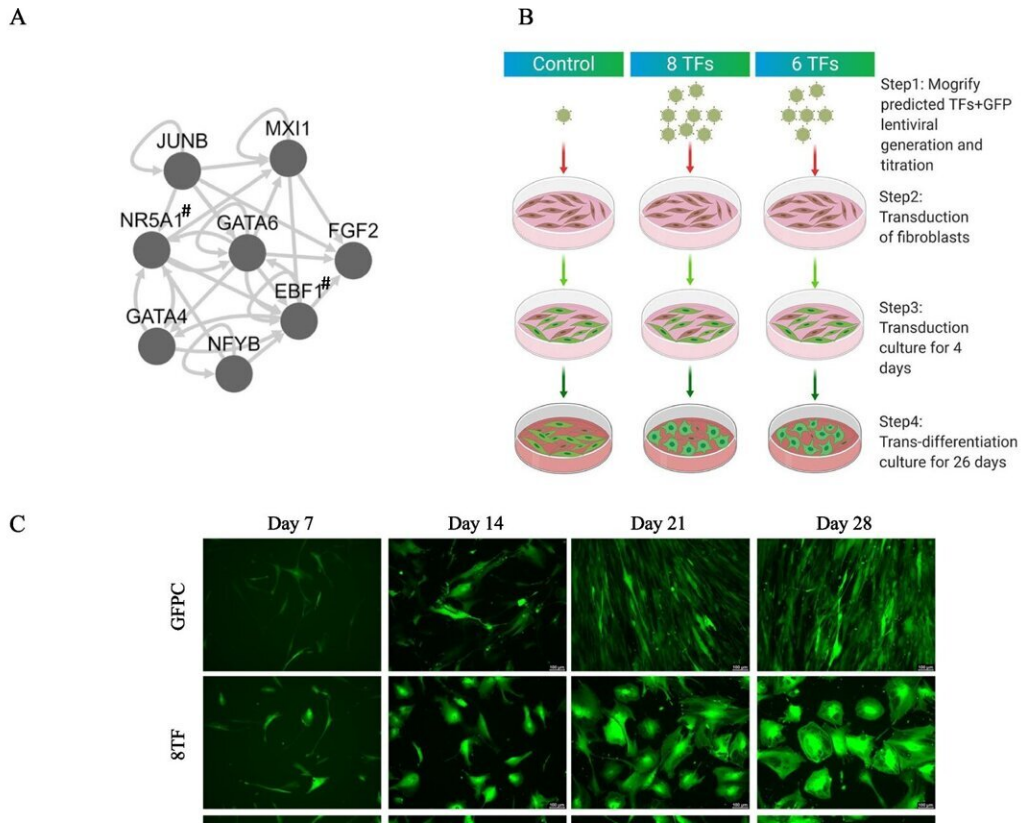
Researchers develop new technique for diagnosing disorders of sex development

July 18 2024, by Rob Clancy



46,XY fibroblast derived SLCs exhibit significant change in morphology over the 1-month trans-differentiation and show subcellular expression of Sertoli markers. A) Mogrify-predicted transcription factors required for dermal fibroblasts to Sertoli cell trans-differentiation. B) Outline of the trans-differentiation strategy. C) Representative images of live cells belonging to the indicated groups expressing GFP across the 1-month trans-differentiation culture of 46,XY dermal fibroblasts. Morphometric analysis of cells in (C) showing shape factor (D) and area quantification (E). Credit: *Biology of Sex Differences*

(2024). DOI: 10.1186/s13293-024-00599-y

Disorders/differences of sex development (DSD) are difficult to diagnose because of the multiple phenotypes and genes involved, but a new technique developed at Hudson Institute of Medical Research is set to change all that.

About 1 in 5,000 babies is born with DSD or intersex, where their genetic, hormonal or physical sex characteristics (genitals, gonads and chromosome patterns) are not typically male or female.

Until now, diagnosing the cause of many DSDs has been hampered because the events that determine sex development occur at around week nine of gestation and only in a small number of cells of the gonads of the developing fetus.

But Professor Vincent Harley and his team have developed a model to study this through reprogramming skin cells into testicular cells (Sertoli cells) to understand the changed cell and genetic processes that lead to the Intersex condition in that patient.

"We study the genes involved in formation of the testis in the embryo, but our understanding of this process is limited by the obvious problems in obtaining human samples. So we developed a way of transforming skin cells into the key cells of the testis, the Sertoli cells, which we can then grow and analyze," he said.

Simpler sex development disorder diagnosis critical

Their research, published in the journal *Biology of Sex Differences*, shows how this technique can address the lack of availability of gonadal

tissue from patients at specific developmental stages by allowing diagnostics tests to be carried out on reprogrammed skin cells.

Prof. Harley explains, "Sertoli cells are relevant because they act like an organizing center of embryonic gonadal development and many DSDs arise when these developmental processes go awry."

"Accurate diagnosis is critical to inform the occurrence of life-threatening crises (e.g., congenital adrenal hyperplasia), the response to hormone replacement therapy, eventual gender identity, cancer risk and counseling for future fertility."

"Patients suffer a long diagnostic odyssey, with many never receiving a definitive diagnosis," Prof. Harley said. "Our new model will help identify new causes and mechanisms of DSD in children."

Finding the genes contributing to sex development disorders

A different but related research paper published in *Frontiers in Cell and Developmental Biology* showed a new target for mutations in and around the SOX9 gene which is likely to contribute to DSDs.

The authors, led by Prof. Harley, identified Trpc3, which is a SOX-9 target, and is up-regulated by SOX9. They found that inhibition of Trpc3 expression by Pyr-3 impaired germ and endothelial cell development, suggesting that TRPC3 may mediate SOX9 function during Sertoli, germ and endothelial cell development.

Identifying specific molecular changes

Another significant piece of research from Hudson Institute by Prof.

Harley and colleagues will lead to greater understanding of the mechanisms by which a particular gene on the Y chromosome, called ATR-X, can lead to genital and testicular abnormalities.

The work, published in *iScience*, saw the team establish a mouse model with deleted ATR-X gene that recapitulates these defects (G2/M arrest and apoptosis, i.e., cell death).

Using this model, they were able to identify the specific molecular changes that result in impaired testis formation and spermatogenesis.

These studies advance our understanding of basic biological mechanisms, and the perturbations that lead to sex development disorders including intersex conditions.

More information: Abhinav Parivesh et al, Reprograming skin fibroblasts into Sertoli cells: a patient-specific tool to understand effects of genetic variants on gonadal development, *Biology of Sex Differences* (2024). DOI: 10.1186/s13293-024-00599-y

Zhenhua Ming et al, A role for TRPC3 in mammalian testis development, *Frontiers in Cell and Developmental Biology* (2024). DOI: 10.3389/fcell.2024.1337714

Nayla Y. León et al, Y chromosome damage underlies testicular abnormalities in ATR-X syndrome, *iScience* (2024). DOI: 10.1016/j.isci.2024.109629

Provided by Hudson Institute of Medical Research

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