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For immediate release

Protein protects mouse kidneys from damage caused by acute injuries and chronic renal disease

ANN ARBOR, Mich. – University of Michigan scientists have identified a new and unusual protein that reduces, in laboratory mice, kidney damage caused by chronic renal disease and acute toxic injuries.

Named KCP, for kielin/chordin-like protein, the new protein is the first of its kind found to directly enhance signals from bone morphogenetic proteins or BMPs, which are vital to the normal development and healthy functioning of the kidney.

"KCP is similar in structure to proteins like chordin, which suppress BMP signals during embryonic development," says Gregory R. Dressler, Ph.D., an associate professor of pathology in the U-M Medical School, who directed the research study. "But instead of suppressing the signal, KCP enhances it by strengthening interactions between the BMP protein and its receptor on kidney cells."

"In two different models of mice with renal injuries, we found that KCP activity was required to slow the progression of kidney disease," Dressler says. "Mice that couldn’t secrete KCP protein were more susceptible to renal injuries, had higher mortality rates and showed more fibrosis and scarring than normal mice. Our data suggest that KCP could have the potential to be a therapeutic agent for fibrotic renal disease in humans."

Results of the study were published March 27 by Nature Medicine on its Advance Online Publication Web site.

Developmental biologists like Dressler have been studying bone morphogenetic proteins for decades, because they are so important to the regulation of embryonic development in mammals. BMPs aren’t as familiar to clinical scientists, because only a handful of studies, conducted during the last six years, have examined the effects of BMPs on renal disease. BMP7, in particular, plays an essential role in kidney disease and development.

"When BMP7 binds to the type 1 receptor on a kidney epithelial cell, it triggers signaling proteins called Smads, which are inside the cell, to move to the nucleus where they can change the pattern or degree of gene activity," Dressler explains. "In our study, we found that KCP is secreted primarily by tubular epithelial cells in the kidney. When it attaches to BMP7, it increases the stability between BMP7 and the cell’s receptor, which gives genes more time to express proteins epithelial cells need to recover from injury."

Like many significant scientific discoveries, U-M researchers discovered the protein by accident while searching a library of DNA clones involved in embryonic kidney development. "We were looking for DNA sequences with cysteine-rich domains,
because we knew they were important in BMP signal suppression,” Dressler says. “But as we worked with KCP, we realized it’s not a suppressor at all.”

In initial studies, Dressler and his research team found that cells in cultures containing KCP showed three to ten times the response to signals from BMP7 than similar cell cultures without KCP.

To determine the effects of KCP in experimental animals, Dressler created a strain of knock-out mice that were unable to produce KCP protein, because they lacked the required gene. When he bred the mutant knock-out mice, he was surprised to find they were fertile, with a normal lifespan and no obvious abnormalities.

“Bone morphogenetic proteins have a definite developmental function. If you knock-out BMP7, the kidneys stop developing about 14 days after fertilization,” Dressler says. “But KCP doesn’t appear to affect embryonic development at all. My interpretation is that this protein may be a stress response gene, which is active in adults.”

Jingmei Lin, a U-M graduate student and first author of the study, used two different laboratory procedures designed to produce the effects of human renal disease or injury in experimental animals.

In the first procedure, Lin and Xu Cheng, a U-M research associate, tied off the ureter, or connecting tube leading from one kidney to the bladder, while leaving the other kidney untouched. As a result of this procedure, mice develop a condition called interstitial fibrosis or scarring, which is commonly seen in chronic renal disease in humans. When Lin compared kidneys from the KCP knock-out mice and the control mice, she found significant differences.

Seven days after surgery, kidneys from KCP knock-out mice had twice the amount of fibrosis as kidneys from normal mice. Thirteen days after surgery, knock-out kidneys had 67 percent more interstitial damage than normal kidneys. And what was most surprising was that the knock-out mice developed fibrosis in their unobstructed kidney, while the control mice did not.

“Fibrosis in the control kidney was a surprise, because it’s never been reported before,” Dressler says. “This could be an indication of increased stress on the remaining functional kidney, or an inflammatory response, but clearly KCP protected the control kidney in normal mice from damage.”

To evaluate the impact of KCP on animals after an acute toxic injury to the kidney, Lin and Sanjeevkumar Patel, M.D., a clinical lecturer in internal medicine, injected both sets of mice with folic acid, which causes severe damage to proximal tubular epithelial cells in the kidney. “It’s the kidneys’ job to filter out toxic substances from blood and urine, and proximal tubule cells are particularly sensitive, because this is an area where toxins are present in high concentrations,” Dressler explains. “In people, this is a common cause of renal failure from drug overdoses or exposure to toxic chemicals.”

According to Dressler, mice usually recover from this procedure within seven days. But 23 percent of the KCP knock-out mice died from renal failure, while only 2 percent of the normal control mice died. Kidneys from the experimental mice had large amounts of scarring and cysts, while kidneys from the control mice looked normal.

“Our work supports the idea that BMP pathways play an important role in chronic and acute renal disease,” Dressler says. “If we can understand and learn to manipulate those pathways, then we may be able to improve patient outcomes.”
“My overall goal is to understand the pathways that control the differentiation of cells during development, and apply that knowledge to the disease process, so we can ultimately develop new therapies for kidney disease,” he adds.

Dressler’s research was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Polycystic Kidney Disease Foundation.

Other U-M collaborators in the research study included: Research associates Eun Ah Cho, Inna Levitan, and Matthew Ullenbruch; Sem H. Phan, M.D., Ph.D., professor of pathology; and John M. Park, M.D., associate professor of urology.

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