Researchers answer century old question about 3D structure of mitotic chromosomes

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Using three dimensional modeling techniques, advanced computer simulation and next generation sequencing technology, faculty at the University of Massachusetts Medical School (UMMS) and the Massachusetts Institute of Technology (MIT) have resolved a long-standing debate that has consumed scientists ever since chromosomes were first observed under the light microscope by Walther Flemming in 1878.

In an article that appears in the online edition of *Science*, UMMS Professor Job Dekker, PhD, and colleagues show new evidence for a general principal of condensed, mitotic chromosome organization and structure that is highly adaptable and common to all cells. This new insight into how chromosomes are disassembled and reassembled during cell division will allow researchers to begin answering basic questions about epigenetic inheritance, as well as human disease such as chromosome disorders and cancer.

"Over the last several decades there have been conflicting theories for how the DNA is organized inside these chromosomes," said Dr. Dekker, co-director of the Program in Systems Biology at UMMS and senior author of the *Science* study. "We now have a model that incorporates this seemingly contradictory data and points to a single and simple process for condensed chromosome organization across all cell types. With this knowledge, we can begin asking very specific questions about how inheritance works and what happens when the process goes awry."

One of the most widely recognized biological structures in the cell, the tightly wound and elongated chromosome with its classic X-shaped structure can be easily discerned under a microscope and has been a common image in text books and popular scientific literature for decades. Despite this prevalence, technical limitations in microscopic studies have led to competing models for how the DNA is organized inside these chromosomes.

In its normal state, a cell's DNA is distributed in the cell nucleus over a relatively large area. Previous work from Dekker and colleagues had shown that points of interaction along the chromosome influence gene expression and are the reason why different cell types are organized differently in three dimensions. But in order to separate and be distributed successfully to each daughter cell, the chromosomes need to be tightly condensed and neatly packaged for transport and transmission to daughter cells.

One set of theories posed that the long DNA molecules are coiled up hierarchically into successively thicker fibers to ultimately form the sausage-like mitotic chromosomes. An alternate set of models proposed that the DNA forms a series of loops that are then attached to a linear axial structure that forms the backbone of the chromosome.

Different lines of experimental evidence supported both models, preventing ruling either theory in or out. In order to isolate the 3D structure of the chromosome during metaphase, the authors used a combination of chromosome conformation capture technologies (3C, 5C and Hi-C) developed by the Dekker lab over the last decade to map the points of contact along the mitotic chromosome in different cell types synchronized to divide at the same time. The complex sets of data this yielded provided the backbone for understanding the three dimensional structure and spatial organization of these chromosomes.

Next, Dekker and the team, led by Leonid Mirny, PhD, associate professor at the Massachusetts Institute of Technology, developed sophisticated computer simulations using polymer models of the DNA molecule for the two competing theories for mitotic chromosome organization. Plugging each model into the simulation, Dekker, Mirny and colleagues found that their chromosome conformation capture data was inconsistent with the classical, hierarchical model. Instead, they found that during metaphase the chromosome was being packaged in a two phase process. In the first phase, chromatin loops of 80,000 to 120,000 DNA base pairs form, radiating out from a scaffold and compacting the chromosome linearly. This was followed by axial compression of the chromosome, much like a spring being compressed, resulting in a neat, tightly folded package.

"Each cell type, whether blood, skin or liver cell, has a unique structure and organization that is closely tied to gene expression and function," said Dekker. "When the cell begins to divide that structure is disassembled. The specific patterns or organization tied to cell type are stripped away and the universal mitotic chromosome is formed. The process results in each cell being condensed and repackaged in a way that is common across cells types and points to a fundamental process of cell biology."

"When you look at the condensed chromosome it appears to be highly organized," said Dekker. "But the truth is that the process is very variable and adaptable because these chromatin loops form randomly along the chromosomes, which makes the process incredibly robust and adaptable."

Natalia Naumova, PhD, a postdoctoral fellow at UMMS and one of the lead authors of the study said, "We didn't expect that the chromosome would be organized this way. This stochastic process, which is locally random, results more globally in a high degree of stability and

robustness, which is needed for cells to divide successfully."

The next step for Dekker, Mirny and their teams is to determine what, precisely, is guiding the disassembling and reassembling of the chromosome. "Because most transcription largely ceases in mitosis, and many proteins dissociate from the chromosome, something has to be responsible for reassembling chromosomes after cell division according to their cell type. Understanding the organization of the mitotic chromosome will help to understand how things go wrong in disease caused by chromosome disorder such as cancer or Down syndrome."

More information: "Organization of the Mitotic Chromosome" *Science*, 2013.

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