Stem Cell Research

What happens in the cell nucleus after fertilization

A team of scientists at the Helmholtz Zentrum München shows changes in the immediate environment of DNA after the ovum and sperm fuse to form the zygote. The results suggest why all conceivable somatic cells can develop from the germ cells. The study has been published in the journal '*Genes and Development*'.

Months before the often-cited miracle of birth occurs, numerous events take place that science still does not completely understand. For instance, this includes the question of how a single cell can be the origin of all subsequent cells in the future organism. Exploring how this is possible is the objective of Prof. Dr. Maria-Elena Torres-Padilla, Director of the Institute of Epigenetics and Stem Cells (IES) at the Helmholtz Zentrum München and Professor for stem cell biology at the Ludwig-Maximilians-Universität Munich.

"We are particularly interested in the events that are required when the cells are to divide so many times and develop in so many different ways, for example cells from the skin, and the liver, and the heart," the researcher explains. In a current study, she and her team approached this problem by examining the so-called chromatin, which refers to the DNA and the proteins (histones) around it. "We looked at how certain histones are changed after fertilization, which allowed us to explain a new mechanism."

Small attachments, big effects

The authors discovered that the molecule Suv4-20h2, a so-called histone methyltransferase, travels over the chromatin and attaches small chemical changes (dubbed methyl groups) to the histones. When the addition of these chemical changes occurs, the cell is constrained in its division and development, Torres-Padilla explains. But once fertilization occurs, the attachments disappear and the fertilised ovum can develop into a new organism.

In order to confirm these results, the researchers used an experimental model to test the effect of keeping the Suv4-20h2 active in the fertilized ovum. "We were able to demonstrate that in this case, the methyl groups remain on the histones," explains first author Andre Eid, doctoral candidate at the IES. "This arrests the development and the cells did not progress beyond the first division."

In further experiments, the team was able to show that this mechanism is probably based on the fact that the methyl groups on the histones lead to a defect during the duplication of the genetic material, referred to as replication. This defect causes then a replication 'check point', whereby the cell cycle comes to a standstill.

"Our results have given us insight into the complex connections between the chromatin and the ability of cells to develop into other types of cells - so-called totipotency," Torres-Padilla states as she puts the results into perspective. This is an important step both for human embryology and for the understanding of certain cancers in which the cells display very similar mechanisms that affect their rate of growth.

Further Information

Background:
Specifically, the researchers showed that Suv4-20h2 is responsible for H4K20me3 methylations. Unlike in somatic cells, in germ cells these inhibit cell division and pluripotency.The study is the result of cooperation between the Helmholtz Zentrum München and the Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) in Strasbourg, France, where Torres-Padilla was based before moving to Munich.

Original Publication:
Eid, A. et al. (2016): SUV4-20 activity in the pre-implantation mouse embryo controls timely replication. Genes and Development, doi: 10.1101/gad.288969.116

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The research of the Institute of Epigenetics and Stem Cells (IES) is focused on the characterization of early events in mammalian embryos. The scientists are especially interested in the totipotency of cells which is lost during development. Moreover, they want to elucidate who this loss is caused by changes in the nucleus. Their main goal is to understand the underlying molecular mechanisms which might lead to the development of new therapeutic approaches. www.helmholtz-muenchen.de/ies

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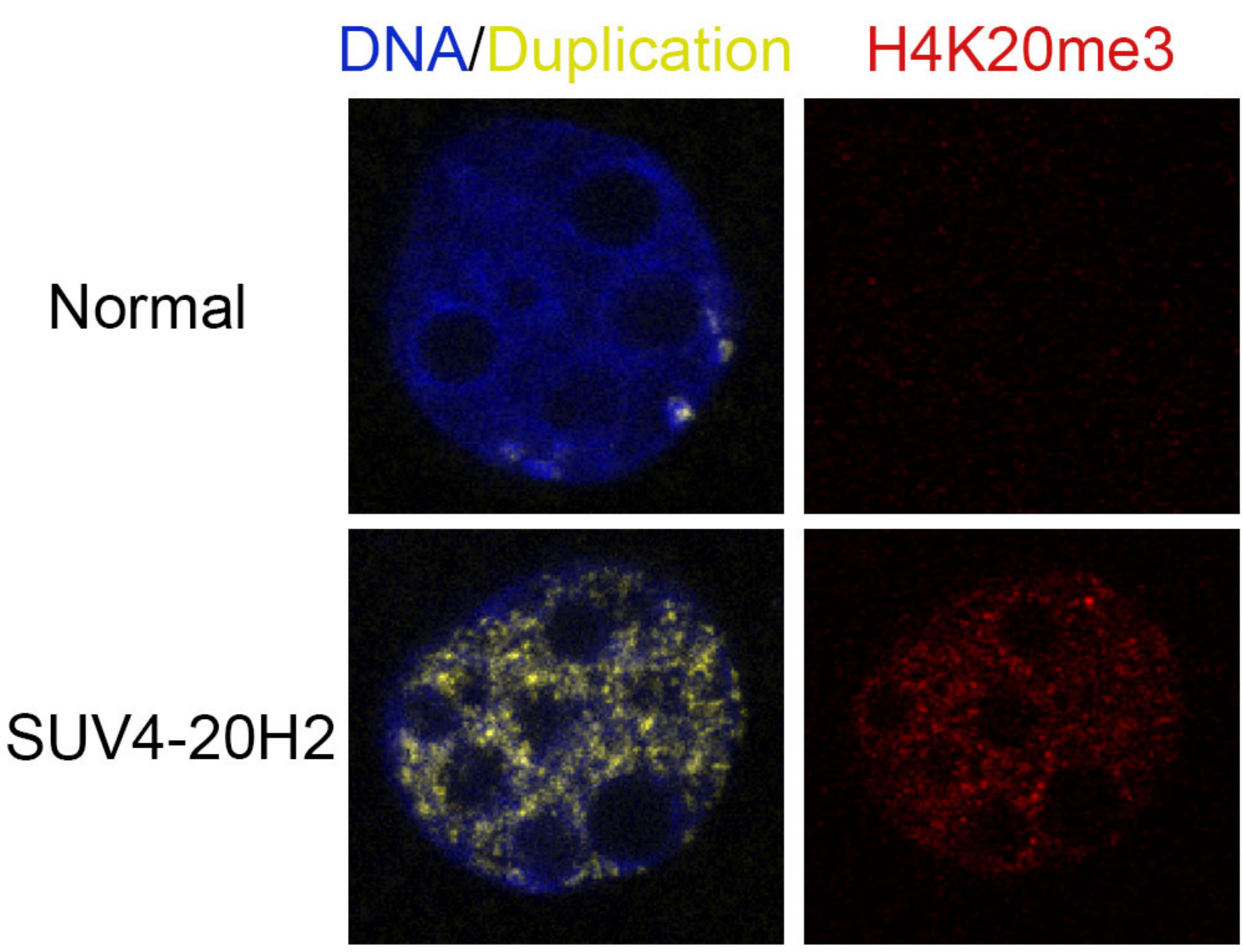
DNA/Duplication
H4K20me3
Normal
SUV4-20H2

The figure shows a normal murine embryo (top two panels) and another with additional expression of Suv4-20 (bottom two panels, methylation shown in red). While the cells without histone modification duplicate their DNA (few yellow cells) and progress to cell division, cells with expression of Suv4-20 are trapped in a duplication state (numerous yellow cells) but cannot progress to cell division. Source: Helmholtz Zentrum München/Andre Eid.