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Scientists identify a critical tumor suppressor for cancer

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Scientists from the Florida campus of The Scripps Research Institute have identified a protein that impairs the development and maintenance of lymphoma (cancer of the lymph nodes), but is repressed during the initial stages of the disease, allowing for rapid tumor growth.

While the study, published in the August 3, 2012 edition of the journal *Cell*, largely focuses on the role of this new tumor suppressor in lymphoma induced by Myc oncoproteins (the cancer-promoting products of Myc oncogenes), the authors show this circuit is apparently operational in all human tumors with MYC involvement, which is more than half of all human tumor types.

"This opens a new therapeutic avenue to exploit for cancers with Myc involvement—including relapsed metastatic tumors and refractory tumors, those that have not responded to treatment," said John Cleveland, a Scripps Research professor and chair of the Department of Cancer Biology, who led the study.

The Myc family of oncoproteins (c-Myc, N-Myc, and L-Myc) regulate critical pathways that contribute to tumors; c-Myc expression, which is activated in human Burkitt lymphoma, is sufficient to induce the growth of several tumor types in animal models.

In the new study, the scientists focused on precancerous and malignant Myc-expressing B cells, part of the immune system affected in human lymphoma. Using transgenic animal models, Cleveland and his team, led

by the efforts of senior postdoctoral fellow Robert Rounbehler, showed that Myc-directed repression of a protein called tristetraprolin (TTP/ZFP36) was important for both the development and maintenance of cancer. The suppression of TTP is a hallmark of human cancers with MYC involvement, Cleveland noted.

The scientists' results showed that overriding this pathway by forced expression of TTP more than doubled the lifespan of Myc transgenic mice. Strikingly, Rounbehler discovered that re-introduction of TTP into Myc-driven lymphoma totally disabled these tumors, indicating an important therapeutic target.

The authors showed that Myc regulates hundreds of genes that contain adenylate-uridylate-rich elements (AU-rich elements), which play an important role in RNA stability and are found in many messenger RNAs (mRNAs) that code for oncogenes, nuclear transcription factors, and cytokines. AU-rich elements direct the mRNA for degradation; they are thought to be vital for controlling expression during cell growth.

"Myc regulates the expression of select AU-binding proteins to control the destruction of certain mRNAs," Cleveland said. "Also, our study strongly suggests that other AU-binding proteins may also, in fact, function as tumor suppressors in other cancers."

More information: "Tristetraprolin is a Tumor Suppressor That Impairs Myc-Induced Lymphoma and Abolishes the Malignant State," *Cell*.

Provided by Scripps Research Institute