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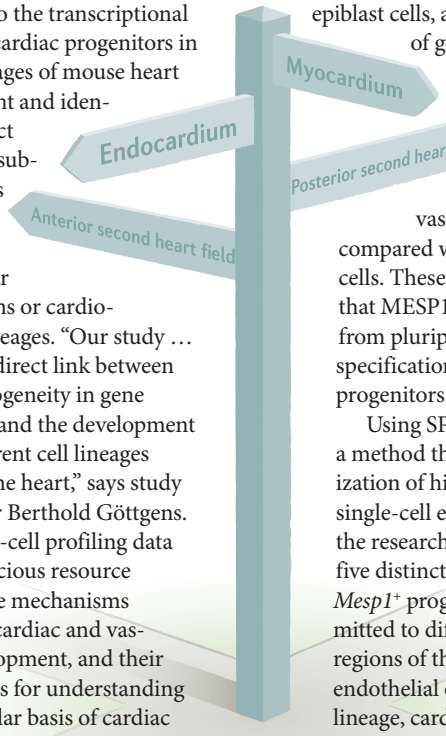
DEVELOPMENTAL BIOLOGY

Early heart decisions

A study using single-cell RNA sequencing (RNA-seq) provides new insights into the transcriptional profiles of cardiac progenitors in the early stages of mouse heart development and identifies distinct progenitor subpopulations that are committed to particular heart regions or cardiovascular lineages. "Our study … provides a direct link between early heterogeneity in gene expression and the development of the different cell lineages that form the heart," says study investigator Berthold Göttgens. "Our single-cell profiling data offers a precious resource to assess the mechanisms regulating cardiac and vascular development, and their implications for understanding the molecular basis of cardiac malformations and heart diseases in patients," adds study investigator Cédric Blanpain.

Heart development starts at gastrulation with the specification of a pool of cardiovascular progenitor cells expressing the transcription factor mesoderm posterior protein 1 (MESP1), which subsequently give rise to all the cardiac cell lineages. To identify the molecular features associated with early cell lineage diversification, the investigators performed single-cell RNA-seq of mouse *Mesp1*$^+$ cardiovascular progenitor cells at early gastrulation (embryonic day 6.25 (E6.25) and E7.25). The analysis showed that these populations of *Mesp1*$^+$ cells have distinct molecular profiles and represent a continuum of differentiation between epiblast cells (E6.50) and later mesodermal cells (E7.25/E7.50). Single-cell RNA-seq of *Mesp1*-knockout cells isolated at E6.75 showed that MESP1 deficiency leads to a developmental block. *Mesp1*-knockout cells were locked in the pluripotent state of epiblast cells, with transcriptional upregulation of regulators of pluripotency as well as markers of epiblast cells, and downregulation of genes associated with epithelial–mesenchymal transition, migration, and cardiovascular commitment compared with wild-type cells. These findings indicate that MESP1 regulates the exit from pluripotency and the specification of cardiovascular progenitors.



Using SPRING analysis, a method that enables visualization of high-dimensional single-cell expression data, the research team identified five distinct populations of *Mesp1*$^+$ progenitor cells committed to different lineages and regions of the heart, including endothelial or endocardial lineage, cardiomyocyte lineage, and anterior and posterior second heart field progenitors. The investigators also showed that expression of *Notch1* marked the early segregation of progenitors committed to endocardial cells and endothelial cells of the aorta and brain vessels. "These different *Mesp1*$^+$ populations are located in specific domains of the developing embryo," explains Blanpain. "The spatial heterogeneity probably represents the timing of the different progenitor specification and the mechanisms regulating their migration and spatial segregation."

The research team plans to continue investigating the molecular mechanisms that regulate the temporal specification of different cardiovascular progenitors and lineage segregation, expanding the number of profiled cells to clarify differentiation trajectories.

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ORIGINAL ARTICLE Lescroart, F. *et al.* Defining the earliest step of cardiovascular lineage segregation by single-cell RNA-seq. *Science* **359**, 1177–1181 (2018)