Scientists identify cell-fate regulatory programs using single-cell atlas of mouse development

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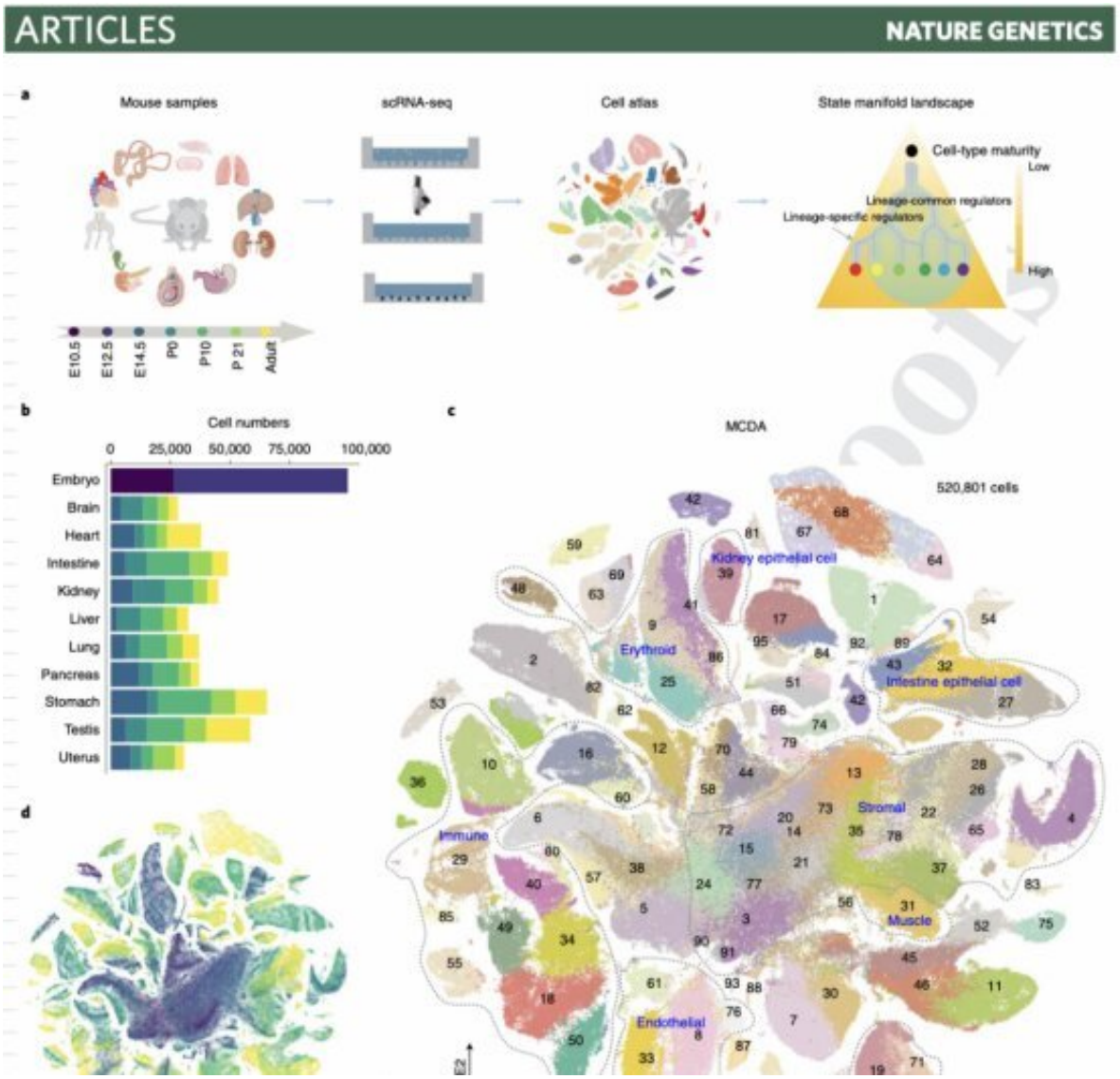


Single-cell transcriptional atlas of mouse differentiation. Credit: Zhejiang

The robustness of the developmental process for multicellular organisms suggests a dedicated regulatory program that governs the trajectories of cell-fate decisions. According to Waddington's epigenetic landscape theory, differentiated cell types arise from an unstable stem/progenitor state and eventually fall into stable cell-fate attractors. The emerging concept of the state manifold derived from single-cell data has further enhanced our understanding of lineage progression. What are the gene-regulatory programs underlying these state manifolds? How are they regulated? These two questions remain enigmatic in this field.

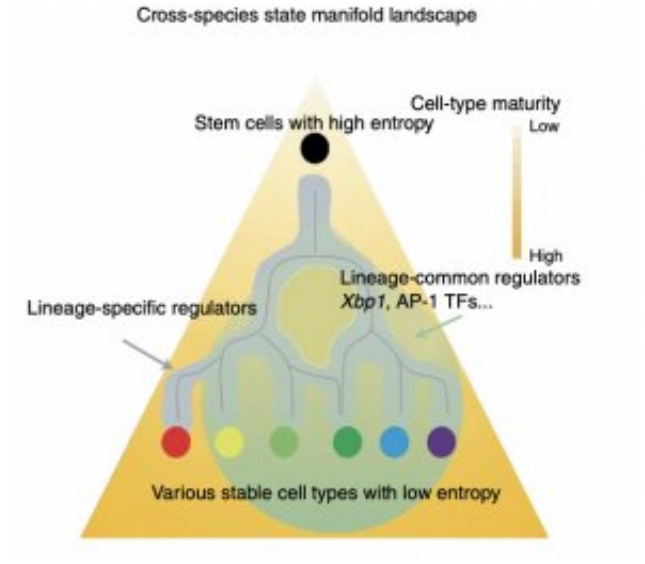
The research team led by Prof. Guo Guoji and Prof. Han Xiaoping from the Zhejiang University School of Medicine has long been committed to research into single-cell sequencing and cell-fate decisions. They developed Microwell-seq, a high-throughput and low-cost scRNA-seq platform using simple and inexpensive devices. Using Microwell-seq, they constructed the world's first mouse cell atlas and human cell landscape, published in *Cell* and *Nature* in 2018 and 2020 respectively.

On this basis, the team performed single-cell transcriptomic analysis on mice at seven life stages ranging from the early embryonic stage to the mature adult stage. Altogether, they profiled more than 520,000 single cells and identified both lineage-common and lineage-specific master regulators involved in core fate-determining circuits in mice. These findings were published in an open-access research article entitled "Systematic identification of cell-fate regulatory programs using a single-cell atlas of mouse development" in the journal *Nature Genetics* on July 11.

In this study, the researchers analyzed the changes of genetic expressions

in mice at different stages ranging from the early embryonic stage to the mature adult stage: the embryonic day (E) 10.5, E12.5, E14.5, the postnatal day (P) 0, P10, P21 and the adulthood (6-10 weeks). The profiled organs involved the neurological, respiratory, digestive, circulatory, urinary and reproductive systems.

Experiments revealed that during the process of lineage development, there was a gradual decrease in transcriptional plasticity. The researchers constructed a systematic regulatory network of transcription factors, identified more than 900 regulons, and determined 15 different expression patterns, including both lineage-common and lineage-specific regulatory programs. They compared the differentiation idiosyncrasies of different cell lineages and identified common regulatory factors for cell-fate decisions.



Credit: Zhejiang University

The researchers integrated the development atlases of invertebrates and

vertebrates and explored the conserved features of development. They built a cross-species state manifold landscape, in which lineage-specific regulators and lineage-common regulators were involved in directing the emergence of cell types and stabilizing cell states. In particular, they identified Xbp1 as an evolutionarily conserved regulator of cell-fate determinations across different species. This study demonstrated that Xbp1 transcriptional regulation was crucial for the stabilization of the gene-regulatory networks for a wide range of mouse cell types.

This study offers genetic and molecular insights into cell-fate decisions and serves as a basis for the theory of the "state manifold."

More information: Lijiang Fei et al, Systematic identification of cell-fate regulatory programs using a single-cell atlas of mouse development, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01118-8

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