Researchers identify new, cancer-causing role for protein

August 27 2009

Hui-Kuan Lin, Ph.D., is an assistant professor in M. D. Anderson's Department of Molecular and Cellular Oncology. Credit: M. D. Anderson

The mainstay immune system protein TRAF6 plays an unexpected, key role activating a cell signaling molecule that in mutant form is associated with cancer growth, researchers at The University of Texas M. D. Anderson Cancer Center report in the Aug. 28 edition of *Science*.

"The mechanism that we discovered activates Akt and also contributes to hyperactivation of a mutant form of Akt found in breast, colon and other cancers," said senior author Hui-Kuan Lin, Ph.D., assistant professor in M. D. Anderson's Department of Molecular and Cellular Oncology.

Akt is a signaling protein that plays a central role in numerous biological functions, including cell growth and programmed cell death, or apoptosis, Lin said. Deregulated Akt expression has been found to contribute to cancer development.

"Our novel findings are that Akt undergoes ubiquitination to be activated, and that TRAF6 regulates that process. We've found that TRAF6 is not just involved in the innate immune response, but plays a role in cell growth and carcinogenesis," Lin said.

Ubiquitins are regulatory proteins that work by binding to other proteins. While ubiquitins are best known for marking a defective protein for death by the cell's proteasome complex, Lin said, ubiquitination of Akt is not tied to the proteasome. Ubiquitins are transferred to target proteins by another set of proteins called ligases.

Akt resides in the cell's cytoplasm and must be recruited to the cell membrane in order to be activated by attachment of phosphate groups to specific locations on the protein, Lin explained. The mechanism that gets Akt to the membrane had not been understood.

Because one type of ubiquitination involves protein movement, Lin's team launched a series of cell line experiments that showed Akt is ubiquitinated, and in a way not involving the proteasome.

Screening a different class of ubiquitin ligases showed that overexpression of TRAF6 E3 ligase promotes Akt ubiquitination. Subsequent experiments showed that Akt ubiquitination is required to move Akt to the cell membrane, and leads to Akt's phosphorylation and activation.

Next, the researchers analyzed a mutant form of Akt implicated in human breast cancer, finding that increased Akt ubiquitination

contributes to the hyperactivation of Akt in the mutant cells. "We discovered this oncogenic Akt mutant is hyperubiquitinated," Lin said. "If you disrupt its ubiquitination, you deactivate the mutant."

The team found depleting TRAF6 in prostate cancer cells reduced Akt activation. And mice with TRAF6 knocked down developed smaller prostate cancer tumors than those with active TRAF6. "We believe that TRAF6 is a previously unrecognized oncogene and is a new potential target for treating human cancers," Lin said.

Having discovered this Akt activation pathway, Lin and colleagues are now trying to identify the enzyme that normally turns it off.

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