KEAP1 Keeps major cancer-promoting protein at bay

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This is Mien-Chie Hung, Ph.D., chair and professor of M. D. Anderson's Department of Molecular and Cellular Oncology. Credit: M. D. Anderson

A tumor-suppressing protein snatches up an important cancer-promoting enzyme and tags it with molecules that condemn it to destruction, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center reports this week in the journal *Molecular Cell*.

"KEAP1 is a recently discovered tumor suppressor, but how it works has not been known. IKKß is a known oncoprotein that promotes cancer in at least two different ways, but we did not know how it was regulated. We think we've answered both questions with this research," said senior

author Mien-Chie Hung, Ph.D., chair and professor of M. D. Anderson's Department of Molecular and Cellular Oncology.

The researchers showed that KEAP1, short for the tongue-twisting Kelch-like ECH-associated protein 1, binds to IKKß and attaches molecules known as ubiquitins to the oncoprotein, which targets it for dissolution by the cell's proteasome complex.

They also showed that underexpression of KEAP1 is associated with poor survival among breast cancer patients, and that it's mutated and inactivated in some breast, liver, lung and colon tumors.

"KEAP1 underexpression or inactivation is involved in multiple cancers, so we are working now to identify its activation mechanism, which could lead to development of new anti-cancer drugs," Hung said. He and his colleagues also want to know whether KEAP1 works on other known oncoproteins.

Blocking overexpression of IKKß, short for IkB kinase ß, is crucial for at least two reasons. Hung and colleagues have shown that the protein inhibits at least two other important tumor suppressors. More importantly, IKKß activates the NF?B (nuclear factor ?b) signaling pathway, which regulates expression of genes involved in the immune response, cellular proliferation, growth of new blood vessels, cell survival, tumor invasion, and the lethal spreading of cancer known as metastasis.

Hung and colleagues first demonstrated that the presence of KEAP1 inhibits the NF?B signaling pathway and then conducted a series of experiments to find out how that happens. They found that depletion of KEAP1 leads to the accumulation of IKKß, and then discovered that the tumor suppressor binds to a specific site on IKKß, capturing it to feed it to the proteasome.

Hung likens this snatching of IKKß to plucking stuffed animals with a mechanical claw out of an arcade game, imagery that wound up on the cover of Molecular Cell.

KEAP1 is a ubiquitin ligase that attaches to the target protein and works in a complex with another protein, CUL3, that connects the ubiquitins to the bound protein.

The team analyzed both KEAP1 and CUL3 expression in the tumors of 119 breast cancer patients and correlated the findings to overall survival. They found that underexpression of KEAP1 alone was associated with poor survival. Patients with strong expression of both KEAP1 and CUL3 had an 80 percent survival rate at five years while those with little expression of either had a 43 percent 5-year survival rate.

Next, they sequenced KEAP1's genes in 26 cancer lines (18 breast, four liver, four lung) and in 119 primary tumors (17 breast, 78 liver, 13 lung, 11 colon) and found two functional genetic mutations that shut down the protein's ability regulate IKKß. The mutations affected the portion of the protein that binds to IKKß.

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