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STEM CELLS

Ringing the changes

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> ...RING1-mediated mono-ubiquitylation of H2A has a key role in maintaining Pol II in a previously uncharacterized poised conformation...

Understanding the molecular mechanisms that allow embryonic stem (ES) cells to self-renew, and yet retain the potential to differentiate into different cell types, would open the door to their use in cell replacement medicine — the 'holy grail' of stem cell research. A group led by Ana Pombo and Amanda Fisher now provides new mechanistic insight into ES cell pluripotency by showing that RING1, a member of the polycomb repressor complex-1 (PRC1) family, keeps the transcriptional state of developmental regulator genes poised for future expression.

Transcription of genes by RNA polymerase II (Pol II) is a precisely regulated process that requires initiation of transcription followed by productive elongation to generate full-length mRNAs. Many factors that control transcription are known to modify chromatin. But ES cells have an unusual chromatin profile: many developmental regulator genes ('bivalent' genes) that are not yet expressed are marked by histone modifications that are typical of both transcriptionally active and repressive chromatin.

STOCKBYTE

Recent genome-wide studies of human cells by Guenther *et al.* have shown that most genes that were previously considered to be inactive (because they do not produce detectable transcripts) harbour histone marks that are typically associated with active transcription. Furthermore, chromatin immunoprecipitation coupled to DNA microarray analysis (ChIP-chip), using an antibody specific for the form of Pol II that initiates transcription, showed that Pol II is recruited to most protein-coding genes but does not complete elongation.

So, what are the mechanisms that keep Pol II poised and prevent the production and accumulation of mRNA transcripts? To address this question, Pombo and colleagues examined the binding of different phosphorylated forms of Pol II to multiple bivalent genes in mouse ES cells. They found that Pol II that is phosphorylated on Ser5 (Ser5P), which is associated with transcriptional initiation, was present at the promoters and coding regions of these genes. However, phosphorylation on Ser2 (Ser2P), which is known to mark transcriptional elongation, was absent. These observations correlated with the very low levels of transcription of bivalent loci found in ES cells. Similarly to Ser5P, RING1B, a ubiquitin E3 ligase that catalyses monoubiquitylation of histone H2A at Lys119 (a mark of gene repression), was also abundant.

Could RING1B be the missing link that is responsible for maintaining Pol II in a poised conformation? The answer is yes. Using an inducible knockout system, the authors depleted RING1 in undifferentiated ES cells. This caused a global reduction of H2A ubiquitylation, but also resulted in the de-repression of genes associated with ES-cell differentiation. However, there was no increase in Ser2P at bivalent loci, and Ser5P levels remained unchanged.

The authors propose that, at bivalent genes, RING1-mediated monoubiquitylation of H2A has a key role in maintaining Pol II in a previously uncharacterized poised conformation by preventing transcriptional elongation. Whether this is a general regulatory mechanism of gene transcription remains to be investigated.

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ORIGINAL RESEARCH PAPER Stock, J. K. *et al.* Ring1-mediated ubiquitination of H2A restrains poised RNA polymerase II at bivalent genes in ES cells. *Nature Cell Biol.* 25 Nov 2007 (doi:10.1038/ncb1663)
FURTHER READING Guenther, M. G., Levine, S. S., Boyer, L. A., Jaenisch, R. & Young, R. A. A chromatin landmark and transcription initiation at most promoters in human cells. *Cell* **130**, 77–88 (2007)