Protein complex FACT able to unwind nucleosomes without expending energy

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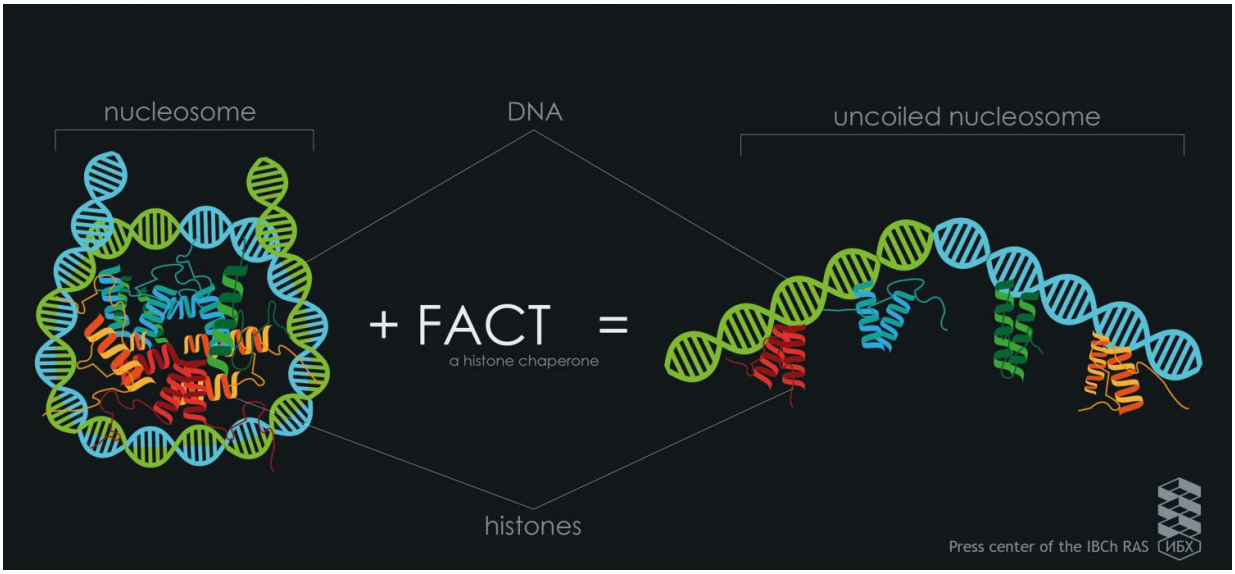

Credit: Snezana Mazhekenova.

A group of researchers from the Institute of Bioorganic Chemistry of the RAS and Moscow State University, in collaboration with the University of Utah, has for the first time successfully made use of the FRET microscopy method to demonstrate the ability of nucleosomes to reversibly unwind under the action of FAST without expending any energy. The data obtained will illuminate the role this protein complex plays in actively dividing cells in tumor tissues. The results were published in *Nature Structural & Molecular Biology*.

"This research work can be viewed as a perfect example of the successful collaboration between the two research groups," says Kseniya Kudryashova, Ph.D., a researcher with the Bioengineering Department of the Institute of Bioorganic Chemistry of the Russian Academy of Sciences.

The DNA molecule is compactly coiled within cell nuclei. Correctly placed genomes provide special proteins that, together with the DNA, form a structure called chromatin. The nucleosome acts as the unit of compaction for the chromatin. Nucleosomes are often compared to a thread spool, in which the DNA 'thread' is wound on a barrel of histone proteins – the 'spool.' The dense packing of chromatin in the nucleus is violated during transcription, when there is an active reading of genetic information from DNA. The FACT Conservative Protein, which has become a research focus, facilitates the transcription of chromatin protein. Although the interaction of FACT with the nucleosome has been demonstrated in earlier works, this is the first time that scientists have discovered the important details of the process.

The researchers studied the interaction of the FACT protein factor with the spFRET-microscopy nucleosome method. "As a result of the productive work that was started back in 2010, scientists were able to develop the spFRET method from scratch and apply it specifically in the study of nucleosomes," explains Kudryashova. "Based on this method, scientists are able to work with the microscopy of single molecules. Fluorescent markers are introduced in adjacent loops of the nucleosomal DNA. One of the markers serves as an energy donor, while the other as the acceptor. The donor can be excited using a laser of a specific wavelength. If the donor is located close to the acceptor, energy is transferred to the acceptor. The closer the position of the marker, the brighter the signal from the acceptor. In this way, it is possible to monitor the distance between adjacent DNA loops and assess how much the nucleosome is compactly folded. This is a unique development for

Russia that allows us to study structural changes in the nucleosome complexes with a resolution of a few nanometers, with the information collected from each molecule individually."

Using this method, scientists for the first time demonstrated the ability of the nucleosome to unwind reversibly under the action of FACT in vitro (test tube) without expending energy, which is quite unusual, given that the ATP-dependent remodeling complexes for chromatin reorganization expend a lot of energy.

During the formation of the FACT-nucleosome complex, DNA strands are completely straightened, but remain bound to the histone proteins. If FACT is removed from the complex, then everything goes back to square one—the DNA nucleosome winds itself on the base of the histones. Thus, FACT is a rare example of an ATP-independent (with non-natural sources of energy) chromatin-remodeling complex.

According to Mary Valieva, the first author of the article, the ability of FACT to reversibly change its chromatin structure in a cell may activate certain genes through the reorganization of DNA components. However, nothing more specific can be said about similar processes occurring inside cells, as the issue is still poorly understood. The author notes that the study of this protein complex is important not only scientifically, but also from a medical perspective. This is because tumor tissues contain large quantities of FACT. That is why scientists are now investigating the role played by this protein complex in actively dividing cells.

More information: Maria E Valieva et al. Large-scale ATP-independent nucleosome unfolding by a histone chaperone, *Nature Structural & Molecular Biology* (2016). DOI: 10.1038/nsmb.3321

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