

Research Roundup

Hyperdynamic proteins keep stem cells on their toes

Chromatin has a staid and static image. But Eran Meshorer, Tom Misteli (National Cancer Institute, Bethesda, MD), and colleagues suggest that ES cells are kept pluripotent thanks to hyperactively mobile chromatin proteins.

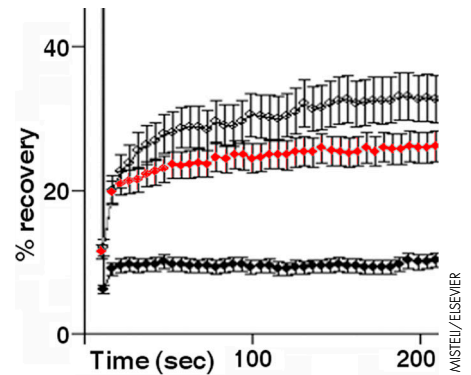
Chromatin proteins provide architectural integrity to DNA. Despite their structural role, they do not stay statically bound but release and reform their bonds continuously. Using FRAP to measure protein dynamics, the group showed that chromatin proteins in differentiated cells are exchanged within minutes to hours, whereas ES cells contain a pool of such proteins that turns over at the rate of seconds. The fast-moving protein fraction is present in several types of pluripotent cells but strikingly absent in committed precursor cells. This quick exchange may be what keeps the genome breathing—open and ready to take on any fate.

Frenetic protein activity also seems to be necessary for differentiation. When chromatin proteins were mutated to bind more tightly to DNA, cells failed to differentiate, whereas mutations increasing the pool of loose proteins led to faster than normal differentiation. The team postulates that in ES cells the proteins may be acting as building blocks where regions of silent (nontranscribing) chromatin are formed as the cell differentiates and shuts down unused areas of the genome.

Misteli hints that chromatin protein dynamics is probably just the tip of the iceberg in the search for what distinguishes pluripotent cells from committed ones, and says the group is looking for other properties of chromatin, such as histone modifications, gene activity, and chromatin structure that may differ in ES cells. They are also examining the underlying question of what the

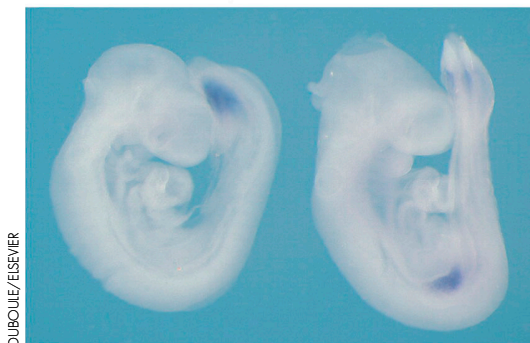
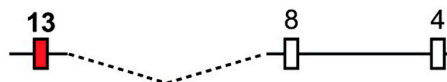
mobility might mean for gene expression. “If [ES] chromatin is really more open,” he says, “there might be more transcription.” **JCB**

Reference: Meshorer, E., et al. 2006. *Dev. Cell.* 10:105–116.



Chromatin protein dynamics (measured by fluorescence recovery) is fast in ES cells (white) but slower in differentiating (red) or differentiated (black) cells.

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Hoxd13 expression (purple) moves anterior and occurs earlier when a deletion brings it closer to a positive downstream element (right).

Making *HoxD* waves

When developmental biologists first got their hands on DNA, perhaps the most remarkable finding was that the order of genes on the chromosome reflected the genes' time and location of expression. Genes at the tail end of each cluster were expressed proximally and early; those at the front of the cluster were expressed distally and later. Now, Basile Tarchini and Denis Duboule (University of Geneva, Switzerland) find that simple placement of two gene regulatory elements explains the entire expression sequence for the *HoxD* cluster, which patterns forelimb development.

Two waves of *HoxD* expression control limb formation in vertebrates: an early wave, which generates proximal structures such as the forearm, and a later wave, which forms distal structures such as digits. By breeding mouse strains with targeted meiotic recombinations, Duboule and colleagues created deletions and duplications of the *Hoxd* genes, and they looked for changes in regulation.

Earlier work by the group showed that the later wave of digit development is controlled by a positive regulatory element located outside the *HoxD* cluster. Analysis of the 19 strains of mice generated for this study identified a different mechanism for the forelimb, in which gene expression is regulated by a positive and a negative regulator, each located on either side of the cluster. The asymmetry in *HoxD* expression is thus simply a factor of a gene's relative distance from the positive or negative influence, and the balance between the two forces.

The group is now applying the same technique to tease out the trunk patterning mechanism, a more complicated endeavor because many more genes are involved. “But we have good evidence that it's quite close to the one that's organizing the proximal limbs,” he says.

If the similarity holds, it would support the idea that proximal limb structures are phylogenetically much older ones. Duboule proposes that when proximal limbs evolved, nature co-opted the similar trunk patterning mechanism to also regulate limb development. But digit development, which is thought to have occurred about 300 million years ago, required nature to come up with a new approach. **JCB**

Reference: Tarchini, B., and D. Duboule. 2005. *Dev. Cell.* 10:93–103.