IN BRIEF

TELOMERES

Telomere elongation in induced pluripotent stem cells from dyskeratosis congenita patients

Agarwal, S. *et al. Nature* 17 Feb 2010 (doi:10.1038/nature08792)

Induced pluripotent stem cells show prolonged self-renewal, which is accompanied by telomere elongation in both mice and humans. Does this mean that cells with defects in telomere elongation cannot become pluripotent? This study shows that fibroblasts from patients with X-linked dyskeratosis congenita — which have shortened telomeres because of a mutation in dyskerin, an RNA-binding protein that stabilizes telomerase RNA component (TERC), thus maintaining telomerase activity — can be reprogrammed and that their telomere length increases with continued passage. Telomere elongation results from increased TERC levels following reprogramming, in part caused by increased transcriptional competence mediated by binding of pluripotency-associated transcription factors to the *TERC* locus. This is a feature of the pluripotent state, as TERC levels decreased following fibroblast differentiation. These data reveal a mechanism that maintains telomerase activity in pluripotent cells that could be used to treat patients with dyskeratosis congenita.

AUTOPHAGY

The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1

Komatsu, M. *et al. Nature Cell Biol.* **12**, 213–223 (2010)

p62 targets specific cargos for degradation by autophagy. When autophagy is impaired, p62 accumulates with toxic protein aggregates, and this has been associated with the activation of the liver oxidative stress response and liver damage in mice. Komatsu *et al.* now reveal why excess p62 has such a toxic effect. In normal conditions, the transcription factor NRF2 (nuclear factor erythroid 2-related factor 2; which induces the expression of detoxifying enzymes) is constitutively degraded by the ubiquitin–proteasome pathway following binding to the ubiquitin ligase KEAP1 (kelch-like ECH-associated protein). The authors find that p62 binds to KEAP1, which inhibits the KEAP1–NRF2 interaction and, therefore, NRF2 degradation. The resulting hyperactivation of NRF2 leads to liver damage; indeed, removal of NRF2 in autophagy-deficient mice rescues liver disease.

SMALL RNAS

Stc1: a critical link between RNAi and chromatin modification required for heterochromatin integrity

Bayne, E. H. *et al. Cell* **140**, 666–677 (2010)

RNA interference pathways can promote the assembly of heterochromatin. In fission yeast, heterochromatin, which is characterized by histone H3 Lys9 (H3K9) methylation, is found at centromeres, telomeres and the mating type locus. Small RNAs transcribed from these regions during S phase generate small interfering RNAs (siRNAs) that are loaded into the Argonaute 1 (Ago1)-containing RNA-induced transcriptional silencing (RITS) complex. These siRNAs guide the RITS complex to complementary nascent transcripts and induce heterochromatin formation by recruiting a complex (CLRC) containing the H3K9 methyltransferase Clr4. Bayne *et al.* now identify the LIM domain-containing protein Stc1 as being the key factor that mediates the interaction between Ago1 and CLRC. Once the RITS complex has been guided to specific chromatin domains, Stc1 recruits CLRC and induces heterochromatin formation.