Deficiency in p53 anti-tumor protein delays DNA repair after radiation

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Researchers at Moffitt Cancer Center have found that a deficiency in an important anti-tumor protein, p53, can slow or delay DNA repair after radiation treatment. They suggest that this is because p53 regulates the expression of two enzymes (JMJD2b and SUV39H1) that control the folding of DNA.

According to the researchers, p53 is highly inducible by radiation. Activation of p53 stabilizes chromosomes by promoting the repair of heterochromatin DNA, which controls the expression of nearby genes and ensures accurate distribution of chromosomes during cell division.

Their findings, which published online Feb. 4 in *Oncogene*, are significant because they shed light on the consequence of p53 deficiency that frequently occurs in tumors and further explain the function of p53 in the development of cancer.

Crucial to multicellular organisms, p53 is a tumor suppressor that regulates the cell cycle and helps prevent cancer by maintaining genetic stability and inhibiting gene mutation. But after irradiation, p53 deficiency results in abnormal levels of SUV39H1 and JMJD2b, enzymes that play a vital role in the structure of chromosomes, especially in DNA damage control and repair.

"Different tumor types have variable responses to ionizing radiation," explained study lead author Jiandong Chen, Ph.D., senior member of the Cancer Biology and Molecular Medicine Program at Moffitt. "Radiation therapy is more effective if tumors are defective in repairing damaged DNA. The p53 pathway is compromised to different degrees in all tumors, which may explain the fact that radiation often kills tumor cells more than normal cells."

In this study, the researchers worked with multiple cancer cell lines.

"We found that p53 activates JMJD2b and represses SUV39H1," Chen said. "Depletion of JMJD2b, or sustained expression of SUV39H1, delays the repair of heterochromatin DNA after ionizing radiation," explained Chen. "The DNA repair function of p53 may be particularly important in higher organisms because of the increased complexity of their genomes."

Although they note that there is no general consensus on the relationship between p53 mutation status and treatment response, in certain narrow settings such as breast cancer, p53 mutation is associated with favorable response to chemotherapy.

"We can conclude that the chromatin modifiers SUV39H1 and JMJD2b are important mediators of p53 function in maintaining the stability of highly repetitive DNA sequences, and developing new drugs that target these enzymes may benefit cancer therapy," the researchers wrote.

More information:
www.nature.com/onc/journal/vao …
/full/onc20136a.html

Provided by H. Lee Moffitt Cancer Center & Research Institute