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Complex interactions between proteins Rbm38 and p53 govern tumor suppression, aging

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Scientists have long known the p53 protein suppresses tumors. However, a recent animal study by UC Davis researchers has uncovered a complicated relationship between p53 and another protein, Rbm38, highlighting how the body calibrates protein levels. Too much Rbm38 reduces p53 levels, increasing the risk of cancer. Too little Rbm38 allows p53 overexpression, causing premature aging. The study was published in the journal *PNAS* on Dec. 15.

"The p53 protein is necessary for tumor suppression," said Xinbin Chen, professor at the UC Davis Schools of Medicine and Veterinary Medicine. "When Rbm38 suppresses p53, organisms develop tumors. Knocking out Rbm38 increases p53, which we thought might be a good thing. But too much p53 suppresses cell-cycle progression, causing cell death, premature aging and even cancer."

The relationship between p53 and Rbm38 can best be described as a loop: p53 regulates Rbm38 expression, while Rbm38 suppresses p53. Sometimes the results are unpredictable, even contradictory. Higher Rbm38 levels have been found in certain breast and colorectal cancers and dog lymphoma. However, increased Rbm38 is also associated with better prognoses in glioblastoma, ovarian cancer and other forms of breast cancer.

Considering the complex role Rbm38 plays in cancer, Chen and his team

wanted to understand what would happen if Rbm38 was removed from the equation. Would increased p53 levels enhance tumor suppression?

The answer was a resounding no. Knocking out Rbm38, and thus increasing p53, caused problems with blood formation, increased sensitivity to ionizing radiation and premature aging.

"We found that the mice had problems with wound healing, anemia and other aging phenotypes," notes Chen. "Increased p53 levels cause apoptosis, which leads to shorter lifespans."

Perhaps most surprising, the animals also had increased cancer risk, boosted by the accelerated aging. The loss of Rbm38 influenced a number of inflammatory genes associated with cancer. This was particularly apparent in mice without p53, as well as those that had lost p53 function with age.

These intricate interactions are cause for both caution and excitement. While too much p53 can be a bad thing, carefully manipulating these two proteins could have therapeutic benefits.

"The mutual regulation between Rbm38 and p53 is critically important to both aging and tumorigenesis," said first author Jin Zhang. "It's possible we can target Rbm38 to make p53 levels go up in tumor cells, which could kill tumor cells and suppress cancer progression."

More information: Mice deficient in Rbm38, a target of the p53 family, are susceptible to accelerated aging and spontaneous tumors , *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1415607112

Provided by UC Davis