MedicalXpress

Researchers link protein to tumor growth

August 31 2010

(PhysOrg.com) -- Johns Hopkins researchers working on mice have discovered a protein that is a major target of a gene that, when mutated in humans, causes tumors to develop on nerves associated with hearing, as well as cataracts in the eyes.

The protein, named YAP, is linked to the NF2 tumor suppressor gene via a relay of chemical signals that is responsible for shaping and sizing tissue growth by coordinating control of cell proliferation and death, according to research published July 19 in *Developmental Cell*.

The study provides strong evidence that YAP someday could serve as a therapeutic target for those afflicted by the ringing ears, hearing loss and cataracts that characterize neurofibromatosis type 2, which develops when the NF2 gene malfunctions, according to Duojia Pan, Ph.D., a professor of molecular biology and genetics at the Johns Hopkins University School of Medicine and an investigator of the Howard Hughes Medical Institute.

Pan's lab has long been exploring the signaling pathway known as Hippo, a collective of biochemically linked proteins that functions like a chain reaction in everything from flies and mice to humans in order to keep organs appropriately sized by relaying a "stop growing" message.

It was in 2003 that Pan's team identified the gene they named Hippo when they saw that an abnormal copy of it led to an unusually large eye in a developing fruit fly. Two years later, they established that Hippo sits in the middle of a succession of signals working together to limit the

expression of genes that otherwise promote cell division and cell survival. In 2007, they showed that by genetically manipulating the hippo pathway in a mouse liver, the organ grew to five times its normal size and became cancerous.

The new experiments not only reveal the mechanism of a disease gene — recent studies estimate that the incidence of neurofibromatosis type 2 may be as high as 1 in 25,000 people — but also move researchers closer to putting their hands on Hippo's trigger, where Pan thinks "the key to organ size control lies."

The team discovered the YAP-NF2 link by studying mice that had been genetically altered so that their livers were missing the NF2 protein.

"We found out that mutatating NF2 in mouse liver leads to tumor formation," Pan says. "The liver lacking NF2 was profoundly enlarged by tumors, the same as those in which we previously had perturbed the Hippo pathway."

The hypothesis was that NF2, via the Hippo pathway, suppresses YAP, Pan explains: If removing NF2 resulted in too much YAP, which caused liver tumors, then getting rid of YAP should correct the problem.

To test this, the team genetically altered those mice whose livers were missing the NF2 protein by breeding them to mice that enabled the silencing of the YAP gene. Some of the progeny had no NF2 and no YAP. As a byproduct, the same breeding also produced some progeny that had no NF2 and 50 percent of YAP activity.

"We found we could correct the problem by shutting down YAP," Pan said, "and more than that, we were surprised to discover that even just tamping down the YAP activity by 50 percent resulted in largely normal-looking liver tissue."

The team showed that when they decreased the YAP protein by 50 percent in the liver of a normal mouse (with no NF2 mutation), no abnormal consequences resulted. However, when they did the same in the context of having removed NF2, the happy consequence was that the liver was appropriately sized and tumor free.

“The exquisite sensitivity of the NF2-deficient tumors to YAP was striking,” Pan says. “This is very powerful, positive data, which we discovered by accident during the process of breeding the mutant mice.”

“This matter of sensitivity makes YAP an important potential therapeutic target,” Pan says. “The level of YAP is very critical for NF2-related tumor development. If someone made a drug to target this protein, it only has to be potent enough to weaken its activity by 50 percent to see a consequence.”

More information: www.cell.com/developmental-cell

Provided by Johns Hopkins University