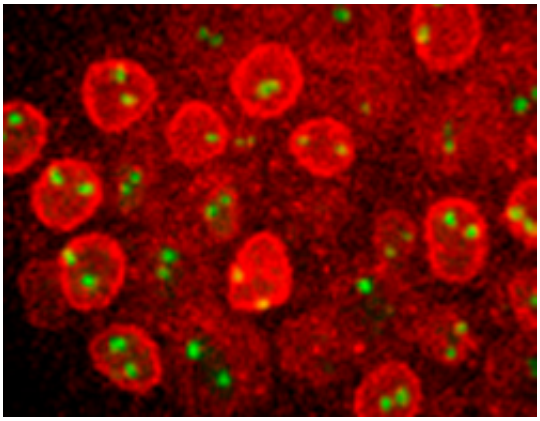
How packing away DNA stabilizes cell fate decisions

December 2 2015



Cell nuclei within C. elegans embryo. Without the intact CEC-4 anchor, heterochromatin (green) shifts to the center of the nucleus.

Susan Gasser and her group at the FMI have identified in C. elegans a much sought-for anchor protein, a previously uncharacterized chromodomain protein called CEC-4 that directly sequesters inactive chromatin at the nuclear membrane. In a study published in *Cell*, they described the mechanism of how CEC-4 contributes to the 3D organization of the nucleus, and identified a new paradigm for the contribution of nuclear anchoring towards stabilizing cell fate decisions.

Despite the fact that our genes are physically very dynamic, shifting rapidly and randomly within the interphase nucleus, there are also subnuclear compartments in which genes are sequestered when they are

inactive and other zones that harbor genes which are likely to be expressed. Whether this sub-compartmentalization happens by chance or whether the inactive DNA is indeed intentionally packed away has remained unclear. Even more significantly, the importance of the observed 3D organization for cell fate decisions and the development of the organism has stayed elusive.

Adriana Gonzalez-Sandoval, a PhD student in Susan Gasser's group at the Friedrich Miescher Institute for Biomedical Research (FMI), has exploited a genetic screen in C. elegans based on fluorescence microscopy, to identify a protein that anchors inactive DNA to the inner face of the nuclear envelope. The factor is a previously uncharacterized C. elegans chromodomain protein (CEC-4), which associates stably with the nuclear membrane and binds chromatin containing methylated H3K9– which is either inactive or on the way to becoming inactive. "This is the anchor that the community has been looking for a long time," commented Gasser. "Our findings show for the first time that there is indeed a specific molecular mechanism in place that leads to the observed nuclear organization of inactive chromatin. It does not happen by chance. The characterization of this protein was only possible thanks to the amazing people in FMI facilities and our C-NIBR collaborators."

But as is often the case in science, this long sought-after player in nuclear organization did not act as expected. "We were extremely surprised to see that under normal growth conditions transcription did not change in the absence of this anchor," commented Gonzalez-Sandoval. "Even though the protein existed and clearly anchored heterochromatin to the nuclear periphery, it did not matter: Without CEC-4 the worms developed normally, the necessary genes were transcribed, and inactive genes were left untouched. We were left wondering, what is this anchor good for?"

Well, order—or as the proverb says, "a place for everything and

everything in its place"—is most useful under conditions of perturbation or stress. Indeed, in a second set of experiments, Gonzalez-Sandoval showed that CEC-4 stabilizes development when the worm embryos are forced to differentiate into muscle. The scientists found that anchoring chromatin contributes to the robust maintenance of an induced muscle differentiation program and the suppression of other cell fates. "This was a puzzling result at first, but given the biological context, it rather reveals a basic tenet of how the spatial segregation of genes contributes to differentiation," commented Gasser. "Instead of driving differentiation, sequestration "keeps things on track" and helps restrict the outcome of induction to only muscle genes." While there is no obvious impact on development under standard laboratory conditions, by perturbing development at the right stage, the scientists were able to reveal the contribution that nuclear anchoring makes towards stabilizing cell fate decisions.

"Although in many ways unexpected, our results provide a compelling insight: They allowed us to separate positioning from repression and helped us establish a new paradigm for the contribution of nuclear anchoring towards the stabilization of cell fate decisions," commented Gasser. "And although the findings are based on C. elegans, the histone marks implicated are conserved as is the phenomenon of tissue specific heterochromatin sequestration at the nuclear envelope."

More information: Adriana Gonzalez-Sandoval et al. Perinuclear Anchoring of H3K9-Methylated Chromatin Stabilizes Induced Cell Fate in C. elegans Embryos, *Cell* (2015). DOI: 10.1016/j.cell.2015.10.066

Provided by Friedrich Miescher Institute for Biomedical Research