Slip-sliding away…

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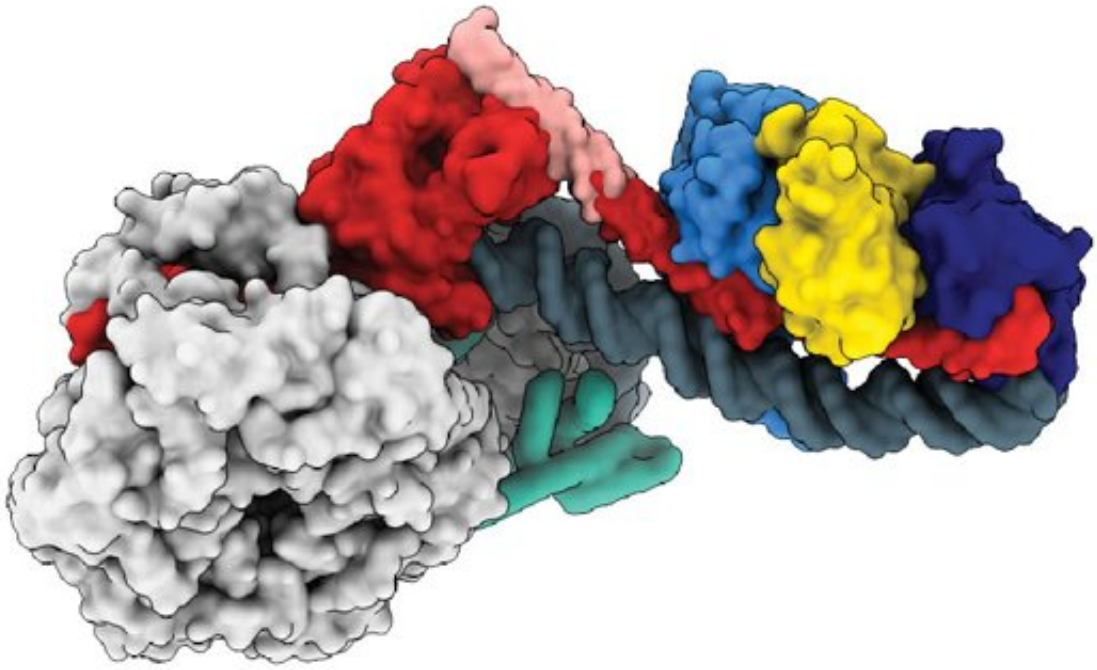

Structural Model of the INO80-Remodeller. Credit: Hopfner-Lab/LMU, Nature

In the cell nucleus, the genomic DNA is packaged into a tightly condensed form, which is referred to as chromatin. The basic unit of chromatin organization is the nucleosome, a DNA-protein complex consisting of a defined length of DNA wrapped around a bead-like structure which is made of histone proteins. The individual nucleosomes are connected by a short length of linker DNA, forming a string of beads which are in turn packed together by special cross-linking proteins. The

detailed structure of chromatin regulates access to the genes, and therefore plays a vital role in the control of gene expression. In response to metabolic signals, environmental changes and developmental processes, mechanisms are triggered that dynamically modify chromatin structure, making genes accessible for activation whose products enable the cell to adapt to changes in local conditions. Large protein complexes called chromatin remodellers play a central role in this process. These molecular machines act locally to disrupt the contacts between nucleosomal histones and DNA and effectively slide the nucleosome along the DNA. Now a research group led by Professor Karl-Peter Hopfner at LMU's Gene Center in collaboration with a team around Dr. Philipp Korber at the Biomedical Center, has dissected the function of an important module of the remodeller INO80 in this process. The new findings have just been published in the journal *Nature Structural & Molecular Biology*.

In a study that appeared in April of this year, Hopfner's team had determined the three-dimensional structure of a large portion of INO80, based on cryo-electron microscopy of the flash-frozen complex bound to a nucleosome. This allowed them to deduce the molecular mechanism that enables INO80 to detach DNA from nucleosomes. The INO80 complex includes a pair of motor proteins which actively feed the exposed linker DNA into and around the nucleosome, effectively sliding the nucleosomal particle with respect to the DNA. In the new paper, Hopfner and colleagues now describe the function of a further critical element of the remodeling machinery. "To our surprise, we found that the INO80 complex includes subunits that serve as an integrated yardstick, which measures the length of the DNA between neighboring nucleosomes," Hopfner says.

Up until now, no high-resolution structural data were available for the Arp8 module of the INO80 complex. This sub-complex is comprised of the protein actin and the actin-related proteins (Arps) Arp4 and Arp8. In

the cell cytoplasm, actin polymerizes into filament networks that constitute a major component of the internal support system that maintains cell shape. This cytoskeleton also plays a vital role in cell migration, and organizes a host of processes including intracellular protein transport. But as Kilian Knoll and Sebastian Eustermann, joint first authors of the new study, point out: "It has been clear for over 20 years that actin is also present in the cell nucleus. It is an integral component of INO80 and related molecular machines, but its function has remained obscure." By determining the crystal structure of the Arp8 module of the INO80 complex, the LMU researchers have now deciphered its function. Arp8 itself interacts with nuclear actin in association with Arp4, and this module then binds to a long helical segment of the INO80 complex. As the authors demonstrate experimentally, this helix is essential for the nucleosome sliding activity of INO80. Recognition of the exposed linker DNA, says Eustermann, triggers remodelling activity, allowing the INO80 motor to drive the DNA around the nucleosome. If the linker overhang is too short, movement of the DNA comes to a halt. The Arp8 module plays a direct and vital role in the remodelling process insofar as it measures the length of the exposed linker DNA, i.e., the distance between adjacent nucleosomes, and stimulates nucleosome repositioning. The LMU study thus identifies, for the first time, a molecular function for nuclear actin in the restructuring of chromatin. Since remodelling complexes are known to be involved in tumorigenesis, these new insights into their modes of action may have implications for cancer therapy.

More information: Kilian R. Knoll et al. The nuclear actin-containing Arp8 module is a linker DNA sensor driving INO80 chromatin remodeling, *Nature Structural & Molecular Biology* (2018). DOI: 10.1038/s41594-018-0115-8