting link between glucose metabolism and the Hippo pathway in tissue maintenance and cancer prevention."

Tumor cells are known to reprogram their signaling pathways and metabolism to support their uncontrolled growth and survival. Chen's team hopes to spur further investigation through their discovery of new protein-related causes for this metastasis.

More information: AMPK modulates Hippo pathway activity to regulate energy homeostasis, *Nature Cell Biology*, DOI: 10.1038/ncb3113

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