STEM CELLS

Avoiding commitment

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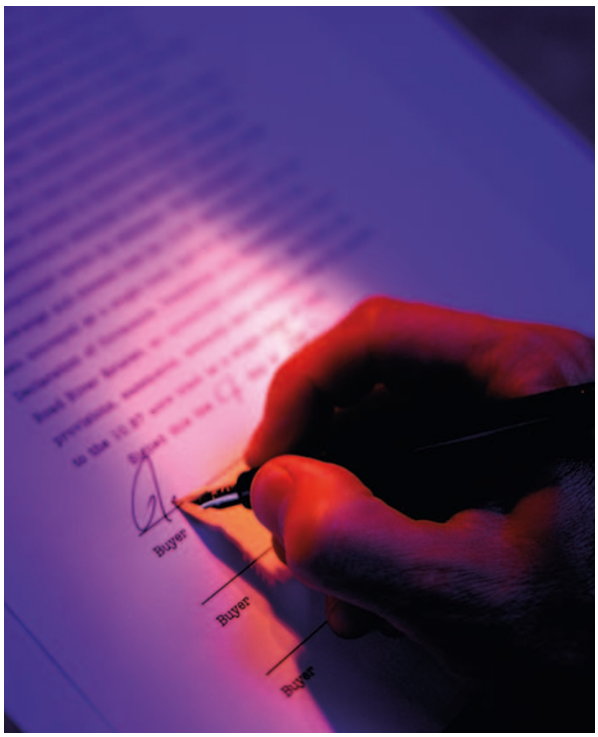
Embryonic stem (ES) cells are characterized by pluripotency, the ability to differentiate into any of the three germ-cell layers. In *Cell*, Szutorisz *et al.* show that the proteasome, a 'chambered protease' best known for its function in the unfolding and degradation of proteins tagged with ubiquitin, is unexpectedly also important for preventing the inappropriate transcription of genes that promote ES-cell differentiation.

In eukaryotic cells, DNA is packaged into chromatin, which controls gene expression in part by limiting the access of transcription factors to DNA. It might be anticipated that, in ES cells, most chromatin would adopt a closed structure to prevent the activation of genes that lead to cell differentiation. However, much of the chromatin is in an open conformation, and therefore genes that control differentiation are accessible for transcription; this indicates that additional non-chromatin-based mechanisms inhibit transcription in these pluripotent cells.



Starting from this basis, Szutorisz *et al.* studied the *λ5–VpreB1* locus — a tissue-specific gene that is inactive in ES cells but that is activated during the early stages of B-lymphocyte development. In ES cells, chemical inhibition of the proteasome or small interfering RNA knockdown of specific proteasome subunits caused increased transcription at several intergenic regions of this locus, including an intergenic element that has enhancer activity during B-cell development. Focusing on this regulatory element, it was shown that proteasome inhibition caused the initiation of aberrant transcription at many new sites. This result indicates that the proteasome prevents the initiation of transcription from hidden promoters in the *λ5–VpreB1* locus.

How might the proteasome suppress transcription? Szutorisz and colleagues found that proteasome inhibition led to increased binding of RNA polymerase II and other components of the pre-initiation complex (PIC), mostly to the intergenic regions that had shown aberrant transcription in the previous proteasome-blocking experiments. Next, the authors showed that subunits of the proteasome are associated with these regions. Different proteasome subcomplexes are targeted to different regulatory regions of the *λ5–VpreB1* locus in ES cells, and the authors propose that the proteasome inhibits aberrant transcription from PICs that form on cryptic promoters that are accessible in the ES-cell open chromatin environment. At these PICs, the proteasome subunits assemble into a functional 26S proteasome, which inhibits inappropriate transcription by catalysing the degradation of PICs bound to promoter sequences.

The protective effect of the proteasome might represent a generalized mechanism of controlling transcription, as the inhibition of proteasome function also caused increased transcription at several other tissue-specific loci. It can be envisaged that regulating the recruitment of the proteasome to DNA elements might have a role in controlling ES-cell-fate decisions.

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ORIGINAL RESEARCH PAPER Szutorisz, H. *et al.* The proteasome restricts permissive transcription at tissue-specific gene loci in embryonic stem cells. *Cell* **127**, 1375–1388 (2006)