Team uses internet network theory to decipher the first epigenetic communication network

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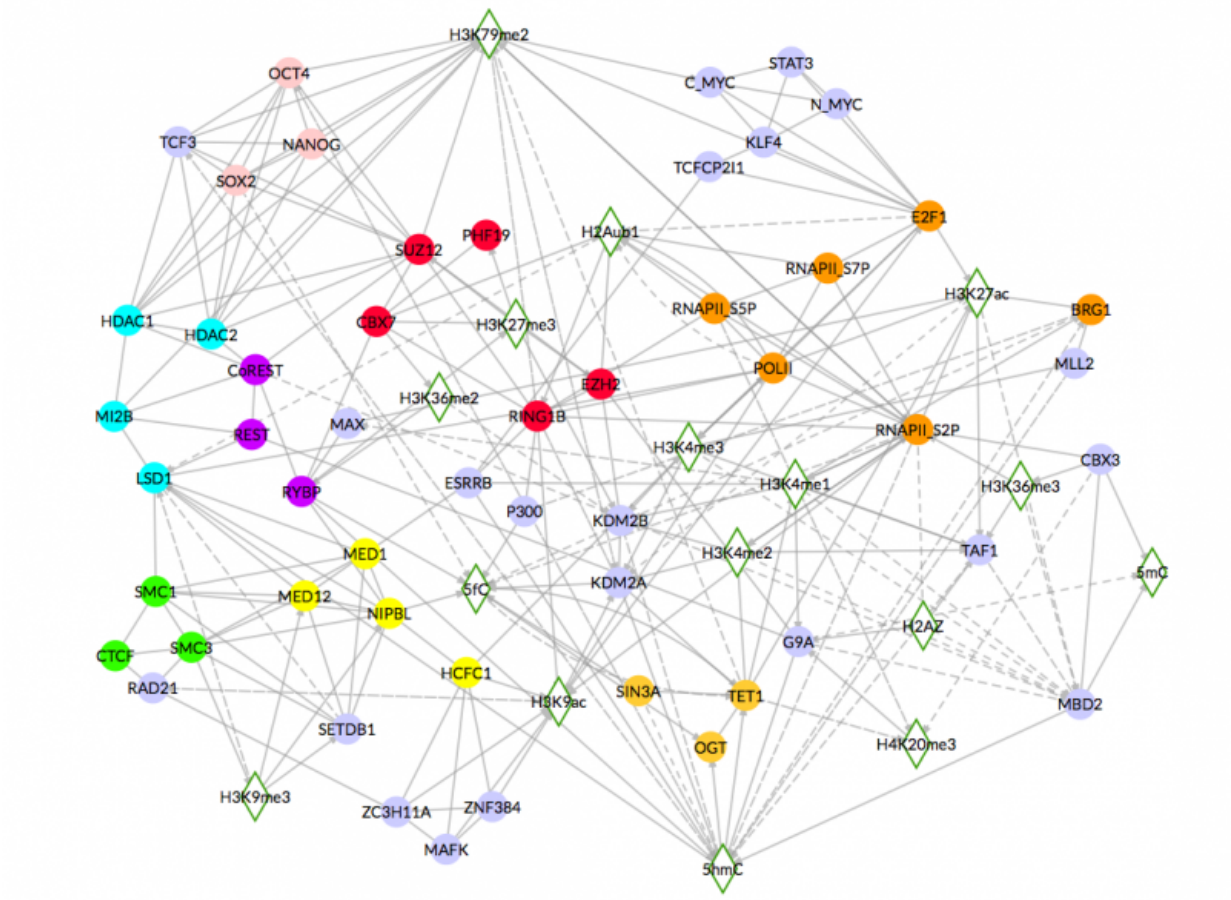

The epigenomic communication system of embryonic stem cells can be explored interactively on the following website: http://epistemnet.bioinfo.cnio.es. Credit: CNIO

One of the big questions for which there is still no clear answer in biology is how, based on the four universal letters that make up DNA, it is possible to generate such different organisms as a fly or a human, or the different organs and tissues they comprise. In recent years, researchers have discovered that the system is much more complicated than was originally thought. The letters are important, but histones and nucleotide chemical modifications can make up genetic instructions to reinterpret the information contained in the DNA. Reinterpretation of genetic instructions can lead to the development, for example, of an eye or the pancreas in the embryo. Alterations of this make up of the DNA code can also be linked to pathological processes and to the appearance of diseases, such as cancer.

The team of the Structural Computational Biology Group of the Spanish National Cancer Research Centre (CNIO), headed by Alfonso Valencia, the Centre's Vice-Director of Basic Research, has used network theory to build and study the first communication network between the components that constitute this genomic make up, known as epigenome. The conclusions were published today in the journal *Cell Reports*.

Epigenomics: Turning Genes On Or Off

Epigenomic marks can be thought of as a switch panel that determines which parts of the genome are turned on and will be visible to the cell. Consequently, the same genetic information contained in all the cells of a living being can generate hundreds of different cell types, using certain genes and disregarding others.

In order to study this aspect in greater depth, the researchers collected data from literature that include 3 chemical modifications in cytosine (letter "C" of DNA), 13 modifications of histones (the proteins around which DNA is wrapped) and 61 DNA associated proteins, from mouse embryonic stem cells.

The authors apply mathematical algorithms used to measure the popularity and influence of websites (such as Wikipedia or Facebook) to the network of epigenomic communication. They reached the conclusion that the 5hmC mark (chemical modification of the cytosine with a hydroxymethyl group in position 5') is the most influential component of this network in stem cells.

5hmC As Epicentre

"We have approached systems biology by studying chromatin signals [the DNA with chemical modifications and proteins that bind to it] as a comprehensive system and from this we have built the first communication network between these signals," says Daniel Rico, the CNIO researcher who has directed the study together with Valencia. "In this case we are speaking of an internal communication system inside each cell,, more specifically within the nucleus."

As described in the paper, 5hmC acts as a key signal that connects with complexes that modify cytosines and histones to regulate gene expression. Through these connections, 5hmC regulates changes in the compaction of the chromatin, cellular differentiation processes and the energy metabolism in embryonic stem cells.

At the same time, phylogenetic analyses conducted for the proteins in the network also point to 5hmC as the center of the coordinated evolution, or co-evolution, of these chromatin related proteins.

The next step is to establish whether the results can also be assigned to other cell types. "We knew that 5hmC was extremely abundant in embryonic stem cells, but now we also know that this is true for other cell types, such as neurons or certain tumours," assert the authors of the paper.

And they add: "Cancer cells have stem cell features; therefore it seems appropriate to investigate whether these results can also be transferred to cancer epigenomes, which would provide new outlooks on how they are regulated."

More information: Epigenomic Co-localization and Co-evolution Reveal a Key Role for 5hmC as a Communication Hub in the Chromatin Network of ESCs. David Juan, Juliane Perner, Enrique Carrillo de Santa Pau, Simone Marsili, David Ochoa, Ho-Ryun Chung, Martin Vingron, Daniel Rico, Alfonso Valencia. *Cell Reports* (2016). DOI: 10.1016/j.celrep.2016.01.008

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