MedicalXpress

Stabilizing cancer-fighting p53 can also shield a metastasis-promoter

May 22 2008

Efforts to protect the tumor-suppressor p53 could just as easily shelter a mutant version of the protein, causing cancer cells to thrive and spread rather than die, according to research by scientists at The University of Texas M. D. Anderson Cancer Center reported in the current issue of the journal *Genes and Development*.

"As we develop therapies to restore the function of p53, we need to make sure we first know what version of this gene is present in a patient's tumor and then decide how to treat it," said senior author Guillermina Lozano, Ph.D., professor and chair of M. D. Anderson's Department of Cancer Genetics.

The research shows that attempting to restore normal expression of p53 protein by blocking another protein that normally degrades p53 can have the perverse effect of protecting mutated p53 and promoting metastasis.

The p53 gene is inactivated in many types of cancer. Its normal role is to halt the division of a defective cell and then force the cell to kill itself or deprive the cell of its ability to reproduce. As such, reactivation of p53 is thought to have great therapeutic potential.

Normally, p53 levels are low, but it springs into action in response to DNA damage or activation of cancer-promoting genes, or oncogenes.

Lozano, an expert on mouse models of human cancer, and colleagues developed mice with a specific mutation of p53 that mimics a common

genetic mutation in human cancers. The mutated gene, called p53H, expresses a defective version of the p53 protein.

When mice had the p53H mutation on both genes (p53 H/H), the researchers found that the p53 protein was not detectable in normal tissue but was present in 79 percent of tumors. However, tumors in these mice did not metastasize.

Enter Mdm2, a protein whose normal job is to degrade p53 when it's no longer needed. Mdm2 also degrades the mutated version of the p53 protein.

The researchers developed p53 mutant mice that lacked one or both copies of Mdm2. Mice with the double-mutant p53 that also had no Mdm2 died sooner and developed more aggressive metastatic tumors than mice with only the p53 mutation.

The frequency of metastasis went from zero in the p53 H/H with normal Mdm2, to 9 percent in mice lacking one copy of Mdm2 to 17 percent in mice with no Mdm2. Metastasis - the invasive spread of cancer to other organs - causes 90 percent of all human cancer deaths.

Absence of a second tumor-suppressing gene, p16, also promotes stability of mutant p53.

"The importance of this study cannot be overemphasized," the researchers concluded. Drugs that try to protect normal p53 by inhibiting the p53-degrading protein Mdm2 also would protect mutant p53 "with dire consequences."

By the same token, chemotherapy that seeks to stabilize p53 could also stabilize the mutant version. Detecting the type of p53 present in a tumor is possible with current lab technology, Lozano said.

The study raises the possibility of suppressing cancer metastasis by eliminating mutant p53 stability, which the researchers note is more feasible than converting mutant p53 to the normal type.

Source: University of Texas M. D. Anderson Cancer Center