Cell memory mechanism discovered

15 August 2013

The cells in our bodies can divide as often as once every 24 hours, creating a new, identical copy. DNA binding proteins called transcription factors are required for maintaining cell identity. They ensure that daughter cells have the same function as their mother cell, so that for example muscle cells can contract or pancreatic cells can produce insulin. However, each time a cell divides the specific binding pattern of the transcription factors is erased and has to be restored in both mother and daughter cells. Previously it was unknown how this process works, but now scientists at Karolinska Institutet have discovered the importance of particular protein rings encircling the DNA and how these function as the cell's memory.

The DNA in human cells is translated into a multitude of proteins required for a cell to function. When, where and how proteins are expressed is determined by regulatory DNA sequences and a group of proteins, known as transcription factors, that bind to these DNA sequences. Each cell type can be distinguished based on its transcription factors, and a cell can in certain cases be directly converted from one type to another, simply by changing the expression of one or more transcription factors. It is critical that the pattern of transcription factor binding in the genome be maintained. During each cell division, the transcription factors are removed from DNA and must find their way back to the right spot after the cell has divided. Despite many years of intense research, no general mechanism has been discovered which would explain how this is achieved.

"The problem is that there is so much DNA in a cell that it would be impossible for the transcription factors to find their way back within a reasonable time frame. But now we have found a possible mechanism for how this cellular memory works, and how it helps the cell remember the order that existed before the cell divided, helping the transcription factors find their correct places", explains Jussi Taipale, professor at Karolinska Institutet and the University of Helsinki, and head of the research team behind the discovery.

The results are now being published in the scientific journal *Cell*. The research group has produced the most complete map yet of transcription factors in a cell. They found that a large protein complex called cohesin is positioned as a ring around the two DNA strands that are formed when a cell divides, marking virtually all the places on the DNA where transcription factors were bound. Cohesin encircles the DNA strand as a ring does around a piece of string, and the protein complexes that replicate DNA can pass through the ring without displacing it. Since the two new DNA strands are caught in the ring, only one cohesin is needed to mark the two, thereby helping the transcription factors to find their original binding region on both DNA strands.

"More research is needed before we can be sure, but so far all experiments support our model" Martin Enge, assistant professor at Karolinska Institutet, says.

Transcription factors play a pivotal role in many illnesses, including cancer as well as many hereditary diseases. The discovery that virtually all regulatory DNA sequences bind to cohesin may also end up having more direct consequences for patients with cancer or hereditary diseases. Cohesin would function as an indicator of which DNA sequences might contain disease-causing mutations.

"Currently we analyse DNA sequences that are directly located in genes, which constitute about three per cent of the genome. However, most mutations that have been shown to cause cancer are located outside of genes. We cannot analyse these in a reliable manner – the genome is simply too large. By only analysing DNA sequences that bind to cohesin, roughly one per cent of the genome, it would allow us to analyse an individual's mutations and make it much easier to conduct studies to identify novel harmful mutations," Martin Enge concludes.

More information: Taipale et al., "Transcription factor binding in human cells occurs in dense clusters formed around cohesin anchor sites", *Cell* online 15 August 2013, DOI: 10.1016/j.cell.2013.07.034

Provided by Karolinska Institutet