Scientists create germ cell-supporting embryonic Sertoli-like cells from skin cells

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Using a stepwise trans-differentiation process, Whitehead Institute researchers have turned skin cells into embryonic Sertoli-like cells.

The main role of mature Sertoli cells is to provide support and nutrition to the developing sperm cells. Furthermore, Sertoli cells have been demonstrated to possess trophic properties, which have been utilized for the protection of non-testicular cellular grafts in transplantations. However, mature Sertoli cells are mitotically inactive, and the primary immature Sertoli cells during prolonged cultures degenerate in the petri dish. Therefore, finding an alternative source of these cells independent of the donor testis cells is of paramount interest both for basic research and clinical applications.

"The idea is if you could make Sertoli cells from a skin cell, they'd be accessible for supporting the spermatogenesis process when conducting in vitro fertilization assays or protecting other cell types such as neurons when co-transplanted in vivo," says Whitehead Institute Founding Member Rudolf Jaenisch. "Otherwise, you could get proliferating cells only from fetal testis."

Jaenisch lab researchers have seemingly overcome the supply and lifespan challenges through trans-differentiation, the process of reprogramming a cell directly from one mature cell type to another without first taking the cell in question all the way back to the embryonic stem-cell stage. Unlike other reprogramming methods that produce induced pluripotent stem cells (iPSCs), trans-differentiation does not

rely on the use of genes that can cause cancer.

As reported in *Cell Stem Cell*'s September issue, scientists trans-differentiated mouse skin cells into embryonic Sertoli-like cells by breaking the process into two main steps, mimicking Sertoli cells' development in the testis. The first step in this progression transformed the skin fibroblasts from their mesenchymal state to a sheet-like epithelial state. In the second step the cells acquired the capability to attract each other to form aggregates as seen in vivo between embryonic Sertoli cells and germ cells.

Next the scientists devised a cocktail of five transcription factors that activate the epithelial cells' embryonic Sertoli cell genetic program. The resulting cells exhibited many of the characteristics of embryonic Sertoli cells, including aggregating, forming tubular structures similar to the seminiferous tubules found in the testis, and secreting the typical Sertoli cell factors. When injected into a mouse fetal testis, the trans-differentiated cells migrated to the proper place and integrated into the endogenous tubules. Overall, the injected cells behaved like endogenous embryonic Sertoli cells, despite expressing a few genes differently.

"The injected trans-differentiated cells were closely interacting with the native germ cells, which shows that they definitely do not have any bad effect on the germ cells," says Yossi Buganim, a postdoctoral researcher in the Jaenisch lab and first author of the Cell Stem Cell paper. "Instead, they enable those germ cells to survive."

In fact, when the embryonic Sertoli-like cells were used to sustain other cells in a Petri dish, Buganim noted that the cells supported by the trans-differentiated cells thrived, living longer than cells sustained by actual native Sertoli cells.

Encouraged by these results in vitro, Buganim says he would like to

investigate whether the embryonic Sertoli-like cells retain this enhanced supportive capacity after transplantation into the brain, where the cells could sustain ailing neurons. If so, they could have applications in the development of neuron-based therapies for neurodegenerative disorders such as ALS and Parkinson's disease.

More information: "Direct reprogramming of fibroblasts into embryonic Sertoli-like cells by defined factors" Yosef Buganim et al., *Cell Stem Cell*, September 7, 2012 print issue.

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