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Researchers discover how tumor suppressor inhibits cell growth

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Genes that inhibit the spontaneous development of cancer are called tumor suppressor genes. One of the major tumor suppressors is p53, a protein that acts in the cell nucleus to control the expression of other genes whose products can inhibit cell proliferation (increase in cell number) and cell growth (increase in cell size). Abnormal cell proliferation and growth are characteristics of cancer. Scientists previously knew which p53 target genes inhibit cell proliferation, but those required for inhibition of cell growth were unknown.

New work by researchers at the University of California, San Diego School of Medicine describes the mechanism by which p53 regulates cells and protects them against DNA damage that might lead to cancer. The study shows that two p53 target genes – called Sestrin1 and Sestrin2 – provide an important link between p53 and a protein kinase called mTOR, a central regulator of cell growth. mTOR is the target for the inhibitory activity of the immunosuppressive drug rapamycin, recently found to have anti-cancer activity.

The discovery by Michael Karin, Ph.D., professor of pharmacology in the Laboratory of Gene Regulation and Signal Transduction at the UC San Diego School of Medicine, and postdoctoral research fellow Andrei V. Budanov, Ph.D, will be published in the August 8 issue of the journal *Cell*.

"The two Sestrin genes appear to be the missing piece of the puzzle that explains how p53 can inhibit the mTOR pathway and thereby negatively

regulate cell growth," said Budanov, who added that while the connection between the two was known, the mechanism wasn't previously understood. The finding may prove to be very important in scientists' search for novel inhibitors that stop or slow cancer tumor growth.

In fact, Budanov obtained results suggesting that the two Sestrins may be tumor suppressors in their own right. DNA damage (genotoxic stress) triggers two major biological responses in mammals: cell cycle arrest, which allows repair and survival of the cell; and apoptosis or cell death – a process in which damaged cells, which could otherwise give rise to cancer, are eliminated.

The major tumor suppressor p53 can either inhibit cell proliferation and cell growth or induce cell death; its different functions are mediated through numerous target genes and depend on the extent of damage to the cell. As more than half of human cancers either lost p53 expression or express a defective version of p53, understanding the mechanisms by which p53 accomplishes its critical tumor suppressive function may lead to development of new cancer preventives and therapeutics.

The UCSD researchers wondered what target genes would allow p53 to inhibit cell growth. The central regulator of cell growth is the protein kinase mTOR, whose activity is inhibited by rapamycin, which is used in prevention of organ transplant rejection. Recent work indicates that rapamycin may also be used to inhibit the growth of tumors and render them more susceptible to chemotherapy.

Previous studies conducted by Budanov showed that the Sestrin1 and Sestrin2 proteins, which are expressed in response to genotoxic stress, serve a protective function and may also inhibit cell growth. It has also been shown that Sestrin1 and 2, as well as their master regulator p53, can control the accumulation of reactive oxygen species (ROS), which play

important roles in cell signaling. Under genotoxic stress, ROS levels can increase dramatically, which can lead to significant damage to cell structures, resulting in oxidative stress.

"We have now shown that in addition to controlling ROS accumulation, Sestrins and p53 also inhibit cell growth by inhibiting the activity of mTOR. This explains how p53 functions as a potent regulator of so many aspects of cell physiology and provides protection against DNA damage and stress," said Budanov.

Knockout mouse models of Sestrin1 and 2 will be an important tool for studying their role in carcinogenesis, according to the researchers. Karin adds that small molecules that mimic the molecular actions of the Sestrins can be used to control cell metabolism and regain control over cancer cells that have lost their p53.

Source: University of California - San Diego