Scientists create new technology and solve a key puzzle for cellular memory

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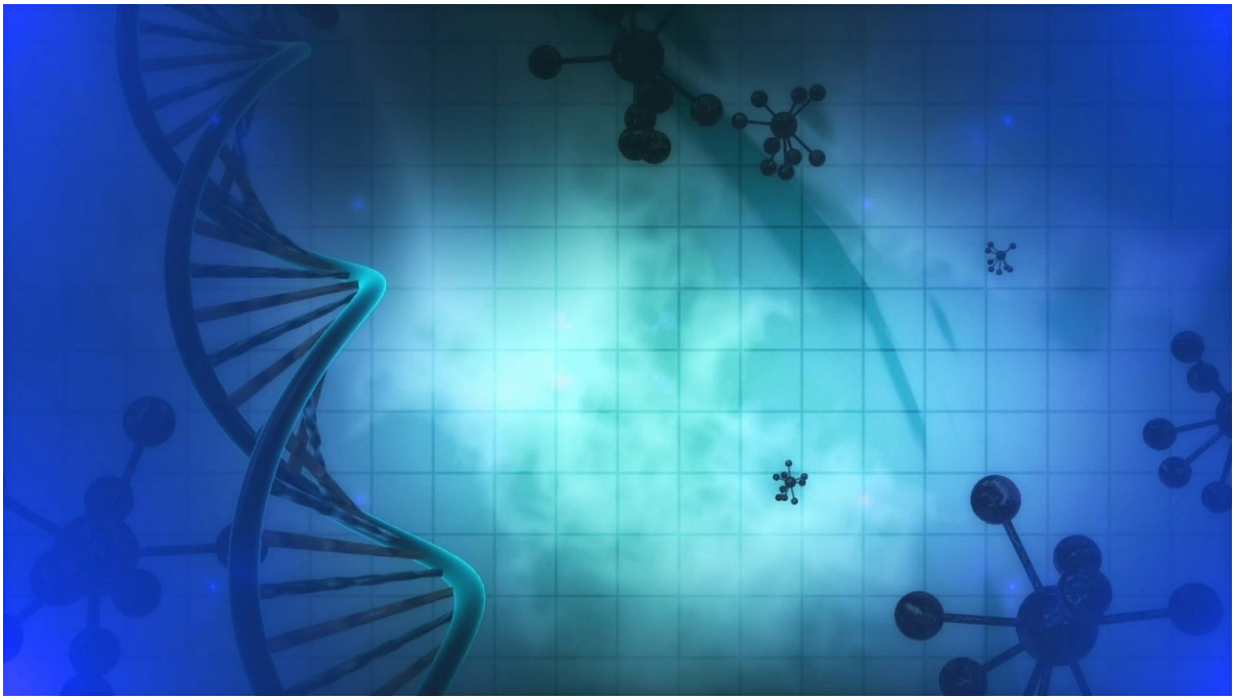

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With a new groundbreaking technique, researchers from University of Copenhagen have managed to identify a protein that is responsible for cellular memory transmission when cells divide. The finding is crucial for understanding development from one cell to a whole body.

Cells divide constantly throughout life. But how do cells remember

whether to develop into skin, liver or intestinal cells? It's a question that has puzzled scientists for many years. Now, scientists from the Faculty of Health and Medical Sciences and the Faculty of Sciences at the University of Copenhagen have come a little closer to understanding this process.

They have developed a technique that gives new insight into epigenetic cellular memory. With the new technique, called SCAR-seq, the researchers have been able to address how epigenetic information stored in histone proteins is transmitted when DNA is copied and cells divide. The new study has just been published in the scientific journal *Science*.

"We have developed a new tool to look at the transmission of protein -based information in general and how it contributes to epigenetic memory of mammalian cells. For the first time, we can see which proteins are on the two new DNA strands that are formed when DNA is copied during cell division. Thus, we can now investigate how protein-based information is inherited and propagated to daughter cells."

"This is the first time we have direct evidence that a specific protein is linking the transmission of epigenetic information on histones with the replication of genetic information in DNA. We knew that histone-based information had to be transmitted to both new DNA strands in one way or another, but we did not know how," says Anja Groth, professor at the Biotech Research & Innovation Center, University of Copenhagen, and co-author of the study.

Inside the human cell, our DNA is wrapped around histone proteins. Together, they form a structure called chromatin. When a cell divides, it is crucial that both the DNA and the entire chromatin structure are copied accurately. Chromatin stores epigenetic information that affects which genes are to be expressed. That is, the epigenetic information in our cells helps to control which genes are "turned on" and "off."

MCM2 is responsible for proper segregation of histones to daughter cells

In the new study, the researchers have studied embryonic stem cells from mice. With SCAR-seq, it has become possible for the researchers to identify a protein that is responsible for transfer of histone proteins from the old DNA strand to the two new DNA strands during replication—namely MCM2. The researchers have had MCM2 in their working model for a long time, but it was not possible to determine its exact function before the development of the SCAR-seq technology.

"It has been a recurring question whether the transfer of histones with their chemical modifications was completely random during DNA replication. In our study, we show that it is not a random but a highly controlled process. Our data show that the histones have a preference for one DNA strand, the so-called leading strand, but that MCM2 counteracts this bias and ensures that there is almost symmetry between the two new DNA strands, that is, an even distribution of histone-based information."

"When we disrupted that mechanism, all histone-based information was transferred to one DNA strand, namely the leading strand, and not to the other, lagging strand. This means that this function by MCM2 is essential for the two new DNA strands to receive the same information stored in histones," says co-author of the study Robin Andersson, assistant professor at the Department of Biology, University of Copenhagen.

The researchers do not yet know how the ability of embryonic cells to form other cell types is affected when the function of MCM2 that ensures proper segregation of the histones is disrupted. This meaning whether these cells still can contribute to the formation of an entire mouse. Among scientists it is frequently discussed how important

histone information actually is for a cell identity and cell fate decisions. This will be the next question the researchers will investigate.

"Understanding this first part of the mechanism for how daughter cells inherit histones and their modifications from the mother cell has a lot of potential. Now, we can start to address what significance this transfer of protein-based information actually has for the cell and for the development of the organism. That is our long-term perspective," says professor Anja Groth.

More information: "MCM2 promotes symmetric inheritance of modified histones during DNA replication" *Science* (2018). science.sciencemag.org/lookup/ … 1126/science.aau0294

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