Disabling Skp2 gene helps shut down cancer growth

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Increased understanding of the Skp2 gene and its relation to cellular senescence may lead to the development of novel agents that can suppress tumor development in common types of cancer, researchers from The University of Texas M. D. Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center report in the journal *Nature*.

Skp2 is involved in promoting cell cycle regulation, cell proliferation, cell growth and the formation of tumors, and it is overexpressed in a variety of human cancers, according to lead author Hui-Kuan Lin, Ph.D., an assistant professor in M. D. Anderson's Department of Molecular and Cellular Oncology.

Lin and colleagues found that inactivating Skp2 after oncogenes are overexpressed stifles cancer growth by causing senescence - the irreversible loss of a cell's ability to divide and grow. Harnessing the power of cellular senescence to push rapidly dividing cells into a dormant state might provide another way to prevent or control common malignancies like prostate cancer.

Experiments Yield Surprising Results

The researchers conducted a series of experiments in tumor cell lines and mouse models that have shed new light on the interplay of Skp2 and cellular senescence.

"We discovered that Skp2 actually exhibits oncogenic activity, which is required for cancer development in multiple tumor models, such as the Pten-deficient and the p19Arf -deficient mouse models," Lin said. "We found that Skp2 regulates tumorigenesis to trigger the cellular senescence program. This program is unexpectedly independent of the p19Arf-p53 pathway, which was previously believed to be critical for cellular senescence."

The researchers also found that induction of cellular senescence did not cause DNA damage, and their results suggest that Skp2 inactivation can suppress cellular transformation to cancer even in the setting of an impaired p19Arf-p53 senescence response.

Moreover, research conducted in mouse models with faulty or inactive tumor suppressor networks showed that Skp2 deficiency and oncogenic signaling elicit a senescence response that restricts formation of tumors.

Novel Findings Point to New Therapeutic Approaches

Lin said these studies suggest that in the future Skp2 might be an effective therapeutic target for tumors with deregulated Akt signaling due to the loss or inactivation of Pten functions. Pten, which is commonly lost in human cancers, acts as a tumor suppressor gene by suppressing Akt signaling. Skp2 and Pten loss are believed to cooperate in triggering cellular senescence to restrict invasive prostate cancer.

"We now want to examine whether Skp2 is required in other tumor model systems, such as a HER2 model, to determine whether it is globally required for an oncogenic event," said Lin, who previously was affiliated with Memorial Sloan-Kettering Cancer Center's Department of Pathology and Cancer Biology and Genetics program and continued his research at M. D. Anderson. "We are testing whether Skp2 might be widely used for different types of cancer or perhaps used to trigger this

newly described cellular senescence program."

The researchers also are working to develop a Skp2-specific small molecule inhibitor to establish that the protein is indeed an important therapeutic target in cancer treatment. They believe that Skp2-based therapy might also be used as a general cancer treatment that could be combined with existing cancer therapies.

Provided by University of Texas M. D. Anderson Cancer Center