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Gail Gallessich

UCSB Scientists Discover New Drug Target for Kidney Disease

Two discoveries at UC Santa Barbara point to potential new drug therapies for patients with kidney disease. The findings are published in this week's issue of the Proceedings of the National Academy of Sciences.

Over 600,000 people in the U.S., and 12 million worldwide, are affected by the inherited kidney disease known as autosomal-dominant polycystic kidney disease, or ADPKD. The disease is characterized by the proliferation of cysts that eventually debilitate the kidneys, 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 lifelong dialysis for survival, explained Thomas Weimbs, director of the laboratory where the discoveries were made. Weimbs is an associate professor in the Department of Molecular, Cellular and Developmental Biology and the Neuroscience Research Institute at UCSB.

First, Weimbs and his research team discovered a molecular mechanism that sheds light on the disease. The mechanism concerns polycystin-1, a protein that is mutated in ADPKD patients. The team discovered how this protein regulates a well-known transcription factor called STAT3. Transcription factors transcribe information from DNA to RNA, from specific genes. Second, the team discovered that STAT3 is strongly, and aberrantly, activated in polycystic kidneys.

"The clinical significance of these discoveries lies in the fact that STAT3 is also known to be aberrantly activated in many forms of cancer and is considered an important drug target for cancer therapy," said Weimbs. "Numerous STAT3 inhibitors are currently being developed and tested, and several experimental drugs are already available. Our results suggest that STAT3 activation is a driving force for the cyst growth that leads to polycystic kidneys in ADPKD. Therefore, STAT3 may be a highly promising drug target for the treatment of ADPKD."

Weimbs explained further that STAT3 is a signaling molecule that is activated in response to many different growth factors binding to specific receptors on the surface of kidney cells. In response to these growth factors hitting the cell, STAT3 is activated. That causes STAT3 to turn on the expression of certain genes. This activity causes the cells to proliferate, as they do in cancer.

"In polycystic kidney disease, we have strong proliferation, but it is similar to having benign tumors -- where the tumor stays in place," said Weimbs. "The cysts keep growing, but they do not metastasize or invade other tissues as do cancerous tumors. Polycystic kidneys are full of small, benign tumors or cysts. This is still very destructive, because eventually the disease will destroy the kidney."

The research team is currently testing STAT3 as a drug target in mice with ADPKD.

The first author of the paper is Jeffrey J. Talbot, a postdoctoral fellow in the Weimbs lab. The other co-authors from UCSB are Jonathan M. Shillingford, Shivakumar Vasanth, Nicholas Doerr, and Sambuddho Mukherjee. Additional co-authors are Terry Watnick, Johns Hopkins University School of Medicine; and Mike Kinter, Oklahoma Medical Research Foundation. The National Institutes of Health funded the research.

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† Top photo: This image shows immunohistochemical staining (dark brown) of activated STAT3 in a mouse polycystic kidney. Note the strong signal in cysts compared to normal kidney tubules.

Credit: Weimbs Lab, UCSB

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