Center for Stem Cell Biology and Regenerative Medicine

Division of Mammalian Embryology
再生発生学分野

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Our lab aims to understand mechanisms underlying the cell fate decisions in early mammalian embryos and to apply their principle for future reproductive and regenerative medicine. In particular, we use pluripotent stem cells and early embryos from various mammals, which will enable us to investigate conserved mechanisms among the mammals and to develop novel technology by the use of species-specific features.

1. Rat post-implantation epiblast-derived pluripotent stem cells produce functional germ cells

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In mammals, pluripotent cells transit through a continuum of distinct molecular and functional states en route to initiating lineage specification. Capturing pluripotent stem cells (PSCs) mirroring in vivo pluripotent states provides accessible in vitro models to study the pluripotency program and mechanisms underlying lineage restriction. Here, we develop optimal culture conditions to derive and propagate post-implantation epiblast-derived PSCs (EpiSCs) in rats, a valuable model for biomedical research. We show that rat EpiSCs can be reset toward the naïve

pluripotent state with exogenous Klf4, albeit not with the other five candidate genes (Nanog, Klf2, Esrrb, Tfcp2l1, and Tbx3) effective in mice. Finally, we demonstrate that rat EpiSCs retain competency to produce authentic primordial germ cell-like cells that undergo functional gametogenesis leading to the birth of viable offspring. Our findings in the rat model uncover conserved principles underpinning pluripotency and germline competency across species.

2. Origin and segregation of the human germline

Aracely Castillo-Venzor [7,14], Christopher A Penfold, Michael D Morgan [15,16], Walfred Wc Tang [7], Toshihiro Kobayashi, Frederick Ck Wong [7], Sophie Bergmann [5, 6], Erin Slatery [5,6], Thorsten E Boroviak [5,6], John C Marioni [15,16], M Azim Surani [7]

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Human germline-soma segregation occurs during weeks 2-3 in gastrulating embryos. Although direct studies are hindered, here, we investigate the dynamics of human primordial germ cell (PGCs) specification using in vitro models with temporally resolved single-cell transcriptomics and in-depth characterization using in vivo datasets from human and nonhuman primates, including a 3D marmoset reference atlas. We elucidate the molecular signature for the transient gain of competence for germ cell fate during peri-implantation epiblast development. Furthermore, we show that both the PGCs and amnion arise from transcriptionally similar TFAP2A-positive progenitors at the posterior end of the embryo. Notably, genetic loss of function experiments shows that TFAP2A is crucial for initiating the PGC fate without detectably affecting the amnion and is subsequently replaced by TFAP2C as an essential component of the genetic network for PGC fate. Accordingly, amniotic cells continue to emerge from the progenitors in the posterior epiblast, but importantly, this is also a source of nascent PGCs.

Publications

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