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Changes in cancer epigenome implicated in chemotherapy resistance and lymphoma relapse

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Genomic studies have illuminated the ways in which malfunctioning genes can drive cancer growth while stunting the therapeutic effects of chemotherapy and other treatments. But new findings from Weill Cornell Medical College investigators indicate that these genes are only partly to blame for why treatment that was at one point effective ultimately fails for about 40 percent of patients diagnosed with the most common form of non-Hodgkin Lymphoma.

The study, published April 20 in *Nature Communications*, suggests that global changes in cancer cells' epigenome that turn normal genes on when they should be off, and vice versa, may be a powerful force in determining disease progression. The investigators made this discovery by reviewing biopsies taken from patients with diffuse large B-cell lymphoma (DLBCL) before treatment and again after the treatment failed and cancer resurged. They compared the two samples and found that the epigenome in these patients' cancer cells had substantially changed after treatment.

They also found that the global epigenome of pre-treatment biopsies was substantially different in patients whose disease did not recur compared to patients whose disease came back. The researchers found more cell-to-cell heterogeneity, that is, a greater variety of epigenetic patterns in patients who relapsed.

The epigenome, which surrounds genetic DNA like a bubble, is powerful; it can determine which genes are turned on or off, influencing the production of proteins—the workhorses of human biology. The epigenome can modify gene expression by adding or removing a chemical compound, known as a methyl group, to a specific place in a gene's DNA. Adding a methyl group to a gene turns the gene off, and removing a methyl group allows a gene to turn on when it shouldn't.

This explains why the findings are so significant, investigators say, because drugs that disrupt the epigenetic machinery in cancer cells might reverse treatment resistance and help chemotherapy and other drugs to do their jobs.

"This is the first study I know of in cancer that looks at changes in the epigenome before and after treatment, and what we found could ultimately make traditional treatments much more effective," said senior author Dr. Olivier Elemento, an associate professor of physiology and biophysics and head of the Laboratory of Cancer Systems Biology in the HRH Prince Alwaleed Bin Talal Bin Abdulaziz Al-Saud Institute for Computational Biomedicine at Weill Cornell.

"The epigenome is flexible and can change faster than the genome can, but changes in the epigenome are lasting—they are maintained from one cell division to the next," Dr. Elemento said.

Epigenetic modifications can therefore be inherited, or can be influenced by a person's environment, such as diet and pollutants. Yet the cause of global epigenetic changes in cancer, including DLBCL, Dr. Elemento added, is unknown.

To help uncover the role of epigenetic involvement, Dr. Elemento utilized biopsies banked by collaborators Dr. Giorgio Inghirami and Dr. Wayne Tam, who are blood cancer pathology specialists and lymphoma

researchers at Weill Cornell.

In each sample set, investigators looked at sites in the epigenome where a methyl group was added or removed after cancer recurred. They found a change in methylation that occurred between 39,808 and 1,035,960 specific methylation sites, depending on the cancer sample. In addition, they identified between 78 and 13,162 differently methylated regions in the epigenome in relapsed cancer.

"These are massive changes—given that the epigenome has 20 million methylation sites, our study shows that in some cases, up to one-twentieth of the entire epigenome is changed after treatment," Dr. Elemento said. "There are many more epigenetic changes than there are altered genes in DLBCL."

"Once you have changes in methylation, the end result is an imbalanced expression of proteins," added Dr. Inghirami, a professor of pathology and laboratory medicine at Weill Cornell. "The tumor after chemotherapy is not the same as the tumor before treatment. This why it is so critical to have biopsies before any treatment of either primary as well as of relapsed lesions."

Given how important the epigenome seems to be in cancer, the investigators say future success in this new avenue of research and treatment depends on collecting cancer biopsies from patients before and after treatment. They hope that this work will ultimately allow clinicians and researchers to predict treatment resistance in individual patients.

"By studying more samples, it may ultimately be possible to scan the most informative regions of the epigenome of a patient's lymphoma at diagnosis to predict whether treatment will be successful and whether the cancer may recur," said Dr. Tam, an associate professor of clinical pathology and laboratory medicine at Weill Cornell.