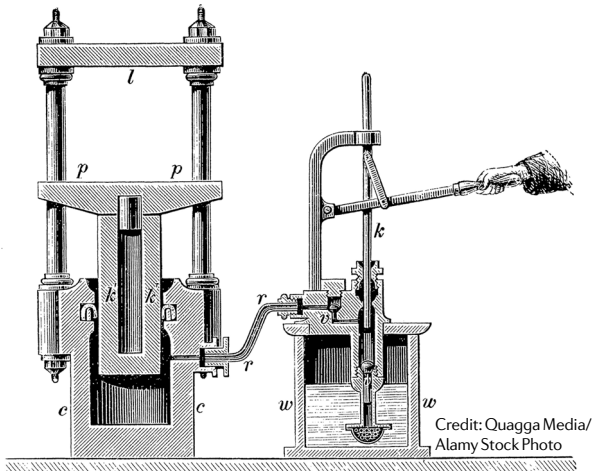

MECHANOBIOLOGY

Embryonic hydraulics

Development is in large part driven by mechanics, but our understanding of the underlying mechanisms is largely incomplete. Chan et al. now show that hydraulic forces have important roles in the early development of mouse embryos.

The mammalian blastocyst comprises a fluid-filled cavity (blastocoel) and two cell lineages: trophectoderm, which forms an outer layer and generates extra-embryonic tissues, and the inner cell mass (ICM), which gives rise to the embryo proper. The authors demonstrated that when the blastocyst forms, the blastocoel initially expands in volume until it reaches a steady state characterized by cycles of collapse and re-expansion without further growth. The increase in blastocoel volume was accompanied by a build-up of pressure in the blastocoel and increase in trophectoderm stiffness. This stiffening in turn was associated with cell stretching and increased cortical tension, which was coupled with cytoskeletal remodelling and maturation of tight junctions. Changes in the blastocoel volume led to equivalent changes in trophectoderm cell cortical tension, but when measured at steady state, cortical tension was comparable in mature blastocysts of various sizes, suggesting that hydraulically generated cortical tension sets the threshold for blastocyst size.

The authors next showed that the build-up of tension in the trophectoderm eventually compromises the stability of cell junctions upon entry into mitosis of the trophectoderm cells. This was associated with junction leakiness, fluid efflux from the blastocoel and blastocyst collapse, which could be promoted or suppressed — thereby regulating blastocyst size — by increasing or decreasing cellular contractility, respectively. Thus, interplay between blastocoel volume expansion and concomitant increase in trophectoderm cortical tension regulates the size of the blastocyst.

Finally, in embryos with smaller cavities, ICM-to-trophectoderm cell ratio was increased; the opposite effect was observed when blastocoels were expanded. This suggests that mechanics of the early embryo — based on the regulation of hydraulic pressure in the blastocoel — have a large impact on early mammalian development, including the regulation of blastocyst size and the first cell-fate decisions in the embryo.

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ORIGINAL ARTICLE Chan, C. J. et al. Hydraulic control of mammalian embryo size and cell fate. *Nature* https://doi.org/10.1038/s41586-019-1309-x (2019)

REGENERATION

Histone methylation boosts liver regeneration

The liver can regenerate following injury, owing to the ability of differentiated, quiescent hepatocytes to re-enter the cell cycle. This switch is thought to involve epigenetic regulation. Wang et al. now show that decreased DNA methylation of transposons induces redistribution of repressive histone methylation and results in enhanced liver regeneration following injury.

The authors analysed mouse hepatocyte transcriptomes at several time points following partial hepatectomy (PH). Of particular interest was a cluster of proliferation-related genes, whose expression was lowest in quiescent hepatocytes and peaked by 48 h after PH, which coincides with the peak of regenerative cell proliferation.

The cluster includes the DNA methylation genes DNA (cytosine-5)-methyltransferase 1 (*Dnmt1*) and its cofactor *Uhrf1*. Hepatocyte-specific deletion of *Uhrf1* (*Uhrf1*^{hepKO}) caused global loss of DNA methylation in the liver, but the mice appeared normal and showed little difference in gene expression compared with control mice. However, *Uhrf1*^{hepKO} mice displayed a kinetically altered gene-expression response to PH: although the genes whose expression was altered were similar in *Uhrf1*^{hepKO} and control mice, liver regeneration genes — especially cell cycle and proliferation genes — were activated earlier and for longer in *Uhrf1*^{hepKO} livers. Consequently, *Uhrf1*^{hepKO} hepatocytes entered mitosis earlier and liver mass recovered more quickly.

Surprisingly, although transposons are silenced by DNA methylation, most were not activated in *Uhrf1*^{hepKO} livers, despite their loss of DNA methylation. Instead, significantly higher levels of histone H3 Lys27 trimethylation (H3K27me3) — a gene-repressive modification — were

DEVELOPMENT

Tracing cell fate

Reporting in *Nature*, Chan et al. describe a CRISPR–Cas9-based 'molecular recorder' that, in mice, provides information on both cell state and cell lineage from fertilization to adulthood.

The molecular recorder comprises a DNA 'target-site' cassette, containing Cas9 'cut sites' and an 'integration barcode', and a cassette encoding single-guide RNAs (sgRNAs). When both cassettes are integrated into cells in the presence of Cas9, sgRNAs guide Cas9 to cut sites where it generates double-strand breaks, the repair of which produces heritable insertions or deletions (indels). Indels, which serve as a cellular 'barcode', can be identified using single-cell RNA sequencing (scRNA-seq) and used to trace the lineage of cells.

The authors isolated embryos expressing their recorder at around embryonic day (E) 8.5 or E9.5 and collected whole transcriptome scRNA-seq data for cells from seven embryos; these cells represented up to 2,461 unique lineages. As most embryos contained cells with unmodified cut sites, this system should record information post-E9.5.

The authors next determined the phenotype of cells from their embryos by comparing their scRNA-seq profile with known gene annotations relating to wild-type mouse gastrulation (that is, E6.5–E8.5). They also reconstructed phylogenetic trees, in which each branch represented an indel. By overlaying these trees with their data on cellular state, the authors found that fewer cell types are represented in the tree


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