Protein identified as enemy of vital tumor suppressor PTEN

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A protein known as WWP2 appears to play a key role in tumor survival, a research team headed by a scientist at The University of Texas MD Anderson Cancer Center reports in an advance online publication of *Nature Cell Biology*.

Their research suggests that the little-studied protein binds to the tumor-suppressing protein PTEN (phosphatase and tensin homologue deleted on chromosome 10), marking it for destruction by proteasomes, which degrade proteins and recycle their components.

PTEN plays a role regulating the cellular reproduction cycle and prevents rapid cell growth, a hallmark of malignant cells. Its gene is mutated or deleted in many types of cancer, the researchers noted.

The WWP2 (atrophin-1 interacting protein 2) protein was discovered in the laboratory of Junjie Chen, Ph.D., professor and chair in MD Anderson's Department of Experimental Radiation Oncology and senior author of the paper.

"We were trying to find regulators of PTEN when we isolated the protein WWP2 as a putative PTEN-associated protein," Chen said. He noted that WWP2 caught the researchers' attention because it is similar to the NEDD4-1 protein, which has been proposed as a regulator of PTEN function.

First suspect doesn't affect PTEN

WWP2 is an E3 ubiquitin ligase in the NEDD4-like protein family. Ubiquitins attach to other proteins, labeling them for degradation by proteasomes. NEDD4-like proteins play important roles regulating gene transcription, embryonic stem cells, cellular transport and activation of T cells.

"But when NEDD4-1 is deleted in mice, researchers have not seen a clear change in PTEN protein level," Chen noted. "These findings suggest that there may be other PTEN regulators.

"Because WWP2 is part of the NEDD4-like family, we decided to take a look at it to see if it's the real regulator of PTEN," Chen continued. "When you knock down WWP2, you see an increase in PTEN level, whereas with WWP2 overexpression you can see a decrease in PTEN. This finding indicates that WWP2 may be involved in PTEN's regulation."

Overall, the study results suggest that WWP2 can regulate PTEN stability, Chen said.

Possibly a cancer-driving gene

The team uncovered evidence that WWP2 is a potential oncogene - a driver in tumor formation and growth. In one experiment, mice with normal WWP2 developed prostate cancer tumors after nine weeks that were more than three times the size of tumors in mice with WWP2 silenced.

Chen noted that more research is needed to determine whether WWP2 is functionally important in tumors or in tumor formation. "We need to

look at real tumor samples to determine whether tumors with reduced PTEN expression could result from the overexpression of WWP2."

He added that some early studies suggest that WWP2 may operate in tumors, but a correlation between WWP2 overexpression and PTEN downregulation in tumors has not been established.

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