

## Long-Range Chromosomal Interactions

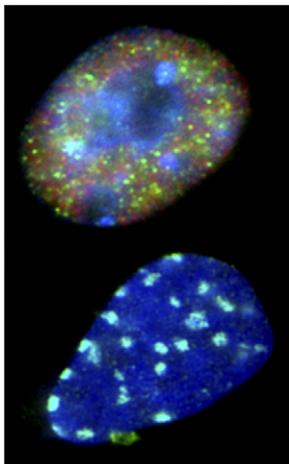
Polycomb proteins bind to regulatory DNA sequences called Polycomb response elements (PREs) to mediate silencing. Repression is enhanced when there are two copies of the element present, a phenomenon called pairing-sensitive silencing. This phenomenon is very important in *Drosophila* development, where long-range interactions exist between multiple PREs such as the *Fab-7* element. A recent study by Vazquez et al. visualizes an interaction between multiple copies of another PRE, *Mcp*, in live cells using real-time microscopy. The authors examine the *Mcp* element in the nuclei of fruit fly imaginal discs. They use the lacO/GFP-lacI system in which bacterial *lacO* operator elements are inserted near an *Mcp* element and expression of a GFP-tagged version of the lacI repressor (which binds to lacO sequences) allows these DNA sequences to be followed in real time. Using this approach, the authors show interactions among up to four *Mcp* elements including those on different chromosomes. By visualizing the interactions over time, they found that they were quite stable. It has been recently shown that siRNAs are important in stabilizing the interactions of Polycomb proteins and the maintenance of silencing at the PRE *Fab-7* locus. It will be interesting to determine if that is the case for silencing mediated by the *Mcp* element.

*J. Vazquez et al. (2006). Mol. Biol. Cell Published online February 22, 2006. 10.1091/mbc.E06-01-0049.*

## Telomere Anchoring and DNA Double-Strand Break Repair

Targeting DNA elements to the nuclear periphery is emerging as a common method for regulating gene expression. In yeast, telomeres are frequently anchored to the nuclear envelope, and this association occurs through two redundant pathways involving the DNA double-strand break (DSB) repair protein,  $\gamma$ Ku, and the silencing factor Sir4p. Regions adjacent to telomeres (subtelomeres) are subject to gene silencing. Therizols et al. now show that components of the Nup84 nuclear pore complex appear to be involved in both anchoring telomeres and subtelomeric gene silencing. The authors show that deletion of several of the genes encoding Nup84 nuclear pore complex proteins affects the positioning of telomeres at the nuclear periphery, indicating that the nuclear pore may help to anchor telomeres. Mutations in Nup84 also affect gene silencing in subtelomeres. Interestingly, DSBs in subtelomeric regions are not repaired in Nup84 mutants, resulting in decreased survival of the mutant cells. Therefore, it appears that localization of telomeres to the nuclear envelope correlates with DSB repair of subtelomeric regions. This study is a nice example of how subnuclear localization of telomeric DNA may be important for a critical cellular process: efficient DSB repair. The next step will be to discern whether this holds true for all yeast chromosomes and to determine the precise molecular interactions between the nuclear pore complex and telomeres. One candidate for a protein that bridges telomere position and DSB repair is Esc1, a nuclear inner membrane protein that is also involved in tethering of telomeres. Mutations in the gene that encodes this protein affect DSB repair but not silencing, suggesting that these two functions are separable.

*P. Therizols et al. (2006). J. Cell Biol. 172, 189–199.*



**A nucleus of an undifferentiated embryonic stem cell (top) and an ES cell-derived neural progenitor cell (bottom) labeled with DAPI (stains DNA; blue), Oct4 (ES cell marker; red) and HP1 (heterochromatin marker; green). Image courtesy of Tom Misteli.**

## Movers and Shakers in Embryonic Stem Cell Chromatin

Mammalian embryonic stem cells (ESCs) lose their pluripotency as they undergo differentiation. Meshorer et al. examined whether changes in the nuclear organization of the genome are related to this loss of pluripotency. They monitored the dynamics of chromatin in mouse ESCs by visualizing the behavior of structural chromatin proteins as the murine R1 cells differentiated into neural progenitor cells (NPCs). Immunofluorescent staining of HP1 $\alpha$  (a heterochromatin marker) and FISH revealed larger non-uniform heterochromatin spots in ESCs compared with smaller, more discrete heterochromatin spots in NPCs, indicative of large-scale genome rearrangements during differentiation. Using the fluorescence recovery after photobleaching assay, the authors showed that HP1 $\alpha$ -GFP was more dynamic in the heterochromatin of ESCs compared to NPCs. They report similar findings for core histones and certain linker histones. Together with biochemical data, it appears that several important chromatin architectural proteins are less tightly bound to DNA and more free to exchange with soluble pools in ESCs. Importantly, when the authors interfered with the dynamic exchange of histones in ESCs, the cells did not differentiate. Remarkably, the authors show that the extremely dynamic nature of these chromatin proteins appears to be a feature of other mammalian pluripotent embryonic stem cells but not of lineage-specific stem cells, indicating that it is a hallmark of pluripotency. These results indicate that global reorganization of heterochromatin and changes in the dynamics of chromatin-associated proteins are key events during the differentiation of ESCs.

*E. Meshorer et al. (2006). Dev. Cell 10, 105–116.*

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