

Fate before gene expression: Epigenetic priming of cell lineages in the mammalian epiblast

The diversification of mammalian cell lineages is essential to embryonic development, organ regeneration and tissue engineering. Shortly after implantation in the uterus, the pluripotent cells of the mammalian epiblast generate three germ layers: ectoderm, mesoderm and endoderm. Although clonal analyses suggest early specification of epiblast cells towards specific cell lineages, single-cell transcriptomes do not identify lineage-specific markers in the epiblast and thus, the molecular mechanisms underlying such specification remains unknown. We studied the chromatin accessibility of single epiblast cells from the pre-gastrulation mouse embryo, which revealed distinct cell clusters characterized by selective opening of regulatory regions associated to endoderm, ectoderm or mesoderm specification. Epiblast cells with mesodermal priming showed an endothelial/endocardial epigenetic signature, which agrees with the early diversification of the endothelial lineage from that of other mesodermal fates. Performing a behavioral analysis of fate-classified clonal groups followed by live imaging, we found that endothelial precursors show early differentiation from the rest of mesodermal derivatives shortly after their recruitment to the mesodermal fate at gastrulation. These results reveal heterogeneous states of pluripotent epiblast cells before gastrulation and suggest that epigenetic landscape regionalization prime different regions of the epiblast to their future germ layer contributions.



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Miquel Sendra is an HFSP postdoctoral fellow jointly affiliated with IBDM in Marseille and IMBB-FORTH in Heraklion. He is an experimental embryologist with strong training in bioinformatics and single-cell genomics. Miquel completed his PhD at the Spanish National Center for Cardiovascular Research (CNIC) in Madrid, where he investigated early heart development in the mouse embryo using live imaging, lineage tracing, and single-cell transcriptomic and epigenomic approaches. During a research internship at the HHMI Janelia Research Campus in the US, he met his current postdoctoral supervisors, Léo Guignard and Tassos Pavlopoulos. His current research integrates live imaging with single-cell multi-omics to investigate how metabolic states control cell growth and proliferation during embryonic development in the crustacean *Parhyale hawaiensis*.

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