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Researchers develop a screen for identifying new anticancer drug targets

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Tumor suppressor genes normally control the growth of cells, but cancer can spring up when these genes are silenced by certain chemical reactions that modify chromosomes. Among the most common culprits responsible for inactivating these genes are histone deacetylases, a class of enzymes that remove acetyl groups from DNA-scaffolding proteins, and DNA methyltransferases, a family of enzymes that add methyl groups to DNA.

Drugs that counteract these enzymes, and thus reactivate tumor suppressor genes, are promising cancer therapies. For example, histone deacetylase inhibitors have been approved for the treatment of a type of T cell lymphoma, and are being tested in clinical trials for the treatment of a wide range of cancers. Similarly, DNA methyltransferase inhibitors have been approved to treat a certain kind of leukemia, and are undergoing clinical studies for the treatment of other cancers. But these medications can have serious side effects. Now, Fox Chase Cancer Center postdoctoral associate Andrey Poleshko, PhD, along with Research Professor Richard A. Katz, PhD, and their colleagues have developed a screen to identify proteins that work in conjunction with these enzymes to repress gene expression. They will present their results at the AACR 102nd Annual Meeting 2011 on Tuesday, April 5.

Finding additional proteins that inactivate tumor suppressor genes, and understanding how they work, could lead to the broadening of this class of therapies beyond the two enzyme families, Poleshko said. "If we can find a way to block the action of such proteins, it may be possible to

reactivate aberrantly silenced tumor suppressor genes and restore controlled growth in certain cancer cells," he noted. Such an approach would avoid interfering directly with the vital chromosome-modifying enzymes.

The researchers genetically programmed human cells to glow fluorescent green upon reactivation of the silent genes they harbor. By shutting down the activity of genes one by one and observing whether cells turned green, they were able to identify factors that help to suppress gene expression.

The method was efficient enough to permit screening of the entire genome, including 21,122 genes, and revealed 128 factors that are involved in regulating gene expression.

Provided by Fox Chase Cancer Center