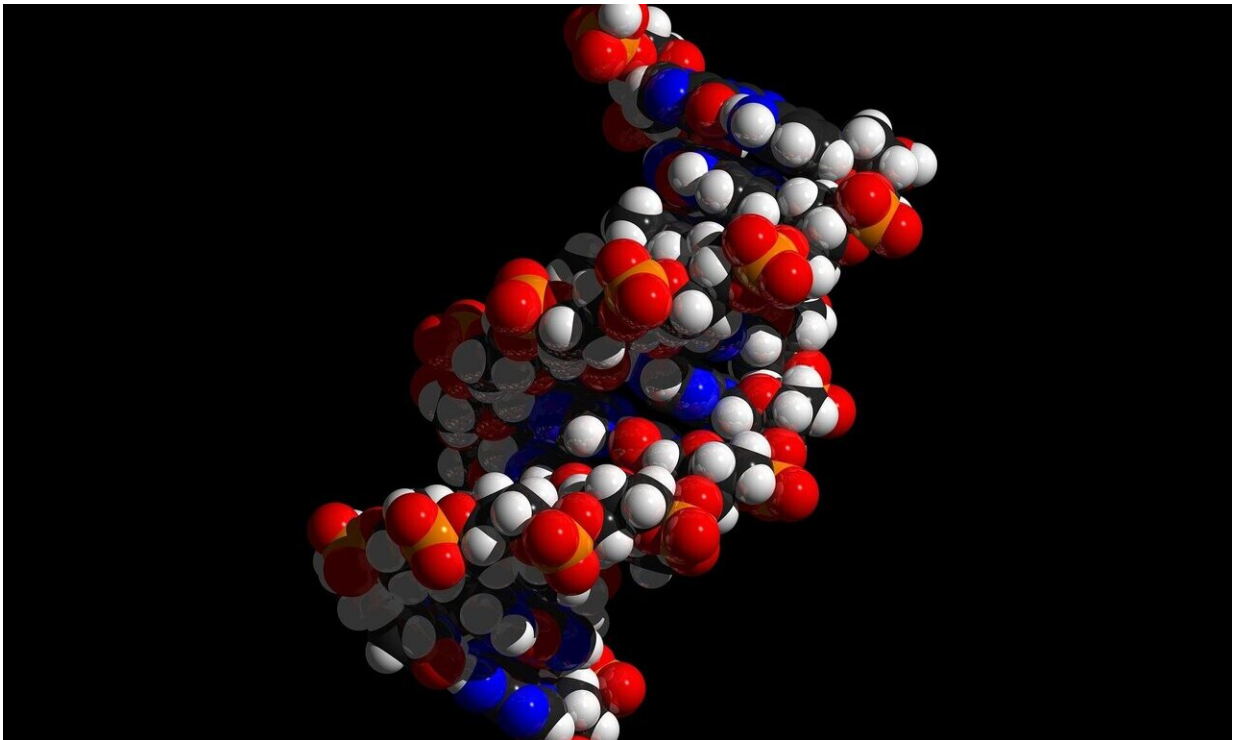


Groundbreaking cohesin study describes the molecular motor that folds the genome

November 22 2019



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New insights into the process of DNA looping have changed old perspectives about how the genome is organized within cells. Discoveries by IMP researchers have now elucidated a fundamental mechanism of life and settle a decade-long scientific dispute.

To pack the genetic information inscribed in roughly two meters of DNA into its nucleus, a human cell must achieve the equivalent of fitting an 80-kilometer-long thread into a sphere the size of a soccer ball. Looking through his microscope back in 1882, German biologist Walther Flemming found a clue about how this trick is done. What he saw were loops of DNA strands inside the nucleus of an egg cell that reminded him of the brushes used at the time to clean gas lanterns, and he named these structures lampbrush chromosomes, having no idea of what they were or what purpose they served.

It took many decades to identify the lampbrush chromosomes as strands of DNA neatly folded into loops, and even longer to realize that DNA is folded into such structures in all cells and at all times; it took until 2019 to find out how this folding is accomplished. In a paper published by the journal *Science*, researchers from Jan-Michael Peters' lab at the Institute of Molecular Pathology (IMP) in Vienna have demonstrated for the first time that a molecular machine actively and purposefully folds DNA via "loop extrusion," and thereby fulfills several important functions in the interphase cell.

That the process of looping DNA is neither random nor arbitrary is evident from how evolutionarily ancient it is. Cells of all organisms perform this function, from bacteria to humans. The primeval function of the folding mechanism is still unknown, and we may never find out, but some vital tasks have been discovered in recent years. By looping DNA, distant regions on the large molecule are brought into close proximity and are able to interact. This [physical contact](#) plays an important role in gene regulation, in which DNA segments called enhancers influence which genes are active. Looping is also essential for the ability of immune cells to produce a diverse array of antibodies.

An idea of how the loops are held in place emerged from work done by Kerstin Wendt, a former postdoc in the lab of Jan-Michael Peters at the

IMP. In 2008, her results suggested that the protein complex cohesin was doing the trick. This large molecule had been identified 10 years prior in the lab of IMP-scientist Kim Nasmyth as the molecular glue that holds sister chromatids together during early mitosis, a discovery for which he was recently awarded the Breakthrough Prize. Conveniently ring-shaped, the cohesin complex was thought to clamp onto DNA like a carabiner.

For a long time, the folded state of DNA was regarded as a static configuration, with cohesin molecules acting much like the rings on a curtain rod, sliding onto DNA without binding to it. An idea of how DNA looping might be achieved came from several scientists, including MIT physicist Leonid Mirny. He proposed that cohesin would initially form tiny loops of DNA that would grow increasingly large until cohesin is stopped in this "extrusion" process by boundaries on the DNA that define where the loops are anchored. However, this loop extrusion hypothesis was too radically different from the established view of DNA being static and cohesin forming passive rings around it, and was therefore received with skepticism by many biologists. It is thanks to the ingenuity and laborious experiments by Iain Davidson and his colleagues that the controversy has now been resolved.

The team involving Davidson, a senior postdoc in the Peters lab at the IMP, was able to reconstitute cohesin function in a simplified system in vitro. Thus, he could watch how single cohesin molecules rapidly extruded single pieces of DNA into loops, exactly as Mirny and others had postulated. His findings, published online on 21 November 2019, are far-reaching and change the entire perception of the genome in several ways:

- Rather than being static, the genome is a highly dynamic structure.
- The folding of genomic DNA is an actively regulated process. It involves looping the DNA molecule by way of extrusion, with

many loops in constant motion.

- The looping process is mediated by cohesin, which must therefore be a molecular motor, similar to other motor proteins such as myosin, which activates muscles.
- The cohesin molecule does not just form carabiner-like rings around DNA, but must attach to DNA dynamically via several binding sites to be able to fold it. This must also be true for a related molecule, condensin, as was shown last year.

"This is a real paradigm shift," says IMP director Jan-Michael Peters.

"Earlier observations gave us some hints, but the work of Iain Davidson is now proof. In my scientific life, few other discoveries were as far-reaching as this one."

The discoveries are expected to soon become textbook knowledge, as have other fundamental discoveries about the genome, such as its duplication by semi-conservative DNA replication or its rearrangement by homologous recombination. For the IMP researchers, the next important question to address is how exactly cohesin binds to DNA, how it then moves the DNA so that it is folded into loops, and how this process is controlled. They have already shown that a protein complex called NIPBL-MAU2 is essential for cohesin's motor function, and not just for loading cohesin onto DNA, as was previously believed.

"We can now use our setup to zoom in further into the intricate molecular process of DNA looping," says Iain Davidson, first author of the new paper. "Solving this mechanism may also help us to understand why certain human diseases are caused by mutations in the cohesin complex."

The paper "DNA loop extrusion by human [cohesin](#)," by I.F. Davidson et al., was published in *Science* on Thursday, 21 November, 2019.

More information: Iain F. Davidson et al. DNA loop extrusion by human cohesin, *Science* (2019). [DOI: 10.1126/science.aaz3418](https://doi.org/10.1126/science.aaz3418)

Provided by Research Institute of Molecular Pathology

Citation: Groundbreaking cohesin study describes the molecular motor that folds the genome (2019, November 22) retrieved 4 May 2024 from <https://phys.org/news/2019-11-groundbreaking-cohesin-molecular-motor-genome.html>

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