Gene editing in the context of human germline biology

- Primordial germ cells (PGC) specification
- Epigenetic resetting
- Transmission of genetic and epigenetic information

Create in vitro models for testing the precision of genome editing, and their consequences for development and cell fate determination

Human Germline Genome Editing London 14 November 2019 The germ plasm a theory of heredity



August Weismann (1834-1914)

There are two types of cells in the body:

- Soma that will perish with each generation
- Germ cells are "immortal" and give rise to endless generations



Human germline development



Irie et al., *Cell* 2015; Tang et al., *Cell* 2015; Kobayashi et al., *Nature* 2017; Kobayashi & Surani, *Development* 2018

PGC specification occurs in the peri-gastrulation postimplantation embryo



Early development in mouse and human has diverged

Experimental design : In vitro models for hPGC specification



Irie et al., Cell 2015 Kobayashi et al., Nature, 2017



Naoko Irie

Simulating human peri-gastrulation development and hPGC fate in vitro



Toshihiro Kobayashi et al, .Nature 2017



- SOX17 is crucial for human PGC specification
- Repression of SOX2 in hPGCs but not in mouse PGC
- SOX15, KLF4, etc. detected in hPGCs; repressed in mice Mechanistic studies in progress using degrons

Sybirna, Pierson Smela, Lee.....

Germ cells versus soma: breaking the Weismann's barrier



Towards in vitro models for generating gametes from somatic cells

Making gametes from mouse induced pluripotent stem cells from skin



Viable gametes and live young generated from mouse induced pluripotent stem cells

Hayashi K., et al. Cell (2011) Hayashi K., et al. Nature (2017)



Detailed molecular analysis of ex vivo hPGC for epigenetic resetting



Progressing towards development to ~ week7 & the onset of gametogenesis

Irie, Drusioti...... Alves-Lopes, Wong, Neupane, Shimamoto...... A model to investigate the precision & consequences of gene editing on development



Investigate development in vitro

Summary.....

- Human PGCs from ESCs and iPSCs are likely to develop towards gametogenesis
- Analysis of *ex vivo* hPGCs is crucial for the *in vitro* models
- Manipulations might however cause heritable epimutations
- In vitro models can validate the precision of genome editing, and be tested for the impact on early development and cell fates.

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