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RESEARCH HIGHLIGHT

Reconstituting mammalian spermatogenesis using stem cells

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While stock markets and economies are smoldering all over the world, stem cell science is on fire. The promise of curing many untreatable forms of human male infertility is now one small step closer based on a recent paper in *Cell*.[1] In this work, scientists from Kyoto University in Japan created mature, fertile sperm from embryonic and induced pluripotent stem cells by grabbing the primitive germ cells called primordial germ cells just as they were being made from their pluripotent precursors *in vitro* and transplanting them back into genetically sterile mice.

As background, stem cells possess the unique ability to either propagate by self-renewal or to differentiate to mature tissues under the influence of appropriate molecular cues. This remarkable dual behavior has focused the research spotlight on using stem cells for regenerative medicine. There are now several classes of stem cells, all varying in degrees of pluripotency.[2] Among these, embryonic stem cells represent the prototypical pluripotent stem cells. Another, more recent stem cell is derived from the reprogramming of somatic cells to pluripotent stem cells (iPSCs) and is based on a set of landmark studies conducted by Yamanaka and others[3] that showed that just four factors (Oct4, Sox2, Klf4 and c-Myc) normally produced in the embryo are sufficient to reprogram differentiated, non-embryonic cells into pluripotent cells. In addition, during development, a small population of embryonic stem cells are allocated to the germ line (primordial germ cells), while the remaining cells give rise to the three germ layers. It is this particular stem cell type that has now captured the research limelight.

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Over the past 2 years, germ line stem cell research has seen spectacular advance which suggests that these particular stem cells are quite plastic and manipulatable for potential cell-based therapy. Some of these advances include:

1. The demonstration by several groups that both adult mouse and human testis stem cells, termed spermatogonial stem cells, can be 'induced' or 'transformed' into embryonic-like stem cells.[4–6]
2. The observation that both human embryonic and adult-induced pluripotency stem cells can be directed down the pathway of germ cell differentiation through meiosis *in vitro*.[7,8]
3. The finding that neonatal, mouse, testis stem cells (gonocytes) can placed in an *in vitro* organ culture system and be prodded into making mature, fertile sperm.[9]
4. The report that both pre- and post-pubertal human spermatogonial stem cells can be propagated *in vitro* for prolonged periods of time.[10,11]

In the Kyoto study, both embryonic stem cells and iPSCs from mice were observed as they began to differentiate into other cell types *in vitro*. From developing epiblast-like cells, using global transcriptome profiling, information from epigenetic programming and cellular dynamics, they defined the most primitive of true germ cells, the differentiating primordial germ cells (PGCs). They observed that PGCs are indeed distinct from epiblast cells and also noted that they are transient in the germ cell lineage. When properly characterized and injected into the testes of genetically (W/W^v) mice, the PGCs formed competent sperm 50% of the time. The sperm was also capable of producing normal F1 mice after assisted reproduction. And, the F1 mice were naturally fertile!

This success took a lot of work, and invoked a host of molecular and expression characterization of developing cells and lots of sweat equity. And not all the results were rosy. When cells slightly different from primordial germ cells were injected into sterile testicles, benign tumors formed, the scourge of stem cell science. This emphasizes the importance of identifying putative surface markers that delineate a pure population of PGCs for use with this approach. Not only that, when iPSCs were used to create PGCs and transplanted into sterile mice testes, some of the offspring died prematurely with 'tumors around the neck region', a finding that will certainly will need further investigation if the technique is to become clinically viable in humans.

Recreating mammalian spermatogenesis, an enormously complex process involving both mitosis and meiosis and multilayered quality control check points, is a scientific and clinical holy grail. Clinically, these techniques hold promise for creating man-made sperm for infertile men who lack germ cells for genetic or acquired (i.e. cancer treatment) reasons. If fully realized in humans, it may be possible to use non-germ cell sources to make sperm; maybe even a simple skin biopsy could be used as starting point. Saitou and colleagues have taken us one step closer to its realization by employing embryonic stem cells and iPSCs as precursors and functionally recapitulating the process in mice.

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