TRANSPOSABLE ELEMENTS

ERE and there for pluripotency

Two new studies from Didier Trono's laboratory shed further light on the repressive mechanisms of endogenous retroelements (EREs) in human embryonic stem cells (ESCs) and on how the silencing of some EREs is reversed in a heterogeneous manner when somatic cells are reprogrammed to pluripotency. These findings have important implications for the use of induced pluripotent stem cells (iPSCs).

More than half of the human genome is comprised of EREs of various types. Appropriate control of their activity is crucial not only for limiting insertional mutagenesis (for the subset of EREs that are mobilization competent) but also because EREs can function as *cis*-regulatory elements to influence the expression of nearby cellular genes to modulate cell behaviour and differentiation potential. An emerging theme is that in human and mouse ESCs many EREs remain silenced, whereas others become transiently and selectively derepressed, and their transcripts have active roles in maintaining the pluripotent state.

> "the heterogeneity of ERE activity ... might affect the differentiation potential or safety of iPSCs"

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TRIM28 (also known as KAP1 and TIF1β) is a transcriptional corepressor that is brought to genomic sites by various zinc-finger protein partners. Once there, this complex recruits the SETDB1 histone methyltransferase to deposit repressive trimethylation marks at histone H3 lysine 9 (H3K9me3). Already known to be an important mediator of ERE silencing in mouse ESCs, Turelli *et al.* investigated the role of TRIM28 in human ESCs. They used chromatin immunoprecipitation followed by sequencing (ChIP–seq) to identify TRIM28-binding sites in the genome and also characterized the EREs that become upregulated following TRIM28 knockdown. Overall, they found that TRIM28 is involved in silencing a broad range of ERE types, including human-specific EREs. Through a more global analysis of the transcriptomic and chromatin changes caused by TRIM28 depletion, the authors showed that derepressed EREs can spread activating histone marks into neighbouring genes, thus emphasizing how the occupancy of ERE sequences by TRIM28-containing complexes has effects outside the EREs themselves to regulate cellular genes. Finally, Turelli *et al.* characterized the complex interplay between DNA methylation and TRIM28-triggered histone methylation for the differential repression of different classes of EREs.

Beyond the repression of many EREs, the activation patterns of particular EREs are characteristic of 'natural' pluripotency in ESCs. Hence, Friedli *et al.* investigated how experimentally induced pluripotency affects ERE expression. The investigators reprogrammed human cord blood cells, human hepatocytes and mouse embryonic fibroblasts to iPSCs by co-expressing the pluripotency factors OCT4, SOX2 and KLF4, and monitored the time course of ERE expression. During the early stages of reprogramming (that is, within the first few days of expression of pluripotency factors), broad types of EREs became expressed; however, most classes were silenced again in the resultant iPSCs, leaving only a small subset expressed.

Interestingly, Friedli *et al.* noticed heterogeneity in the silencing of individual EREs among six iPSC clones derived from the same cord blood sample. This ERE expression heterogeneity was greater than that observed among ESC cell clones and resulted in differential expression of nearby cellular genes that persisted even after the iPSC clones were differentiated into embryoid bodies. These heterogeneously expressed EREs included human endogenous retrovirus H (HERV-H), the expression of which has previously been linked to pluripotency.

The authors point out that the heterogeneity of ERE activity and transcriptional programmes in iPSCs might partly underlie the inefficiency of reprogramming (if pluripotency-associated genes are stochastically activated only in some cells) and might affect the differentiation potential or safety of iPSCs that are used for therapeutic purposes.

Darren J. Burgess

ORIGINAL RESEARCH PAPERS Turelli, P. *et al.* Interplay of TRIM28 and DNA methylation in controlling human endogenous retroelements. *Genome Res.* http://dx.doi.org/10.1101/gr.172833.114 (2014) | Friedli, M. *et al.* Loss of transcriptional control over endogenous retroelements during reprogramming to pluripotency. *Genome Res.* http://dx.doi.org/10.1101/gr.172809.114 (2014)