STEM CELLS

Extending pluripotency with a cocktail

A chemical combination enables culture of pluripotent cells.

As pluripotent stem cells (PSCs) give rise to a wide range of cell types, the use of PSCs facilitates the modeling of health and disease and promises therapeutic application. Now, Hongkui Deng, Juan Carlos Belmonte and Huan Shen from Peking University and The Salk Institute and their colleagues report a chemical cocktail that enables derivation and culture of human and mouse PSCs with bipotential towards both embryonic (Em) and extraembryonic (ExEm) lineages.

At the very early stages of development, cells have the potential to differentiate into cells of any type. But as the development process advances and the embryo implants, this potential diminishes as the cells become either inner cell mass (ICM, from which all tissues in the embryo originate) or trophectoderm or endoderm (ExEm, which give rise to the placenta and yolk sac).

While PSCs that predate the commitment to ICM or trophectoderm have been previously reported, whether they could be stably passaged in culture and could truly give rise to both lineages had not been shown. The goal of Deng and colleagues was to culture PSCs that had this greater differentiation potential.

The researchers searched for combinations of small molecules that target signalling pathways known to drive pluripotency in early development, specifically the OCT4 distal enhancer and TGF-β. After several rounds of screening and optimization, they discovered a chemical cocktail that supported long-term culture and self renewal of dome-shaped colonies of human and mouse PSCs. The same cocktail also enabled reprogramming of fibroblasts into induced PSCs.

Notably, the researchers observed that when they injected a single one of these extended pluripotent stem (EPS) cells into an eight-cell mouse embryo, it contributed to both the Em and ExEm lineages. A single EPS cell could also give rise to completely EPS-derived mice by tetraploid complementation. Further, EPS cells showed interspecies chimeric competency, with a single human EPS cell contributing to Em and ExEm lineages and showing chimerism in postimplantation embryos.

The team of scientists analyzed the transcriptional and epigenetic profiles of EPS cells. Whether these cells resemble embryonic cells at the preimplantation stage is an open question, but by reconstructing an earlier time in developmental history, EPS cells are bound to be a useful tool to model normal and disease processes.

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RESEARCH PAPERS

Yang, Y. *et al.* Derivation of pluripotent stem cells with *in vivo* embryonic and extraembryonic potency. *Cell* **169**, 243–257.e25 (2007).