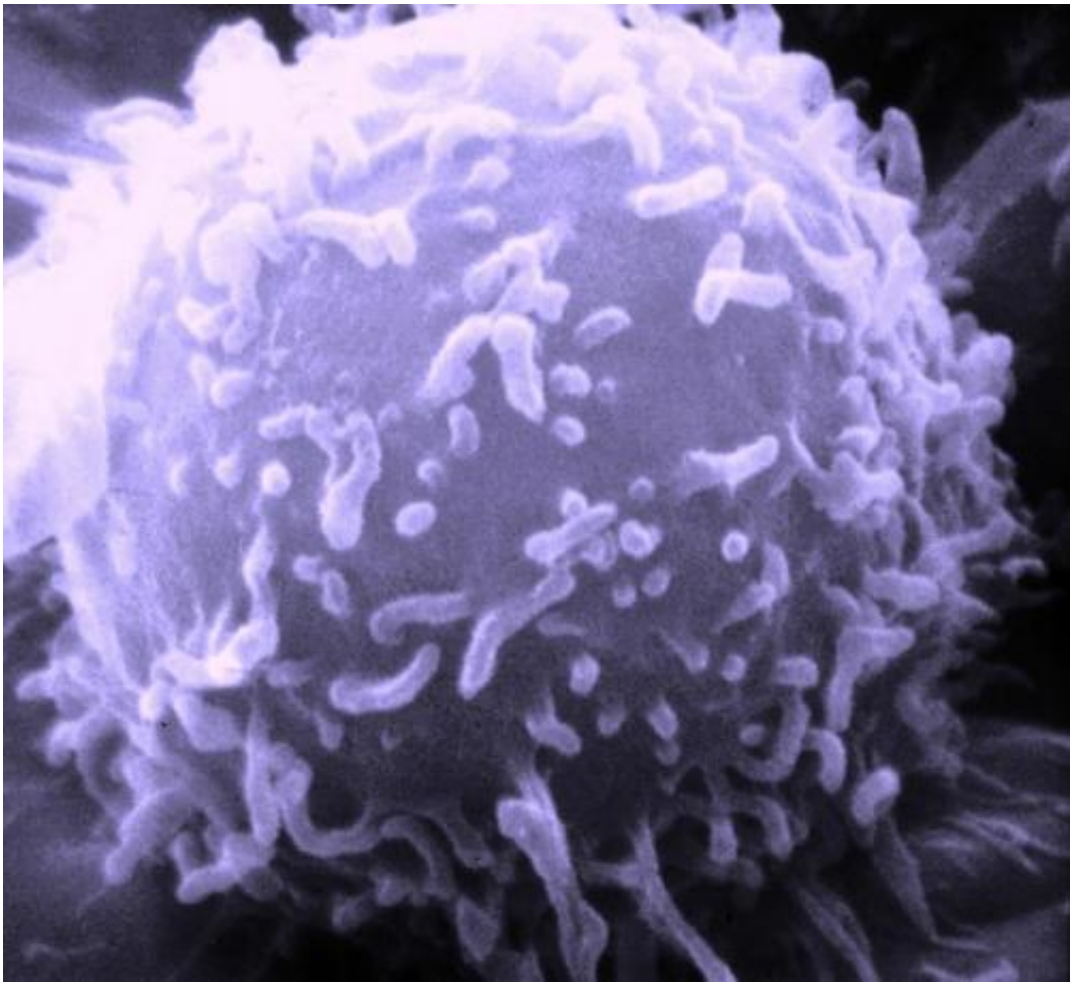
New method characterizes structure of protein that promotes tumor growth

April 13 2015



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

Moffitt Cancer Center researchers have developed a new method to identify a previously unknown structure in a protein called MDMX. MDMX is a crucial regulatory protein that controls p53 - one of the most commonly mutated genes in cancer.

Known as the tumor suppressor gene, p53 protects the body from cancer development by ensuring that DNA remains intact and does not have mutations. If p53 senses DNA damage, it can either stimulate the cells to repair its DNA, or cause cells to stop growing and undergo cell death. Because of its functions, p53 is often called "the guardian of the genome." Mutations in p53 can inactivate its function and lead to cancer development. It is estimated that more than half of all cancers have p53 mutations.

Despite the importance of p53, too much p53 activity could also be a detriment to cells. Therefore, an intricate regulatory network has evolved to block excessive p53 activity, including MDMX that binds to p53 to block its activity.

Moffitt scientists study the structure of MDMX to understand how it blocks p53 activity and to use this information in the development of cancer therapeutic drugs. However, many techniques commonly used to study protein structures have different drawbacks, limiting their usefulness on MDMX.

The researchers developed a novel technique called the proteolytic fragment release assay to analyze the MDMX protein. This assay allows scientists to determine how different segments of a protein interact with one another.

They discovered that a segment of MDMX functions as an auto-inhibitor of its own activity. When MDMX is in a closed structure with the auto-inhibitory segment, it cannot bind to p53. As a result, p53 can either

repair DNA or stimulate cell death. However, if MDMX has a more open structure, it binds to p53 and blocks DNA repair and cell death.

"Our biochemical study of this protein over the past decade has facilitated the development of an MDMX drug that has recently entered clinical trial. The current finding suggests that analyzing the state of MDMX protein in tumors may help identify patients that are more likely to respond to the drug," said Jiandong Chen, Ph.D., senior member of Moffitt's Cancer Biology and Evolution Program. "This publication is a significant step forward in our basic research to help the development of next generation MDMX-targeted cancer drugs. Investigators with expertise in molecular biology, biochemistry, and structural biology working together really helped bring our understanding to a higher level than each of us working alone."

More information: Autoinhibition of MDMX by intramolecular p53 mimicry, *PNAS*, Lihong Chen, DOI: 10.1073/pnas.1420833112

Provided by H. Lee Moffitt Cancer Center & Research Institute