MedicalXpress

Gene linked to pediatric kidney cancer suggests new strategies for kidney regeneration

April 13 2014

Nearly one-third of cases of Wilms tumor, a pediatric cancer of the kidney, are linked to a gene called Lin28, according to research from Boston Children's Hospital. Mice engineered to express Lin28 in their kidneys developed Wilms tumor, which regressed when Lin28 was withdrawn, indicating that strategies aimed at blocking or deactivating the gene hold therapeutic promise for children with Wilms. Studies in the mouse model further suggest that controlled expression of Lin28 can promote kidney development and therefore may hold clues to regeneration of damaged kidneys in adults.

The team, led by George Q. Daley, MD, PhD, of Boston Children's, reported their findings online in the journal *Genes & Development*.

Approximately 500 children in the U.S. are diagnosed with Wilms tumor every year. When examined under a microscope, the tumors resemble immature embryonic kidneys, leading doctors to conclude that Wilms tumors form when kidney development, normally complete by birth, persists into childhood.

Lin28 is closely tied to organ and tissue development in organisms as diverse as worms and humans, and is active in the kidneys early in development. To see whether Lin28 might be a factor in Wilms tumor development, Daley and an international team of collaborators measured the gene's expression in tumor samples from 105 Wilms patients. Nearly

one-third of the tumors exhibited high levels of Lin28 activity.

"We found particular association between Lin28 and high-risk 'blastemal' Wilms tumors," says Daley, director of the Stem Cell Transplantation Program at Boston Children's and an investigator with the Howard Hughes Medical Institute. "These tumors often resist therapy but currently cannot be identified prior to treatment. Lin28 may serve as a biomarker for such treatment-resistant tumors."

Achia Urbach, PhD, lead author on the study, engineered a strain of mice to express a Lin28 transgene in the kidneys. The kidneys of those mice were markedly enlarged and continued to grow as long as the Lin28 gene was active. Eventually, those kidneys took on the appearance of Wilms tumors.

"Our data suggest that when Lin28 is active for too long, it keeps the kidneys from completing their developmental program, which would explain Wilms tumors' resemblance to embryonic kidney tissues" says Urbach, a former Boston Children's researcher, who is now on the faculty of Bar-Ilan University in Israel.

Lin28 is part of a feedback loop with a tumor-suppressing gene called Let-7, with each gene keeping the other in check. Daley and Urbach's team found that they could reverse Lin28's tumor-causing effects in their transgenic model by forcing expression of Let-7, suggesting that treatments targeting Lin28 hold promise for treating Wilms tumors.

The team's insights into the origins of kidney cancer have implications for promoting kidney growth and regeneration. The functional unit of the kidney, called the nephron, forms exclusively during development and if damaged by kidney disease cannot regenerate in the adult. Kidney failure leading to the need for dialysis or kidney transplantation is a major burden to the health care system.

Daley's team showed that a brief, controlled pulse of Lin28 expression in their mouse model increased the numbers of nephrons in newborn mice. Further experimental manipulations of Lin28 may provide a deeper understanding of nephron formation, potentially enabling the restoration of normal numbers of nephrons or their regeneration in damaged adult kidneys.

"Damage to adult kidneys can result in scarring rather than healing, which, if extensive, can lead to kidney failure," Daley says. "Further studies of Lin28 will teach us important lessons about kidney development and point to potential new interventions for kidney disease."

Provided by Children's Hospital Boston