Researchers pinpoint a new enemy for tumor-suppressor p53

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Michelle Barton, Ph.D. is a professor in M. D. Anderson's department of biochemistry and molecular biology. Credit: M. D. Anderson

Researchers at The University of Texas M. D. Anderson Cancer Center have identified a protein that marks the tumor suppressor p53 for destruction, providing a potential new avenue for restoring p53 in cancer cells.

The new protein, called Trim24, feeds p53 to a protein-shredding complex known as the proteasome by attaching targeting molecules called ubiquitins to the tumor suppressor, the team reported this week in

the Proceedings of the National Academy of Sciences Online Early Edition.

"Targeting Trim24 may offer a therapeutic approach to restoring p53 and killing tumor cells," said senior author Michelle Barton, Ph.D., professor in M. D. Anderson's Department of Biochemistry and Molecular Biology.

The discovery is based on an unusual approach to studying p53, which normally forces potentially cancerous cells to kill themselves and is shut down or depleted in most human cancers. Studies of the p53 protein and gene tend to focus on cancer cell lines or tumors, where the dysfunction already is established, Barton said. "We wanted to purify p53 from normal cells to better understand the mechanisms that regulate it."

The team developed a strain of mice with a biochemical tag attached to every p53 protein expressed. After first assuring that the tagged p53 behaved like normal p53, the team then used the tag, or hook, to extract the protein. "We could then identify proteins that were attached to p53, interacting with it, through mass spectrometry," Barton said.

They found Trim24, a protein previously unassociated with p53 that is highly expressed in tumors and is a target of two known oncogenes in distinct forms of leukemia and thyroid cancer.

Subsequent experiments showed that decreased levels of Trim24 led to increased levels of p53 expression in the cell nucleus, and increasing Trim24 expression reduced p53 levels. Loss of Trim24 expression in a breast cancer cell line caused spontaneous programmed cell death - apoptosis. A similar response was confirmed in human lung, colon and prostate cancer cells.

Treating cells with a proteasome inhibitor also led to increased p53

expression. Removing an important binding domain of Trim24 or depleting it completely both led to greatly reduced ubiquitin targeting of p53.

An analogous system in fruit flies showed that a simpler version of Trim24 in the flies plays a similar role regulating p53, demonstrating that the relationship is evolutionarily conserved.

Source: University of Texas M. D. Anderson Cancer Center (news : web)