Centromere regulation and cancer

Dr. Sylvia Erhardt from the ZMBH in Heidelberg is specifically focused on the function of the centromere, the part of the chromosome indispensable for correct segregation of the chromosomes during cell division. Malfunctioning centromeres lead to changes in chromosome number, which is a hallmark of many types of cancer. The researcher was recently awarded the Hella Bühler Prize for her outstanding achievements in cancer research.

Dr. Sylvia Erhardt

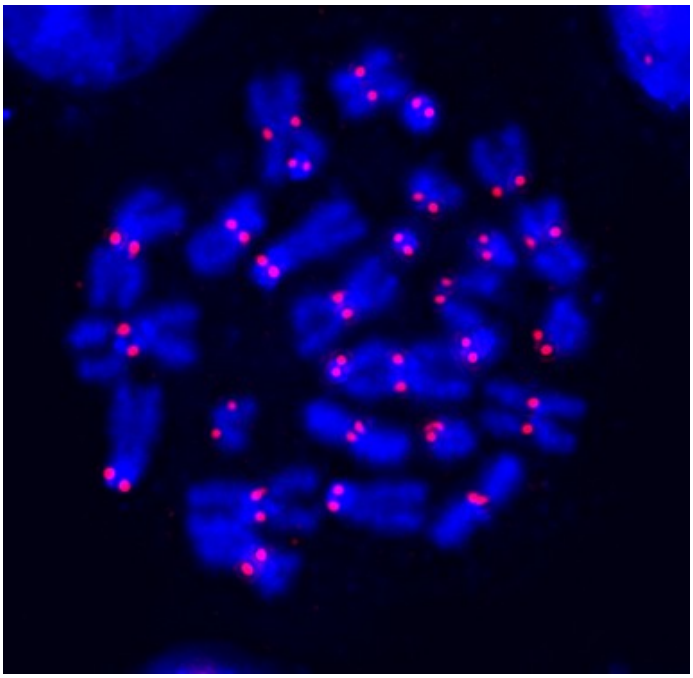
Centromeres are specialised regions on the chromosome that are crucial for the segregation of the duplicated DNA to the two daughter cells during cell division. They are functionally restricted regions that are present throughout the entre cell cycle. However, they become clearly visible under a light microscope when the cells start to divide and the chromosomes start to condense. For Sylvia Erhardt, the centromere is a kind of anchor where the so-called kinetochore forms. Kinetochores are multiprotein complexes on chromatids (i.e. copies of a newly formed chromosome) to which the spindle fibres attach during cell division and drag each sister chromatid to opposite cell poles. Sylvia Erhardt and her team at the Centre for Molecular Biology at the University of Heidelberg (ZMBH) have been focusing for many years on research into the correct assembly and function of the kinetochore at the centromere.

Epigenetic regulation of centromere identity

The DNA in the chromosomes is wound around nucleosomes, which consist of two copies each of the four packaging proteins, i.e. the histones H2A, H2B, H3 and H4. However, in the nucleosomes of the centromeres, and only there, the

histone H3 is replaced by the variant CenH3 (known as CENP-A in humans, CID in the fruit fly). It is therefore an excellent marker for identifying the centromere regions of chromosomes.

However, histones are far more than just DNA packaging proteins; they are also key elements of epigenetic mechanisms through which genes are switched on and off without any change to the DNA sequence. The histones are modified in a characteristic way by specific enzymes. Erhardt and her team are specifically interested in epigenetic regulation of the centromere, and have concentrated on the role of CenH3.



Histone variant CenH3 (shown here in Drosophila S2 cells, and therefore referred to as CID) occurs exclusively in centromeres (stained red with specific antibodies). The chromosomes are counterstained in blue.

The Heidelberg researchers have shown that centromeres are characterised by a specific histone modification pattern. In almost all eukaryotic organisms, the specification of centromere location is passed on from one cell generation to another, regardless of the underlying DNA sequence. This therefore means that centromere identity is regulated by epigenetic mechanisms. The histone H3 variant seems to be one key factor that is thought to regulate centromere identity epigenetically. Defective (as a result of mutations) or absent CenH3 prevents the centromere from correctly interacting with the kinetochore, thereby preventing the error-free connection of DNA to the spindle microtubuli.

Centromeres and cancer

However, if the kinetochore is not working as it should, the chromosomes cannot segregate as they should either. This means that the chromosomes are not correctly distributed to the two daughter cells, and will end up with either too few or too many chromosomes. Such chromosome anomalies (aneuplodies) are characteristic of many human cancers. Erhardt's research project "The Role of Centromere Components in Cancer and Cancer Therapy" examines the relationships between epigenetic centromere regulation and cancer. Detailed insights into centromere function and molecular mechanisms that ensure the correct segregation of chromosomes will lead to new concrete starting points for targeted and more effective cancer therapy.

Sylvia Erhardt has a long-standing interest in epigenetics, beginning early on in her scientific career when she did her degree thesis in the laboratory of Renato Paro (now in Basle, CH), a pioneer and leading epigenetic research scientist. Erhardt went on to graduate in biology at the University of Heidelberg in 1998, do her PhD at the University of Cambridge (UK) and work as a post-doc at the University of California in Berkeley, USA, before returning to the ZMBH in 2008 to set up her own research group. Her Chromatin and Centromere Biology research group is part of the Dynamics of Cell Architecture research area in the CellNetworks excellence cluster. The Heidelberg-based cluster was established under the German federal and state governments' Excellence Initiative. She also runs the Epigenetics and Centromere Biology research unit that is part of the "Organisation and Differentiation of Cells and Stem Cells" ZMBH-DKFZ Alliance.

Sylvia Erhardt (third from the right) with her team in front of the ZMBH.

In early October 2015, Sylvia Erhardt was awarded the 100,000-euro Hella Bühler Prize for her outstanding achievements in cancer research. The money will enable her to further advance her innovative research.

Article

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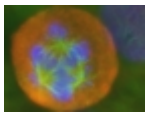
Further information

- ZMBH, University of Heidelberg

The article is part of the following dossiers



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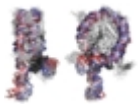

Epigenetics – heritable traits without changing the DNA sequence

cancer | epigenetics | University of Heidelberg | DNA | Drosophila melanogaster | cell cycle | histone