CRISPR/Cas9 + HPSC = human PKD lab model

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CRISPR/Cas9 is hot. News of the revolutionary gene editing technique that is already shaking up bioscience has finally reached the news media and the public. Now comes a first rate example of how CRISPR is changing the pace of biomedical research by linking up with another cutting edge technology—human pluripotent stem cells (hPSCs). Benjamin S. Freedman, now at the University of Washington, and his colleagues in Joseph Bonventre's lab at Harvard Medical School, have used CRISPR/Cas9 to guide hPSCs into becoming a human cell-based lab model system for polycystic kidney disease (PKD). The most common inherited kidney disorder, affecting one in 500 Americans, PKD currently is not curable and, without long-term dialysis or kidney transplant, can be fatal.

Freedman will speak about the PKD model at ASCB 2015 in San Diego on Monday, Dec. 14, 2015, following its earlier publication in *Nature Communications*.

PKD's hallmark is the formation of damaging, balloon-like cysts in kidney tubules. In the early 2000s, cell biologists linked cyst formation to gene mutations that affect the primary cilia, hair-like projections from cells that seem to act as sensory antennae. These fundamental discoveries were made in non-human organisms such as the algae, Chlamydomonas reinhardtii, and the zebrafish, Danio rerio. But the exact disease mechanism in humans is still not well understood in part because there hasn't been a good human model of PKD in kidney cells.

CRISPR gave Freedman et al. a more precise tool to remodel the hPSC genome to include PKD mutations in the disease-linked genes, PKD1 and PKD2. The researchers then used a 3-D cell culture system to coax their mutant and healthy hPSCs down the differentiation pathway into becoming kidney progenitor cells and finally the proximal tubule cells found in kidney nephrons. In the mutant tubule cells, they observed the formation of large, translucent cyst-like structures but not in their healthy controls. These observations and others have convinced the researchers that their CRISPR/Cas9 and hPSC system produces a stable, biologically accurate human model for a common genetic disease where new understanding and new therapies are desperately needed.

More information: Modeling Polycystic Kidney Disease Cystogenesis with Genome?Modified Human Pluripotent Stem Cells, ASCB 2015.

Benjamin S. Freedman et al. Modelling kidney disease with CRISPR-mutant kidney organoids derived from human pluripotent epiblast spheroids, *Nature Communications* (2015). DOI: 10.1038/ncomms9715

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