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GENE REGULATION

Bivalency buffer makes pluripotency connections

Embryonic stem cells (ESCs) have unique regulatory features that enable them to proliferate rapidly and maintain pluripotency. For example, almost all developmental genes have a bivalent chromatin state, which has features of repression and activation and poises genes for expression during differentiation. A new study reveals that undifferentiated embryonic cell transcription factor 1 (UTF1) is a crucial missing link between the core pluripotency network, bivalency and control of proliferation through mechanisms including a previously unappreciated mode of gene regulation called mRNA pruning and buffering Polycomb-mediated silencing.

Expression of *Utf1* is activated by the core pluripotency factors OCT4 (also known as POU5F1) and SOX2. Through a series of chromatin immunoprecipitation studies in mouse ESCs, Jia *et al.* showed that UTF1 preferentially binds to the promoters of bivalent genes. In *Utf1*-null ESCs, some of these bivalent genes are upregulated, and others are downregulated, suggesting that UTF1 is involved in both repression and activation of such genes.

A crucial component of silencing bivalent genes is the Polycomb repressive complex 2 (PRC2), and the authors explored the relationship between UTF1 and PRC2 binding through experiments that manipulated the levels of the proteins and examined their DNA binding. They found that PRC2 and UTF1 compete for binding to the same bivalent genes. Thus, UTF1 limits PRC2 binding and prevents 'oversilencing'.

But how does UTF1 also repress bivalent gene expression? By mass spectrometry, Jia *et al.* found that some components of the mRNA-decapping complex interact with UTF1 in ESCs. Focusing on one of these components, called DCP1A, they showed that UTF1 recruits the decapping proteins to mRNAs that are produced by 'leaky' transcription of bivalent genes. This decapping 'tag' directs the mRNAs to be degraded in the cytoplasm; the authors term this process mRNA pruning.

One of the transcripts repressed by UTF1 in this way is *Arf* (encoded by *Cdkn2a*). In somatic cells, proliferation is limited by a feedback mechanism in which the transcription factor MYC (also known as c-MYC), which promotes proliferation, activates *Arf* transcription, which in turn represses proliferation. The mechanism in ESCs that prevents this feedback and thus allows rapid proliferation has been unknown; through follow-up studies, Jia *et al.* confirmed that UTF1 facilitates this block. Therefore, UTF1 is a link between the core pluripotency factors and ESC-specific rapid proliferation. The authors also looked in the context of differentiation and showed that UTF1 is involved in the coupling of proliferation and differentiation.

This work reveals that UTF1 can tune the repression–activation balance of a bivalent gene. Indeed, the authors found that whether UTF1 has an activating or repressive role at a particular gene is closely tied to genomic characteristics that might make that gene more prone to activation or to silencing. Overall, uncovering the role of UTF1 brings the aim of a cohesive model of pluripotency at least two steps closer.

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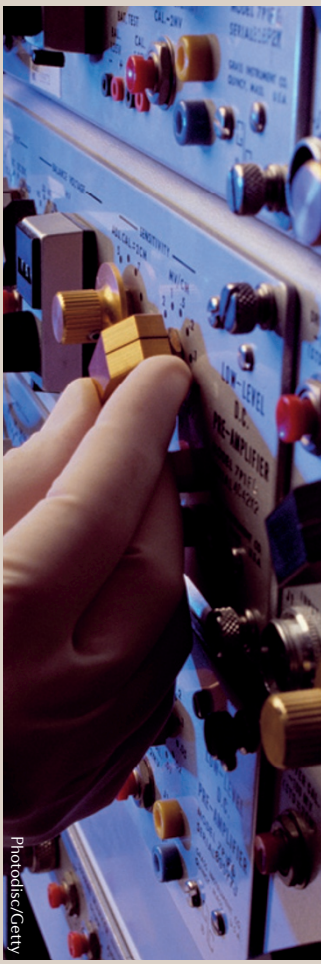
ORIGINAL RESEARCH PAPER Jia, J. *et al.* Regulation of pluripotency and self-renewal of ES cells through epigenetic-threshold modulation and mRNA pruning. *Cell* **151**, 576–589 (2012)



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