Age-Related Epigenetic Changes Up the Cancer Risk

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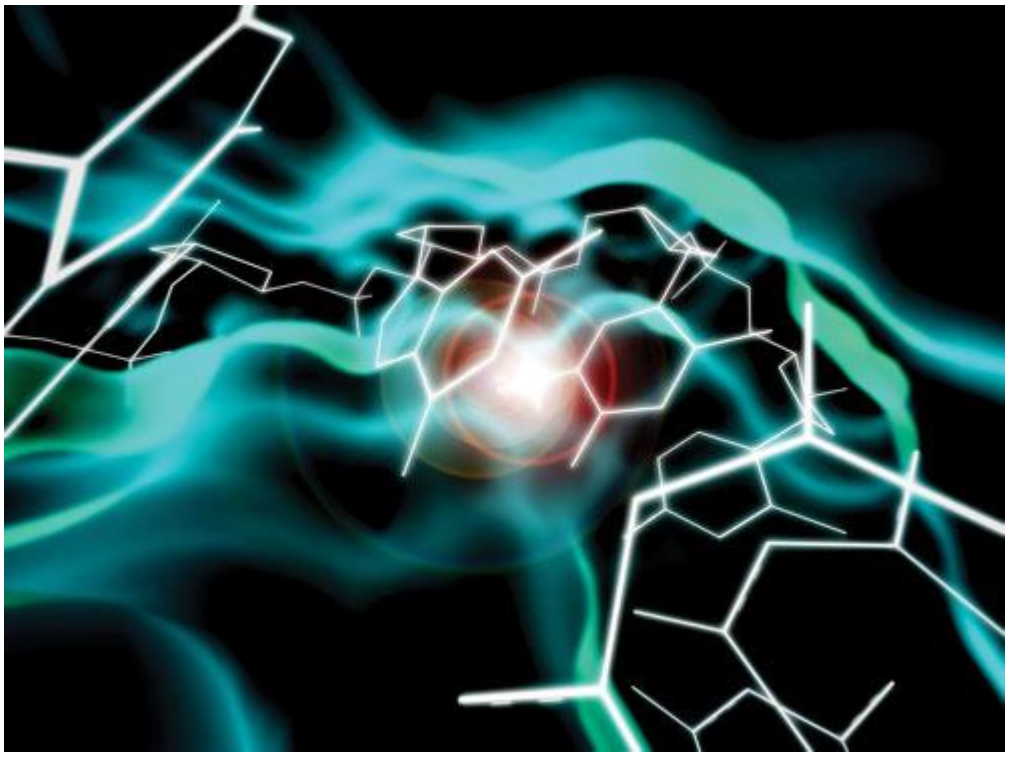

Researchers from the **NIH** say they have demonstrated that a subset of human genomic sites that become increasingly methylated with advancing age are also disproportionately methylated in a variety of human cancers. Their findings ("Genome-wide age-related **DNA methylation** changes in blood and other tissues relate to histone modification, expression and **cancer**") are published in Carcinogenesis.

"You can think of methylation as dust settling on an unused switch, which then prevents the cell from turning on certain genes," said Jack Taylor, M.D., Ph.D., from the **National Institute of Environmental Health Sciences**. "If a cell can no longer turn on critical developmental programs, it might be easier for it to become a cancer cell."

Dr. Taylor and colleague Zongli Xu, Ph.D., made the discovery using blood samples from participants in the Sister Study, a nationwide research effort to find the environmental and genetic causes of breast cancer and

other diseases. More than 50,000 sisters of women who have had breast cancer are participating in the study.

The researchers analyzed blood samples from 1,000 women, using a microarray that contained 27,000 specific methylation sites. Nearly one-third of the sites showed increased DNA methylation in association with age. They then looked at three additional datasets from smaller studies that used the same microarray and found 749 methylation sites that behaved consistently across all four datasets.

As an additional check, they consulted methylation data from normal tissues and seven different types of cancerous tumors in the Cancer Genome Atlas and the National Human Genome Research Institute.

“Based on the Cancer Genome Atlas data, we show that these age-related changes are largely concordant in a broad variety of normal tissues and that a significantly higher (71–91%, $P < 10^{-74}$) than expected proportion of increasingly methylated arCpGs (IM-arCpGs) were overmethylated in a wide variety of tumor types,” write the investigators. “IM-arCpGs sites occurred almost exclusively at CpG islands and were disproportionately marked with the repressive H3K27me3 histone modification ($P < 1 \times 10^{-50}$).

Dr. Taylor said that DNA methylation appears to be part of the normal **aging** process and occurs in genes involved in cell development. Cancer cells often have altered DNA methylation, but the researchers were surprised to find that 70–90% of the sites associated with age showed significantly increased methylation in all seven cancer types. Dr. Taylor suggests that age-related methylation may disable the expression of certain genes, making it easier for cells to transition to cancer.

For future work, Drs. Xu and Taylor want to examine more samples, using a newer microarray that will explore methylation at 450,000 genomic methylation sites. The additional samples and larger microarrays, which will provide 16 times more genomic coverage, will allow them to address whether environmental exposures during adulthood or infancy affect methylation profiles, explained the scientists. These additional studies will help scientists better understand why methylation happens as people head toward their retirement years.