## LncRNAs and self-renewal

Long non-coding RNAs (lncRNAs) have been shown to modulate pluripotency and lineage commitment in embryonic stem cells, but their role in homeostasis has not been explored in detail.

Khavari and colleagues (*Genes Dev.* http://doi.org/hp6; 2012) have used high-throughput transcriptome sequencing and tiling arrays to survey the non-coding RNAs expressed in human progenitors and differentiated cells for several cell types, including keratinocytes, adipocytes and osteoblasts. They have identified an 855-base-pair non-coding RNA (named ANCR) that is greatly downregulated during differentiation. The authors observed that depletion of ANCR using RNAi in primary human keratinocytes induces the expression of genes associated with epidermal differentiation, including key transcription factors. However, the overall expression program affected by ANCR is wider than just these target transcription factor genes. The genes affected by ANCR loss are located throughout the genome, indicating a mode of action different from that reported for other lncRNAs, which are suggested to act on enhancers of proximal genes.

The authors also examined the effect of depleting ANCR in a human skin organotypic assay that recapitulates the stratified organization observed *in vivo*, with undifferentiated cells located near a basement membrane and cells becoming progressively more differentiated towards the surface. They observed the expression of genes normally associated with terminal differentiation in the most basal layer. Further studies will unravel the mode of regulation and action of ANCR in maintaining a progenitor state. NLB

## Replication licensing *in vivo*

To ensure that each DNA segment is only replicated once during the cell cycle, replication requires the 'licensing' of replication origins in late M and G1 phases. The origin recognition complex (ORC), Cdc6, Cdt1 and the Mcm2-7 helicase are needed for replication licensing *in vitro*, but little is known about the dynamic behaviour of licensing components *in vivo*. Blow and colleagues (*J. Cell Biol.* **196,** 233–246; 2012) have now visualized replication licensing in living early *Caenorhabditis elegans* embryos by time-lapse microscopy using fluorescent protein tags.

The authors confirm that Mcm2-7 loading in late M phase depends on ORCs, Cdc6 and Cdt1, but also discover new features of these proteins. FRAP (fluorescence recovery after bleaching) experiments indicate that the dissociation of ORC and Cdc6 from chromatin is decreased in the absence of licensing, but promoted after loading of Mcm2-7, thus creating a negative feedback loop. They also identify the worm orthologues of ORC-3 and ORC-4. Interestingly, although Cdc6 is known to be exported from the nucleus, here ORC-2-5 and ORC-1 are also found to be excluded from the nucleus once the nuclear envelope has reformed after mitosis. Disrupting nuclear export by depleting the transport protein exportin causes extensive re-replication, consistent with the concept that nuclear exclusion of replication proteins is necessary to prevent DNA re-duplication in this system. CKR

## Pulling on cadherin for collective migration

Collective cell migration mediates the tissue rearrangements necessary for embryonic development. Cells migrating collectively experience asymmetric intercellular forces and require intercellular contacts to be maintained. However, although the cadherin cell–cell adhesion molecules are able to respond to mechanical force, little is known about the significance of mechanosensing in collective cell migration. Weber *et al.* now report that the mechanical response of cadherins mediates polarization and directed collective migration of *Xenopus laevis* mesendoderm cells (*Dev. Cell* **22,** 104–115; 2012).

The authors applied force to individual mesendoderm cells adhering to cadherin-coated magnetic beads and observed cell polarization, directional migration and re-organization of keratin intermediate filaments (KIFs). These behaviours required keratin and plakoglobin, a protein that interacts with cadherins and intermediate filaments, as shown using cells from keratin- and plakoglobin-depleted embryos. In assays of two cells adhering to each other on traction permissive matrices, the authors demonstrated that force application recruited plakoglobin to cadherin adhesions, and that plakoglobin was able to reorganize KIFs and link keratin to the mechanosensitive cadherins. Finally, visualization of *Xenopus* embryos during gastrulation showed that plakoglobin and keratin were also needed for mesendoderm polarity and migration *in vivo*. The identification of this mechanoresponsive cadherin pathway highlights the important roles of forces in orchestrating collective cell migration. AIZ

## Genome origami

The three-dimensional conformation of chromosomes is thought to inform and perhaps regulate gene transcription and epigenetic changes. A high-resolution three-dimensional map of the *Drosophila melanogaster* embryonic genome generated by Tanay, Cavalli and colleagues provides fresh insight into the role for chromosomal architecture in these fundamental biological processes (*Cell* http://doi.org/fxrvx7; 2012).

The authors used a modified hydrophobic interaction chromotography technique (combining chromosome conformation capture with parallel sequencing) to generate a genome-wide contact map of *Drosophila* chromosomes. The map confirmed known inter- and intra-chromosomal interactions. A probabilistic model was then developed to interrogate the map further, which predicted the existence of physical chromosome domains exhibiting high levels of contact. Intriguingly, the physical domains correlated with one of four classes of epigenetic marks, reflecting the transcriptional activity of the chromatin. Closer examination of the physical domain borders revealed that these domains were demarcated by insulator binding sites.

The map also revealed that the physical domains corresponding to transcriptionally repressed and active areas are folded differently. The folding of repressive domains seems to facilitate long-range contact between transcriptionally inactive regions on the same chromosome. Transcriptionally active regions, however, form both intra- and inter-chromosomal clusters. Thus, this high-resolution map of chromosome structure and function reveals the existence of physical domains within chromosomes and supports an important role for domain clustering in transcriptional and epigenetic regulation. EJC

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