Looping the genome—how cohesin does the trick

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Twenty years ago, the protein complex cohesin was first described by researchers at the IMP. They found that its shape strikingly corresponds to its function: when a cell divides, the ring-shaped structure of cohesin keeps sister-chromatids tied together until they are ready to separate.

Apart from this important role during cell-divison, other crucial functions of cohesin have been discovered since - at the IMP and elsewhere. One of them is to help fold the DNA, which amounts to about two meters per nucleus, into a compact size by way of creating loops. "We think that the cohesin-ring clamps onto the DNA-strand to hold the loops in place", says IMP-director Jan-Michael Peters whose team worked on the project.

The chromatin-loops are not folded at random. Their exact shape and position play an important role in gene regulation, as they bring otherwise distant areas into close contact. "For a long time, scientists were mystified by how regulatory elements – the enhancers – are able to activate distant genes. Now we think we know the trick: precisely folded loops allow enhancers to come very close to the genes they need to regulate", says Peters. Research results point to cohesin as mediator of this process. Jan-Michael Peters and his team have already shown that the cohesin complex accumulates in areas where loops are formed.

Several scientists recently proposed a so-called "loop-extrusion mechanism" for the folding of chromatin. According to this hypothesis, cohesin is loaded onto DNA at a random site. The DNA strain is then

fed through the ring-shaped complex until it encounters a molecular barrier. This element, a DNA-binding protein named CTCF, acts much like a knot tied in a rope and stops the extrusion-process at the correct position. Defined genome-sequences that were previously located far apart are now next to each other and can interact to regulate gene expression.

In *Nature* online this week, IMP-researchers publish data that support the existence of such a mechanism. First author Georg Busslinger, a PhD-student in Jan-Michael Peters' team, showed in mouse cells that cohesin is indeed translocated on DNA over long distances and that the movement depends on transcription, suggesting that this may serve as a 'motor'.

"The loop extrusion hypothesis has opened up a whole new research area in cell biology and we will probably see many more papers published on this topic in the future", comments Jan-Michael Peters. Understanding cohesin-function is also relevant from a medical perspective since a number of disorders, including certain cancers, are associated with malfunctions of the protein-complex.

More information: Georg A. Busslinger et al. Cohesin is positioned in mammalian genomes by transcription, CTCF and Wapl, *Nature* (2017). DOI: 10.1038/nature22063

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