Newly found enzymes may play early role in cancer

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Researchers have discovered two enzymes that, when combined, could be involved in the earliest stages of cancer. Manipulating these enzymes genetically might lead to targeted therapies aimed at slowing or preventing the onset of tumors.

"We could conceivably reactivate a completely normal gene in a tumor cell - a gene that could prevent the growth of a tumor if reactivated," says David Jones, Ph.D., professor of oncological sciences at the University of Utah and senior director of early translational research at the university's Huntsman Cancer Institute (HCI).

"We believe this could be one of the earliest processes to go wrong in cancer," he adds. "By manipulating these enzymes, we could possibly prevent or slow the onset of tumors."

The enzymes appear to control an "on-and-off switch" for critical genes that could trigger cancer or numerous other diseases and birth defects. The research is published in the December 26 issue of *Cell*.

Using zebrafish that share similar genetics to humans, the HCI scientists identified a previously unknown enzyme process that controls the levels of DNA methylation on genes.

"Methylation is a cellular process that is required for healthy cell growth and development, but it can go awry in cancer and diseased cells," says Brad Cairns, Ph.D., HCI investigator and professor of oncological sciences at the University of Utah. "You can think of DNA methylation as an on-and-off switch. Methylation silences or 'shuts off' genes that need to be turned off or are not functioning as they should, whereas the reverse process called demethylation 'turns on' healthy genes and genes needed at critical times in development," he says.

In cancer, this methylation process goes haywire, leading to tumor growth. Genes that should be "turned on" are not and vice versa.

The significance of this research is the discovery of two enzymes involved in DNA demethylation. Defects in DNA methylation balance are strongly associated with the early development of cancer, other diseases and birth defects, and the scientists say their study is the first clear evidence that this enzyme system plays a critical role in maintaining this balance. They also believe it's a process that can be reversed.

Further research will reveal if DNA methylation levels can be manipulated genetically. If so, it could lead to drugs to reactivate particular genes and suppress tumor growth. Remarkably, this system also helps protect the genome from mutations.

"We discovered a pair of enzymes that can remove methylated DNA, but if these enzymes work improperly, they will instead enhance the rate of mutations in methylated DNA and cause cancer progression," says Jones. "The question now is, when they work improperly, can we find ways to shut them off and prevent these mutations?"

The enzymes leading to DNA demethylation involve the coupling of a 5-meC deaminase enzyme, a G:T glycosylase enzyme and Gadd45, which is not an enzyme.

Source: University of Utah