…embryonic stem cells … are characterized by an unusual combination of epigenetic modifications.

STEM CELLS

Poised for action

DOI:
10.1038/nrm1948

URLs
EED
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=13626

Research highlight
http://www.nature.com/nrg/journal/vaop/ncurrent/full/nrg1873.html

OCT4
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=5460

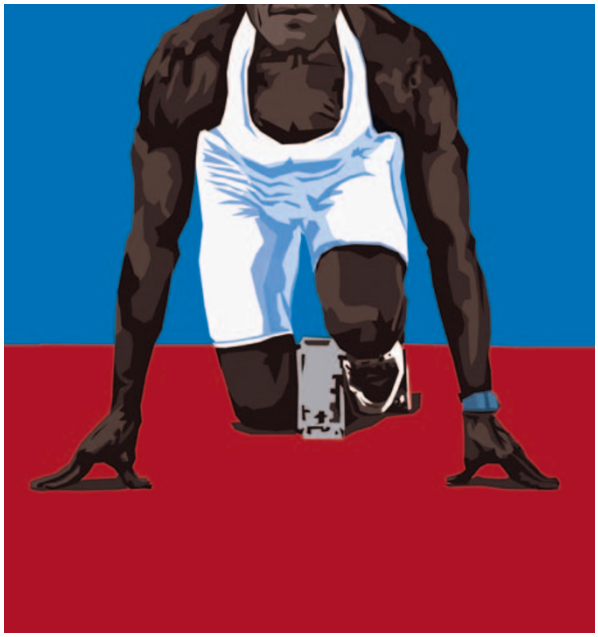
SOX2
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=6657

NANOG
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=79923

The pluripotent nature of stem cells relies on two opposing requirements — to keep differentiation-specific genes switched off while retaining the ability to switch them on quickly when needed. Four new papers reveal how unique chromatin properties of mammalian stem cells allow this delicate balance to be achieved.

Azuara and colleagues showed that many genes in mouse embryonic stem (ES) cells, including several that are involved in differentiation, have an unusual combination of epigenetic modifications. This includes acetylation at histone H3 lysine 9 (H3K9) and methylation at H3K4, which are marks of active chromatin, and trimethylation at H3K27, which is typical of silent chromatin. In most non-stem cells genes have either active or repressive marks, but not both.

An unusual epigenetic profile was also identified by Bernstein and colleagues for mouse ES cells. They identified a bivalent chromatin structure — containing both methylated H3K4 and trimethylated H3K27 — at genes that encode developmentally important transcription factors.



Both groups showed that loss of these distinctive combinations of epigenetic marks is correlated with differentiation. They propose that the presence of both active and repressive marks allows differentiation-specific genes in ES cells to be repressed but also to be primed for activation when the right signals are received.

How are the unique epigenetic profiles of stem cells specified? The involvement of Polycomb group (PcG) proteins was suggested by Azuara and colleagues. They showed that ES cells that are deficient for embryonic ectoderm deficient (EED), a PcG-complex component that is required for H3K27 methylation, express differentiation-specific genes that are otherwise repressed in these cells. This finding is supported in two other ES-cell studies from Boyer *et al.* and Lee *et al.* Both studies identified large numbers of PcG binding sites across the ES-cell genome that correspond to genes with functions in development and differentiation. These genes were also found to be marked with trimethylated H3K27 and to be transcriptionally silent in ES cells.

Similar to Azuara and colleagues, Boyer *et al.* showed that EED deficiency results in the activation of these otherwise repressed genes, and both Lee *et al.* and Boyer *et al.* showed that PcG target genes are activated during mouse ES-cell differentiation. The authors suggest a dynamic role for PcG proteins in which they maintain a repressive chromatin state before differentiation-inducing signals are received, but are displaced to allow gene expression at the appropriate time. Similar conclusions were drawn from four other recent papers — which are discussed in a related Research Highlight in Nature Reviews Genetics — that examined the roles of PcG proteins in other non-pluripotent cell types, indicating that PcG complexes function in a similar way at various developmental stages.

Excitingly, Lee and colleagues also found that the transcription factors OCT4, SOX2 and NANOG — which are known to have important roles in pluripotency and self-renewal — are also present at many PcG binding sites in ES cells. Working out how these proteins contribute to the unique chromatin properties of ES cells will be an important step in tying together key aspects of stem-cell biology.

Louisa Flintoft,
Senior Editor, Nature Reviews Genetics

ORIGINAL RESEARCH PAPERS Azuara, V. *et al.* Chromatin signatures of pluripotent cell lines. *Nature Cell Biol.* March 29 2006 (doi:10.1038/ncb1403) | Bernstein, B. E. *et al.* A bivalent chromatin structure marks key developmental genes in embryonic stem cells. *Cell* **125**, 315–326 (2006) | Lee, T. I. *et al.* Control of developmental regulators by polycomb in human embryonic stem cells. *Cell* **125**, 301–313 (2006) | Boyer, L. A. *et al.* Polycomb complexes repress developmental regulators in murine embryonic stem cells. *Nature* April 19 2006 (doi:10.1038/nature04733)
FURTHER READING Flintoft, L. A developing role for Polycomb proteins. *Nature Rev. Genet.* 9 May 2006 (doi:10.1038/nrg1873) | Meshorer, E. & Misteli, T. T. Chromatin in pluripotent embryonic stem cells and differentiation. *Nature Rev. Mol. Cell Biol.* 17 May 2006 (doi:10.1038/nrm1938)