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dr. christiane menzfeld

tel.: +49 89 8578-2824

menzfeld@biochem.mpg.de
www.biochem.mpg.de/news

The genetic transmission of gene locks

Although all cells in an organism contain the same genes, only some of the genes are activated in a given cells and others remain inactive. Genes coil around histone proteins in the form of DNA threads. If a gene has to remain inactive, its histones are marked by the PRC2 enzyme so that this gene is locked down and cannot be read. When cells divide and the genes are copied, these histone marks must be placed again, at exactly the same location. The mechanism that enables transmission of this information has now been explained by Jürg Müller from the Max Planck Institute of Biochemistry in Martinsried in a study published in the journal *Science*.

In animals and plants, the genomic DNA in the cell nucleus is wrapped around small proteins known as histones. Jürg Müller, Leader of the Biology of Chromatin Research Group at the MPI of Biochemistry explains: “The DNA is like a big library of books. Each book contains the instruction manual for making a protein. Although the same DNA library is present in all cells, some of the books are ‘sealed’, so they cannot be read. A muscle cell requires other protein-building instructions than an intestinal cell.”

An essential mechanism to prevent the expression of genes relies on the chemical marking of histone proteins to permanently “lock down” genes. In the current study, Müller and his team examined how such gene locks are transmitted during cell division.

Histones play a key role in determining how accessible a gene is. When genes need to be permanently locked down, their histones are chemically modified by the enzyme PRC2. “If we imagine the histones as the binder of the book, PRC2 helps to seal that book and prevent that it gets opened and read,” explains Müller.

During cell division, the information about whether a gene needs to remain active or inactive in a given cell has to be transmitted to the daughter cells – or, to continue with the metaphor: All books must be copied and the two copies of certain books must remain sealed. However, the histones available in the mother cell are not sufficient for this and new histones must be added - so that the books do not fall apart.

"We investigated how marked histone proteins present at a gene are distributed during cell division and how newly incorporated histones then become marked by PRC2," says Müller. The scientists discovered that marked histones are distributed in a random manner to the two gene copies in daughter cells. PRC2 then must first bind to specific sequences in the DNA of that gene in order to mark the new histones. "If that DNA, called Polycomb Response Element, is removed from a gene, PRC2 cannot mark the new histones and the only marked histones left are the ones from the mother cell. So with each cell division, the amount of marked histones is further diluted and, after a few divisions, they are completely eliminated," explains Friederike Laprell, first author of the study.

When a cell cannot keep certain books sealed and the instructions in those books become available to a cell, the cell quickly starts to loose or change its identity - a process that results in diseases like cancer. "So it is PRC2 together with the Polycomb Response Element DNA that is present in certain genes that ensures that cells can maintain and propagate their identity for many cell generations," summarizes Müller.

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Am Klopferspitz 18
82152 Martinsried, Germany
Phone: 0049 (0)89 / 8578 - 0
Fax.: 0049 (0)89 / 8578 - 3777
www.biochem.mpg.de
www.mpg.de

Caption:
Like a sealed book, some genes from the DNA library cannot be read as, depending on the cell type, only certain genes are needed. The enzyme PRC2 helps with the “sealing” of genes in the cells.
Illustration: Monika Krause © MPI of Biochemistry

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F. Laprell, K. Finkl and J. Müller: Propagation of Polycomb-repressed chromatin requires sequence-specific recruitment to DNA, *Science*, March 2017

Contact:
Dr. Jürg Müller
Chromatin Biology
Max Planck Institute of Biochemistry
Am Klopferspitz 18
82152 Martinsried
E-Mail: muellerj@biochem.mpg.de
www.biochem.mpg.de/mueller

Dr. Christiane Menzfeld
Public Relations
Max Planck Institute of Biochemistry
Am Klopferspitz 18
82152 Martinsried
Germany
Tel. +49 89 8578-2824
E-Mail: pr@biochem.mpg.de
www.biochem.mpg.de