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DNA methylation pattern in leukemia only appears to be cancer-typical

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Apart from the hereditary information that is encoded in the sequence of bases in DNA, there is a second code of life: Chemical alterations in DNA or in its packaging proteins form an additional regulatory level that determines which genes are read. The most important element of this "epigenetic" code is the labeling of specific DNA areas with methyl groups.

Cancer researchers have known for a long time that tumors and their original tissue vary in their methylation patterns. However, even in a healthy body, various types of cells in one and the same organ also exhibit substantial variations in methylation. Scientists have recently shown that this also holds true for different maturation stages of one cell type. "In B cells, these maturation-related differences affect 30 percent of the whole genome", says epigenetics researcher Christoph Plass from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg.

The maturation program of B cells, which are part of the immune system, is exceptionally well studied and understood. Plass and colleagues from Heidelberg, Essen, Ulm and the Unites States planned to study the methyl patterns in order to find out which development stage of B cells marks the origin of B-cell chronic lymphocytic leukemia (CLL).

The investigators took blood samples from 268 CLL patients, separated the blood cells in cell sorters using specific B-cell maturation markers

and subsequently analyzed the methylation patterns of each individual maturation stage.

The surprising result was that CLL can develop from almost all maturation stages. The massive methylation variations that have been regarded as cancer-typical so far rather reflect the characteristic patterns of the development stages at the moment of cancerous transformation. The cell freezes this methyl pattern, so to speak, and this is followed by only a few changes that are truly cancer-typical. The research team discovered that leukemias that had arisen from more progressive maturation stages responded significantly better to therapy.

The scientists explain the discrepancies with prior studies based on the fact that the latter compared leukemia cells with the whole pool of B-cell maturation stages. "All differences found were attributed to cancer," says Plass, adding that some previous works on the cancer epigenome will need to be re-interpreted in the light of the current results.

Oncologists have been discussing for a long time the possibilities of using epigenetic differences between healthy cells and cancer cells as potential targets for novel therapies. For example, they have supposed so far that cancer-induced abnormally high methylation reduces the activity of genes with cancer-inhibiting properties. Drugs that prevent methyl groups from attaching to DNA therefore have been thought to be capable of curbing cancer growth.

Now, if the supposedly cancer-typical methyl patterns reflect, for the most part, only variations that are part of the normal development process of cells, then these concepts might have to be revised.

Using advanced bioinformatic methods, the researchers led by Plass were able to calculate the small percentage of truly cancer-specific methyl patterns from the wealth of maturation-related variations. The

researchers must now carefully evaluate the biological relevance of these truly cancer-related differences.

"Up until recently, it was technically impossible to study the various maturation stages in such detail as we have done," Plass says, explaining the surprising finding of his current analysis."It took the advanced sequencing technology and the powerful bioinformatic methods that we have available now to make such a detailed comparison possible.

In a next step, Plass wants to examine in other types of cancer whether the methyl patterns that are believed to be cancer-typical also arise from the normal cellular maturation program. In particular, he plans to study other types of blood cancer as well as cancer of the prostate - an organ in which specialized cells are maturing in a continuous process.

More information: Christopher C Oakes et al. DNA methylation dynamics during B cell maturation underlie a continuum of disease phenotypes in chronic lymphocytic leukemia, *Nature Genetics* (2016). DOI: 10.1038/ng.3488

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