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Disorder in gene-control system is a defining characteristic of cancer, study finds

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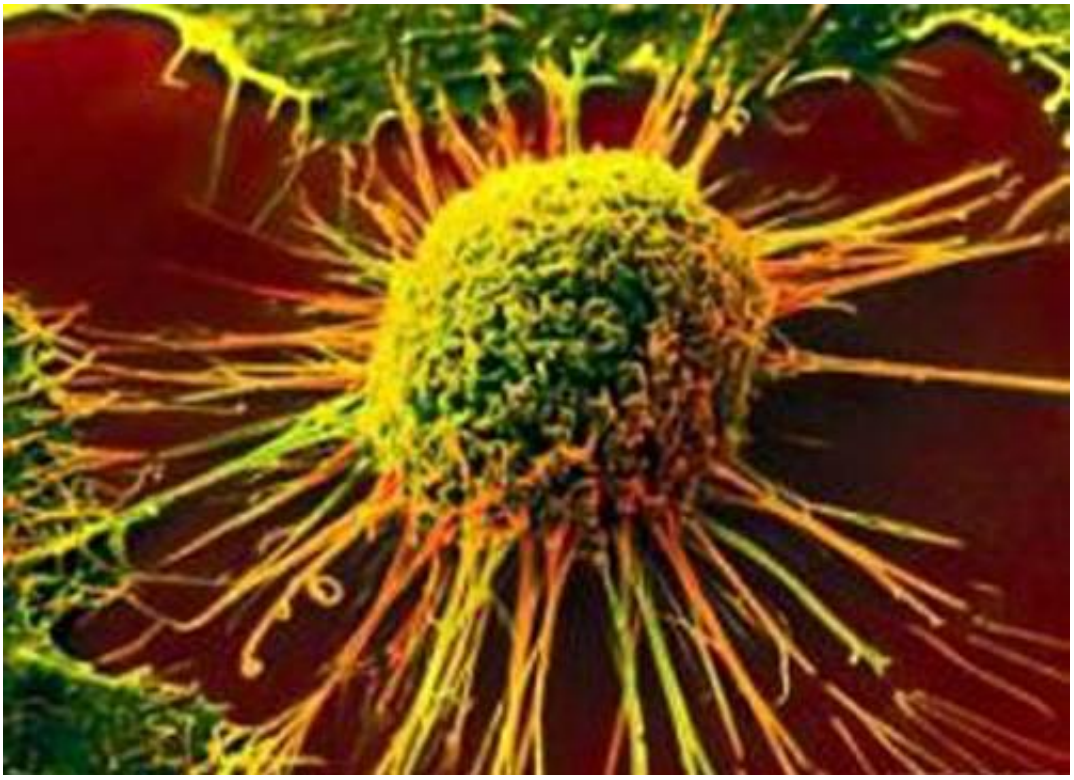

The genetic tumult within cancerous tumors is more than matched by the disorder in one of the mechanisms for switching cells' genes on and off, scientists at Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard report in a new study. Their findings, published online today in the journal *Cancer Cell*, indicate that the disarray in the on-off

mechanism - known as methylation - is one of the defining characteristics of cancer and helps tumors adapt to changing circumstances.

The researchers also showed that derangement in the methylation process has a direct bearing on the effectiveness of cancer therapy. In patients with chronic lymphocytic leukemia (CLL), they found that treatment produced shorter remissions if the tumor tissue showed signs of highly disorganized methylation. The findings demonstrate that such disorganization can actually benefit tumors and render them less vulnerable to anti-cancer drugs.

"The behavior of a cancer cell is dictated not only genetics - by the particular set of mutated genes within it - but also by epigenetics, the system for controlling the expression of genes," said Catherine Wu, MD, of Dana-Farber, Broad Institute associate members, and a co-senior author of the paper. "Expressed genes are active: their information is being used by the cell. One of the ways that cells control gene expression is by attaching chemical units called methyl groups to sections of DNA in a process called methylation. The exact arrangement of methyl groups helps determine which genes are expressed.

"We know that tumors are composed of many subgroups of cells, each with its own array of gene mutations," she continued. "In this study, we wanted to see if that type of genetic diversity coincides with epigenetic diversity. In other words, does the range of methylation patterns mirror the genetic variety we find in tumors?"

To find out, Wu's team partnered with co-senior author Alexander Meissner, PhD, senior associate member of the Broad Institute, using a new technology known as bisulfite sequencing, which allows scientists to track the presence or absence of methyl groups at specific rungs on the DNA ladder. They also devised a simple measure called PDR - percent

discordant reads - for quantifying the extent of irregular methylation within a tissue sample. The higher the PDR, the more variability in how the methyl groups are arranged.

They measured the PDR and the amount of genetic diversity in 104 CLL samples and 27 samples of normal B cells (CLL is a cancer of B cells, which help fight disease). "We thought the epigenetic structure would map right onto the genetic structure," said Meissner, "that is, the degree of genetic diversity in each sample would match the variation in methylation marks in an organized fashion."

To their surprise, the methylation patterns showed a tremendous degree of random disarray. Meissner explains, "We know that individual tumors are checkered with genetically distinct groups of cells. Bisulfite sequencing enabled us to see that the placement of methyl groups across tumor cell DNA also varies substantially among cells in the same tumor. In fact, disorderly methylation pervades the entire tumor."

The results revealed that the diversity within individual tumors apparently proceeds along two independent, yet interrelated tracks: one resulting in a genetic hodgepodge of cell groups, the other resulting in haphazard methylation.

The methylation irregularities, technically known as "local methylation disorder," were highly evident in CLL and, the authors found, in other types of cancer as well.

Because methyl groups control the expression of genes, disorderly methylation might be expected to cause gene activity to be wildly inconsistent even within a single tumor. This, in fact, is what the research team found.

The disruption of methylation machinery might seem hazardous to

tumor survival, but the researchers theorize that tumors can turn the disorderliness to their own advantage.

"Just as in the case of genetic heterogeneity within tumors, increased random variation of the epigenetic profile may augment the diversity of malignant cells," said Dan Landau, MD, PhD, of Dana-Farber and the Broad Institute, a co-lead author of the paper. "The ability of cancers to maintain high levels of diversity is an effective hedging strategy, enabling them to better adapt to therapy, as well as enhancing the 'trial and error' process in search of better evolutionary trajectories."

Added co-lead author Kendall Clement of Harvard University and the Broad Institute, "This research presents a compelling argument for how disrupted methylation leads to increased cancer progression and heterogeneity."

Wu remarked, "Cancer survives through some wildly inventive ways. Methylation disorder is one of the ways it creates the conditions that enable it to adapt."

Provided by Dana-Farber Cancer Institute