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Study details regulation of vital tumor suppressor gene p53

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So vital is the p53 tumor suppressor gene in controlling cancer that its dysfunction is linked to more than half of human cancers. At the same time, the gene's capacity for shutting down cell growth, even causing cells to commit suicide if necessary, is so absolute that it must be tightly regulated to maintain the optimal balance between protecting against cancer and permitting normal growth.

Now, a study by scientists at The Wistar Institute reveals new levels of subtlety in the body's management of this all-important tumor suppressor gene and the protein it produces. The experiments show that, while the addition of a specific molecule at a particular site on the p53 protein prevents it from acting, the addition of a second copy of the same molecule at the same site reverses the effect, sending p53 into action. Further, removal of the second copy returns the protein to its repressed state.

In addition to the implications for understanding the activity of the p53 gene, the findings also outline an important new cycle of gene-regulating modifications involving the addition and removal of the molecules, called methyl groups, that may be widespread in the genome. A report on the study appears in the September 6 issue of *Nature*.

"The p53 tumor suppressor is extremely potent in halting cell growth," says Shelley L. Berger, Ph.D., the Hilary Koprowski Professor at The Wistar Institute and senior author on the study. "So, as critical as p53 is in protecting against the unchecked growth of cancer, you don't want it

constantly on. If it were always on, your cells wouldn't be able to grow normally. Yet it needs to be constantly on call for activation against cancer and other aberrant cellular developments. Our study shows one way that the cell, working at one particular location on the p53 protein, maintains a nuanced but firm control over the gene's activity."

Responsible for tumor suppression throughout the body, the p53 gene is mutated or otherwise disabled in a majority of human cancers. When working properly, the protein produced by the p53 gene acts by binding to DNA to activate other genes that direct cells with damaged DNA to cease dividing until the damage can be repaired. Cells with such damage include cancer cells, since all cancers track to genetic flaws of one kind or another, whether inherited or acquired. If repairs cannot be made, p53 commands the cells with damaged DNA to self-destruct so they are no longer a danger to the body.

This powerful ability of p53 to shut down cell division and induce cell death points to why fine-tuned regulatory mechanisms such as the one outlined in the new study are crucial for cellular survival.

In a previous study published in *Nature* in November 2006, Berger and her colleagues showed that the addition of a single methyl group – a tiny molecule consisting of one carbon and three hydrogen atoms – at a specific site on the p53 protein was sufficient to repress its activity. In the current study, the researchers found that the addition of a second methyl group at the same site reversed the effect. With the pair of methyl groups in place, the site is able to attract and bind a molecule called 53bp1, itself required for the p53 protein to bind to DNA to launch the genes responsible for carrying out its tumor-suppressing mission. With one methyl group in place, the site is said to be monomethylated; with two in place, it is dimethylated.

"An important finding from our study is that the dimethylation mark is

the required recognition site for 53bp1 on the p53 protein," says Jing Huang, Ph.D., lead author on the Nature study. "If you remove that mark, 53bp1 cannot associate with the p53 protein, and p53's activity will be reduced."

Source: The Wistar Institute