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## Research Highlights

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## The architecture of pluripotency

Megan Scudellari<sup>1</sup>

## Does a chromatin-remodelling factor affect the pluripotency of ES cells?

Before the era of molecular biology, researchers could distinguish between the chromatin of differentiated cells and that of stem cells by simply looking at stained nuclei through a microscope. In the former, one can see tightly coiled chromatin, called heterochromatin. But something strikingly different appears in the latter: many stem cells, from human embryonic stem (ES) cells to planarian neoblasts, have open, loose chromatin, diffusely spread out like a tangled spiderweb within the nucleus. Researchers have proposed a link between this open structure and the pluripotency of those cells, suggesting that open chromatin allows for widespread transcriptional activity<sup>1</sup>. Yet so far no molecular evidence has confirmed that belief.

A new paper in *Nature* takes a step toward establishing that proposed link between nuclear architecture and stem cell pluripotency. A cartel of researchers led by Miguel Ramalho-Santos at the University of California, San Francisco, have identified a gene that actively regulates open chromatin in ES cells, and they propose that it is essential for maintaining the pluripotency of those cells<sup>2</sup>.

The team identified Chd1, a chromatin-remodelling enzyme, during a genetic screen to test the roles of 41 genes found to be transcriptionally active in pluripotent mouse ES cells. After silencing *Chd1* by using short hairpin RNAs to interfere with the gene's transcription, the researchers noticed two clear defects: the cells proliferated more slowly, and they lost their pluripotency. The cells were no longer able to form primitive endoderm and had a high propensity toward neuronal differentiation. The team then examined the chromatin of the cells compared to that of unmanipulated cells and found those with reduced levels of *Chd1* had denser foci, more like differentiated cells than ES cells.

"We believe [the change in chromatin] is why the cells get stuck and are not able to form certain lineages," says Ramalho-Santos. "Chd1 is required to maintain the open chromatin state of ES cells."

But more evidence may be required to satisfy the scientific community. "I wasn't entirely convinced that this is the only thing that keeps chromatin open or even that it's a major player in ES cells," says Tom Misteli, a researcher at the National Cancer Institute at the National Institutes of Health and former postdoctoral advisor to Eran Meshorer, a senior author on the paper. "I think there is a link missing, something that proves the actual change in chromatin structure is what affects the behaviour of the cells." Unfortunately, an experiment to induce heterochromatin in ES cells without affecting anything else is "almost impossible," says Misteli. For now, the identification of factors such as Chd1 is a good first step toward understanding the mechanisms contributing to pluripotency, he adds.

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