Preventing cancer development inside the cell cycle

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Researchers from the NYU Cancer Institute, an NCI-designated cancer center at NYU Langone Medical Center, have identified a cell cycle-regulated mechanism behind the transformation of normal cells into cancerous cells. The study shows the significant role that protein networks can play in a cell leading to the development of cancer. The study results, published in the October 21 issue of the journal *Molecular Cell*, suggest that inhibition of the CK1 enzyme may be a new therapeutic target for the treatment of cancer cells formed as a result of a malfunction in the cell's mTOR signaling pathway.

In the study, NYU Cancer Institute researchers examined certain multi-protein complexes and protein regulators in cancer cells. Researchers identified a major role for the multi-protein complex called $SCF^{\beta TrCP}$. It assists in the removal from cancer cells the recently discovered protein DEPTOR, an inhibitor of the mTOR pathway. SCF (Skp1, Cullin1, F-box protein) ubiquitin ligase complexes are responsible for the removal of unnecessary proteins from a cell. This degradation of proteins by the cell's ubiquitin system controls cell growth and prevents malignant cell transformation. Researchers show that inhibiting the ability of $SCF^{\beta TrCP}$ to degrade DEPTOR in cells can result in blocking the proliferation of cancer cells. In addition, researchers discovered that the activity of CK1 (Casein Kinase 1), a protein that regulates signaling pathways in most cells, is needed for $SCF^{\beta TrCP}$ to successfully promote the degradation of DEPTOR.

"Low levels of DEPTOR and high levels of mTOR activity are found in

many cancers, including cancers of the breast, prostate, and lung," said senior study author Michele Pagano, MD, the May Ellen and Gerald Jay Ritter Professor of Oncology and Professor of Pathology at NYU Langone Medical Center and a Howard Hughes Medical Institute Investigator. "It is critical for researchers to better understand how the protein DEPTOR is regulated. Our study shows it would be advantageous to increase the levels of DEPTOR in many types of cancer cells to inhibit mTOR and prevent cell proliferation."

The mTOR pathway (mammalian Target Of Rapamycin) regulates the growth, proliferation, and survival of a cell, and its proper regulation is essential to prevent the formation of cancer cells. DEPTOR interrupts the mTOR pathway by binding to mTOR protein complexes and blocking their enzymatic activities, restraining cell growth. This helps support the proliferation and survival of cancer cells.

Study experiments showed that a reduction of $SCF^{\beta TrCP}$ and CK1 proteins in cells resulted in accumulation of DEPTOR. Also, DEPTOR was destroyed in cells only when $SCF^{\beta TrCP}$ and CK1 were both present. Thus, inhibition of $SCF^{\beta TrCP}$ or CK1 represents a novel and promising way to inhibit the mTOR pathway. A pharmacologic inhibitor of CK1 was tested by researchers and shown to successfully stabilize DEPTOR in cells, while other pharmacological agents had no effect.

"Our study findings demonstrate that DEPTOR is regulated by the protein complex in cells reentering the cell cycle, and deregulation of this event could contribute to the aberrant activation of the mTOR pathway in cancer," said lead author Shanshan Duan, PhD, a post-doctoral fellow in the Department of Pathology at NYU School of Medicine in Dr. Pagano's Laboratory. "This study suggests a novel approach to stop the deregulation of the mTOR pathway in cancer cells with promising small molecule inhibitors of CK1.This study is another step forward in the translation of laboratory findings into more effective

approaches to cancer prevention and treatment."

Provided by New York University School of Medicine

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