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Scientists Discover Genetic Pathway that Could Lead to Drug Therapy for Kidney Disease

Scientists at the University of California, Santa Barbara have reported a discovery at the cellular level that suggests possibilities for drug therapy for kidney disease.

Over 600,000 people in the U.S. are affected by the inherited kidney disease known as ADPKD, short for autosomal-dominant polycystic kidney disease. In the U.S. this is more than the number of individuals affected by cystic fibrosis, muscular dystrophy, hemophilia, Down's syndrome, and sickle cell anemia combined. The disease is characterized by the proliferation of cysts that eventually debilitate the kidney, causing kidney failure in half of all patients by the time they reach age 50.

Currently no treatment exists to prevent or slow cyst formation, and most ADPKD patients require kidney transplants or life-long dialysis for survival, explained Thomas Weimbs, assistant professor of biology at UCSB and director of the lab that made the discovery, which was reported in the January issue of the journal *Developmental Cell*.

Kidney cells are lined with small hair-like cilia. The cilia sense fluid flow as urine is passed through the kidney and they send signals to the kidney cells that line the small canals -- called tubules. It is the loss of cilia function that leads to polycystic kidneys.

"With polycystic kidneys, these tubular cells think they have to repair an injury, and they 'repair' by forming lots of cysts," said Weimbs.

The disease is triggered by polycystin-1, a large protein. If it mutates, then the mutation leads to polycystic kidney disease. Even though polycystin-1 was discovered more than a decade ago, its function has remained unknown.

In this study, Weimbs and his colleagues discovered that, under normal conditions, the polycystin-1 keeps certain parts of the cell localized in the cilia and away from the nucleus. These parts of the cell are known as transcription factors. If there is an injury the flow of urine stops, and the transcription factors migrate to the nucleus of the cell, signaling the cell to divide to replace those cells that have been lost. In patients with this disease the repair mechanism is always turned on because the polycystin-1 is defective, or mutated.

The discovery of this pathway thus opens the door to possible drug therapy for the disease. This is because the inhibition of any step along this pathway should have beneficial effects. Weimbs and his team are currently capitalizing on these findings by testing drugs to specifically affect components of this novel pathway.

About UC Santa Barbara

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