Mouse study finds birth coincides with rapid changes in gene activity

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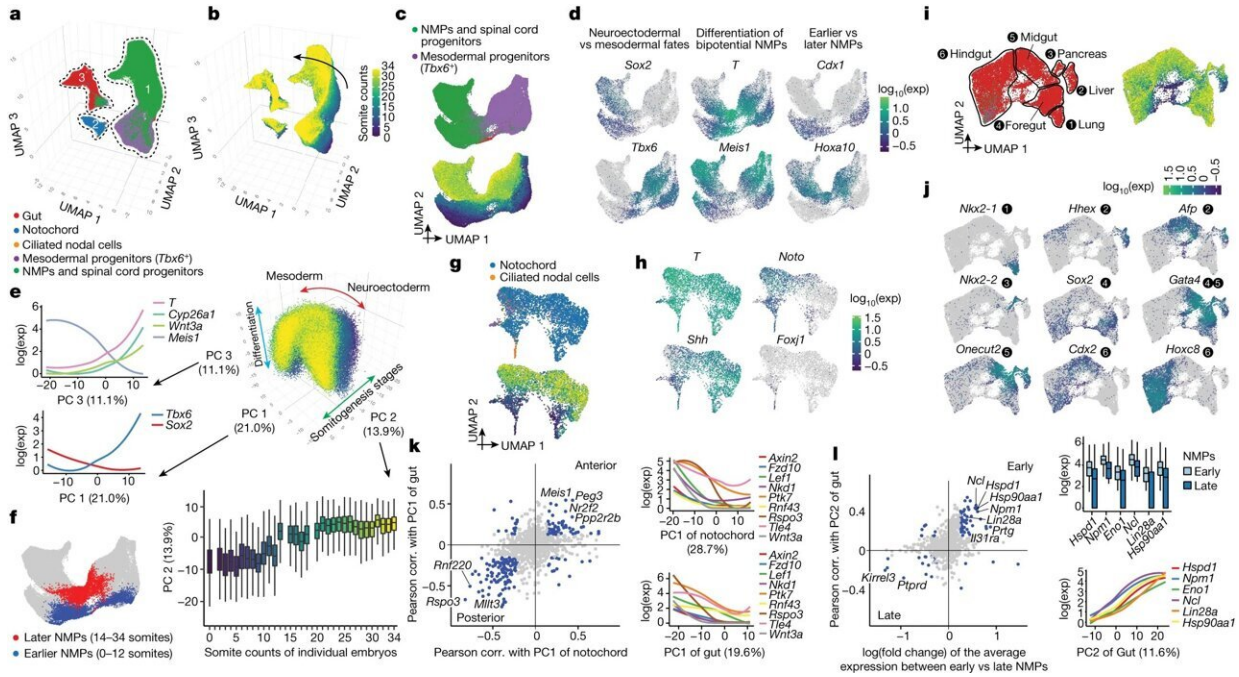

Transcriptional heterogeneity in the posterior embryo during early somitogenesis. **a**, Re-embedded 3D UMAP of 121,118 cells from selected posterior embryonic cell types at early somitogenesis (somite counts 0–34; E8–E10). Three clusters are identified. **b**, The same UMAP as in **a**, colored by somite counts. **c**, Re-embedded 2D UMAP of cells from cluster 1. **d**, The same UMAP as in **c**, colored by marker gene expression for NMP subpopulations (Supplementary Table 12). Exp, expression. **e**, 3D visualization of the top three principal components of gene expression variation in cluster 1. Correlations between top three principal components and the normalized expression of selected genes (left) or somite counts (bottom). **f**, The same UMAP as in **c**, with earlier (n = 4,949 cells) and later (n = 3,910 cells) NMPs highlighted. NMPs: T^{+},

(raw count ≥ 5) and *Meis1*$^{-}$ (raw count = 0). **g**, Re-embedded 2D UMAP of cells from cluster 2. **h**, The same UMAP as in **g**, colored by marker gene expression for notochord or ciliated nodal cells (*Foxj1*$^{+}$). **i**, Re-embedded 2D UMAP of cells from cluster 3. Black circles highlight gut cell subpopulations. **j**, The same UMAP as in **i**, colored by marker gene expression for gut cell subpopulations (Supplementary Table 12). **k**, Left, Pearson correlation (corr.) with PC1 of notochord or gut for highly variable genes. Right, gene expression of selected Wnt signaling genes versus PC1 of notochord or gut. **l**, Left, fold changes between early and late NMPs and Pearson correlation with PC2 of gut are plotted for highly variable genes. Right, gene expression of selected genes (several MYC targets, *Lin28a* and *Hsp90aa1*) versus early and late NMPs or PC2 of gut. In **c**,**g**,**i**, cells are colored by either initial annotations or somite counts. Box plots in **e** (n = 98,545 cells) and **l** (n = 8,859 cells) represent inter-quartile range (IQR) (25th, 50th and 75th percentile) and whiskers represent 1.5× IQR. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07069-w

During its gestation, the house mouse starts out as a single fertilized cell and three weeks later is ready to enter the world as a free-living pup composed of more than 500 million cells.

Scientists are eager to understand how the genome of the house mouse, Mus musculus, orchestrates this routine yet astounding transformation. Although its pregnancies are much shorter, the mouse shares many evolutionary commonalities with humans. It not only offers a useful scientific model of mammalian prenatal development, but also might reveal some basics of what happens during human pregnancies.

It has been difficult, however, to determine the gene activities that drive the timing and appearance of the hundreds of cell types that form a complete newborn mouse, with all its parts in the right place. Due in part to this vast number of cells, the genetic movers of mouse early embryonic development previously have been sampled coarsely at fairly

long intervals, such as day to day observations.

New techniques allow scientists to profile better what is going on genetically in the nuclei—control centers inside individual cells—at shorter, precise intervals and for a total of more than 12 million cells in 83 mouse embryos. This has enabled them to obtain, at the single-cell level, an improved, annotated time-lapse of mouse prenatal development.

Their analysis began when each embryo first shaped itself into a multilayer structure, the gastrula, and continued through birth.

Their findings are published in the journal *Nature*. The lead authors of the paper are Chenqxiang Qiu and Beth K. Martin of the Department of Genome Sciences at the University of Washington School of Medicine in Seattle and Ian C. Welsh of The Jackson Laboratory in Bar Harbor, Maine.

The scientists wrote that they hope their deep sampling will aid "progress towards a more comprehensive, continuous view of transcriptional dynamics throughout prenatal development."

Transcriptional dynamics refers to the timing of cells reading and acting on the plans contained in various parts of their genomes. This time-sensitive activity is vital to producing proteins that guide, for example, the creation and migration of the kinds of cells required at each stage of embryonic development.

The scientists applied a method called optimized single-cell combinatorial indexing RNA sequencing (sci-RNA-seq) to determine the transcriptional states of cells at two- to six-hour intervals from eight days into prenatal development until birth. From this information, the researchers were able to annotate hundreds of cell types and explore the

formation of the kidneys, retina, early neurons, and other tissues.

Combining this latest information with other published data available through open science, the researchers constructed a tree outlining the cell-type lineages and relationships across mouse prenatal development, from the fertilized egg to the newborn pup. Within this tree, they also suggested which genes might be at work in the living, developing embryo to pilot the emergence of hundreds of cell types.

Immediately after the birth of their mouse pups, the scientists noticed that massive, abrupt transcriptional changes had occurred in the nuclei of several kinds of cells, such as those in the airway, liver, and fat tissue. The scientists speculated that these changes might be physiologically necessary due to the profound disruption that occurs between life connected to a placenta and life outside the womb.

A newborn pup suddenly needs to breathe air, maintain normal sugar levels after being cut off from its mother's nutrients, and keep its body at the right temperature. However, many more genes whose adaptive function shortly after birth is not yet known also were turned up. What this means is open for exploration.

The transition from the womb to the outside world, the scientists noted, is already recognized as "fraught with physiological peril."

The researchers added that the kinetic patterns for the rapid transcriptional changes during birth were much more complex than originally realized and that some might pertain to vaginally birthed pups compared to those delivered by C-section.

In discussing their study, the researchers explained that their goal "was not to learn a specific piece of biology, but rather to advance the foundation for a comprehensive understanding of mammalian

development." They added that the dataset examined in this study "is a rich source of hypothesis," such as suggesting transcription factors that might drive the emergence of all prenatal cell types.

The researchers also hope that studies such as these will offer a global framework for studying the genomic basis of mammalian development—perhaps even to include postnatal milestones. A single-cell time-lapse of genetic mechanisms at work throughout the entire mammalian lifespan, from conception to demise, might be the ultimate goal of research of this nature.

More information: Chengxiang Qiu et al, A single-cell time-lapse of mouse prenatal development from gastrula to birth, *Nature* (2024). DOI: 10.1038/s41586-024-07069-w

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