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The Long and Winding Road to Gene Regulation

Small chemical modifications such as DNA methyl groups can tell the cell whether a given gene is expressed or not. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered how the methyl marks can regulate gene activity: They influence where the DNA wraps around its packaging proteins to form complexes called nucleosomes. The removal of the methyl groups makes these nucleosomes unstable, and previously inaccessible DNA regions are released for binding of enzymes that affect gene activity.

The cell precisely controls which genes are active at a given time and which are not. This is, for example, important when a stem cell converts to a specialized cell type during development. Many so-called epigenetic mechanisms are involved in this process. A particularly important epigenetic signal is the methylation of the DNA: individual DNA cytosine groups can be methylated or not, determining whether the information of a gene can be read.

“Numerous studies show dramatic differences in DNA methylation patterns between different cells,” says Dr. Karsten Rippe from the German Cancer Research Center. “However, it remains an open question how changes in DNA methylation affect whether a gene is expressed or not.”

The researchers from the DKFZ suspected that the methylation might change the packaging of DNA: The meter-long DNA molecule is not randomly distributed in the nucleus but orderly packed. The ‘spools’ around which the ‘rope’ of DNA is wound, consist of a complex of histone proteins. The resulting structures – the nucleosomes – are linked by the intervening DNA into a chain.

The DNA parts wound into nucleosomes are often inaccessible to the enzymes that activate and read the genome. Thus, protein binding sites frequently have to be located between the nucleosomes in order to switch a gene on or off.

Rippe's team discovered that the positioning of nucleosomes depends on the methylation of the DNA. The researchers compared differentially methylated DNA in embryonic stem cells and in their differentiated counterparts. Changes in DNA methylation during the cell development appeared to affect the positions of the corresponding nucleosomes. At sites where DNA methylation was replaced by hydroxymethylation, the nucleosomes became labile and could be displaced by the DNA binding protein CTCF. On methylated DNA, however, the nucleosomes were stably associated with the DNA and CTCF could not reach its binding sites.

CTCF is known for its ability to create DNA loops and control the three-dimensional arrangement of the DNA genome in the cell nucleus. It separates active genomic regions from those with no DNA readout to regulate gene expression. As Vladimir Teif, the first author of the study, puts it: “Due to this linkage a DNA methylation signal largely increases its effective range. Rearrangements of the three-dimensional DNA organization result from differential CTCF binding that may comprise regions of up to 100,000 base pairs.”

There are significant differences in DNA methylation between cancer cells and healthy cells. The researchers led by Karsten Rippe now work with samples from leukemia patients to identify patterns of deregulated chromatin organization that can be related to tumor-typical changes in blood cancer cells.

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Teif V.B., Beshnova D.A., Vainshtein Y., Marth C., Mallm J.P., Höfer T. and Rippe K. Nucleosome repositioning links DNA (de)methylation and differential CTCF binding during stem cell development. Genome Res. 24, 1285-1295. DOI: 10.1101/gr.164418.11

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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