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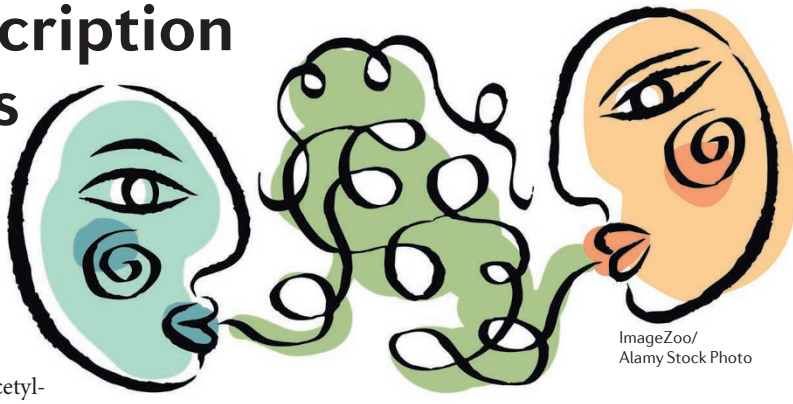
STEM CELLS

Translating hypertranscription in embryonic stem cells



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Cultured embryonic stem cells (ESCs) and pluripotent stem cells in early (peri-implantation) embryos, from which the ESCs are derived, have distinctively decondensed chromatin and high levels of chromatin modifications that are associated with active transcription. Ramalho-Santos and colleagues now report the existence of a positive feedback loop between this permissive chromatin state and translation, which is important for the rapid proliferation of pluripotent stem cells that occurs during early development.

The authors generated a live-cell reporter to visualize transcribed chromatin regions, consisting of EGFP fused to a fragment of a transcription activator that specifically binds to the active-transcription mark trimethylated histone H3 Lys4 (H3K4me3). Using this reporter in a genome-wide RNAi screen for chromatin activators, they identified 303 hits highly expressed in mouse ESCs. These genes encoded transcription regulators and many factors involved in cell growth and protein synthesis, including components of the RNA polymerase I complex, ribosomal proteins, translation factors, and the nutrient sensor mTOR. The fluorescent signal rapidly decreased when translation regulation genes were individually depleted, or when using inhibitors of growth-associated processes — including inhibitors of translation, mTOR and the Myc–Max complex — suggesting that translation positively regulates the permissive state of chromatin in ESCs.

The dependence of chromatin accessibility on translation in pluripotent stem cells was confirmed in reporter-free cells. Treatment of blastocysts and ESCs with cycloheximide (which inhibits translation) or with mTOR inhibitors led to reduced levels of histone modifications found in active promoters and enhancers, including H3K4me3, H4K16 acetylation (H4K16Ac) and H3K27Ac. ChIP-seq revealed that genes that are normally highly transcribed in ESCs, including those encoding ribosomal proteins, had the most prominent reduction in H4K16Ac, which usually concentrates near transcription start sites (TSSs) of active genes. Importantly, translation inhibition had an unexpected rapid effect in reducing the levels of nascent transcripts. Promoter-proximal polymerase pausing was not affected, suggesting that translation inhibition led to overall decreased polymerase occupancy at TSSs and gene bodies.

Proteome-wide analyses revealed that, following translation inhibition, ESCs became rapidly depleted in cell cycle proteins and in regulators of chromatin, transcription and stem cell maintenance, most likely because these proteins are subject to rapid turnover. Analysis of these proteins and those identified in the RNAi screen identified 60 unstable regulators of permissive chromatin in ESCs. Moreover, genome-wide analysis of chromatin accessibility revealed that, following translation inhibition, some regions become less accessible, whereas others become more accessible. Accessibility was lost in regions with active developmental genes and enhancers and at regions bound by transcription factors important for development. Conversely, accessibility was gained at histone genes and near transposable elements, although the functional significance of this remains to be clarified.

ESCs have higher rates of transcription (hypertranscription) than non-pluripotent cells. When comparing the effects of translation inhibition on transcription in different cell types, the authors found that, although transcription is also affected in multipotent neural stem and progenitor cells and in differentiated mouse embryonic fibroblasts, they were less sensitive than ESCs.

Thus, this study indicates that the decondensed, permissive chromatin state of pluripotent stem cells is especially sensitive to translation, creating a positive feedback loop whereby hypertranscription depends on the high output of translation it produces. The authors propose that this feedback loop is important to sustain rapid cell proliferation of ESCs and for embryonic growth. How environmental and developmental signals perturb this transcription–translation feedback loop to regulate developmental transitions and/or other stem cell types remains to be determined.

Kim Baumann

> “the decondensed, permissive chromatin state of pluripotent stem cells is especially sensitive to translation”

ORIGINAL ARTICLE Bulut-Karslioglu, A. *et al.* The transcriptionally permissive chromatin state of embryonic stem cells is acutely tuned to translational output. *Cell Stem Cell* **22**, 369–383 (2018)