Unspooling DNA from nucleosomal disks

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The tight wrapping of genomic DNA around nucleosomes in the cell nucleus makes it unavailable for gene expression. A team of Ludwig-Maximilians-Universitaet (LMU) in Munich now describes a mechanism that allows chromosomal DNA to be locally displaced from nucleosomes for transcription.

In higher organisms the genomic DNA is stored in the cell nucleus, wrapped around disk-shaped particles called nucleosomes, each consisting of two pairs of four different histone proteins and accommodating two loops of DNA. Packed in this way to form chromatin, the DNA is protected, but it is inaccessible to the enzymes that mediate DNA transcription, repair and its replication. However, so-called chromatin-remodeling factors, including histone chaperones, ensure that chromatin is maintained in a dynamic state by locally modifying nucleosome structure, interacting with histone subunits and detaching stretches of the packaged DNA from the nucleosome core.

One such factor is the FACT complex which, unlike other histone chaperones, is essential for cell division and DNA repair. FACT interacts specifically with the H2A-H2B histone dimer, which forms part of the canonical nucleosomal particle. "However, until now, we had no structural insight into how these histones are recognized, and how this interaction between FACT and H2A-H2B relates to other biological functions of the FACT complex" says Professor Andreas Ladurner, who is at the LMU's Adolf Butenandt Institute. "So basically, we had no real idea what a reorganized nucleosome might look like."

FACT masks a DNA-binding site

To close this gap in our knowledge, Ladurner and his colleagues first looked at the structure of the H2A-H2B-binding domain of the FACT complex on its own. "This analysis provided some hints as to how FACT might interact with its histone partners, but not enough information to allow us to propose a molecular mechanism for the reorganization of nucleosomes," reports Maria Hondele, first author of the new study. "However, using high-resolution X-ray crystallography, we were ultimately able to determine the structure of the whole complex formed between FACT and the histone dimer."

The conformation of the complex revealed that binding of FACT blocks a site on the histone dimer that has a high affinity for DNA. This interaction releases the DNA from the nucleosome sufficiently to permit gene transcription to proceed past the nucleosome. "And in contrast to the conventional view, this mechanism works without unwrapping the DNA completely from the nucleosome," says Ladurner. Thus, the new study affords detailed insights into the mechanisms underlying the dynamic regulation of chromatin accessibility in the cell nucleus.

More information: www.nature.com/nature/journal/ … ull/nature12242.html

Provided by Ludwig Maximilian University of Munich

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