

Gene packaging tells story of cancer development

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To decipher how cancer develops, Johns Hopkins Kimmel Cancer Center investigators say researchers must take a closer look at the packaging.

Specifically, their findings in the December 2, 2008, issue of *PLoS Biology* point to the three dimensional chromatin packaging around genes formed by tight, rosette-like loops of Polycomb group proteins (PcG). The chromatin packaging, a complex combination of DNA and proteins that compress DNA to fit inside cells, provides a repressive hub that keeps genes in a low expression state.

"We think the polycomb proteins combine with abnormal DNA methylation of genes to deactivate tumor suppressor genes and lock cancer cells in a primitive state," says Stephen B. Baylin, M.D., Virginia and D.K. Ludwig Professor of Oncology and senior author.

Prior to this discovery, investigators studying cancer genes, looked at gene silencing as a linear process across the DNA, as if genes were flat, one dimensional objects. Research did not take into account the way genes are packaged.

To better understand the role of the PcG packaging, the team compared embryonic cells to adult colon cancer cells. The gene studied in the embryonic cells was packaged by PcG proteins, in a low expression state, and had no DNA methylation. When the gene received signals for cells to mature, the PcG loops were disrupted and the gene was highly

expressed. However, when the same gene was abnormally DNA methylated, as is the case in adult, mature colon cancer cells, the PcG packaging loops were tighter and there was no gene expression. "These tight loops touch and interact with many gene sites folding it into a structure that shuts off tumor suppressor genes," says Baylin. However, when the researchers removed DNA methylation from the cancer cells, the loops loosened somewhat, back to the state of an embryonic cell, and some gene expression was restored.

DNA methylation is a normal cellular process, but when it goes awry and genes are improperly methylated, it can shut down important tumor suppressing cell functions.

Demethylating agents, drugs that target and remove abnormal DNA methylation from genes, have been introduced as potential new cancer therapies. For these therapies to be fully effective, Baylin says, researchers may also need to look for agents that disrupt PcG loops.

Source: Johns Hopkins Medical Institutions

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