Podocyte Development

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They hypothesized that endothelin may play a role in podocyte function. “Endothelin interacts with CD2AP, a critical protein which when lost in mice or mutated in humans results in nephrotic syndrome,” Sodi said. “Moreover, it interacts with dynamin and synaptopin, which when also deleted in mice results in severe proteinuria. This made endothelin an attractive candidate.”

Sodi and colleagues used fluorescent images to demonstrate that endothelin colocalized with podocyte marker-neprhin in glomeruli. The protein was also found in late-stage clathrin-coated pits with F-actin, dynamin, and synaptopin 1, verifying endothelin’s role in maintaining the glomerular filtration barrier. A second experiment comparing triple knockout mice (bred lacking all three isoforms of endothelin) with wild type mice found the knockout mice had a significantly high level of proteinuria, as well as dilated tubules and accumulation of mesangial matrix in glomeruli.

When asked if the confirmation of endothelin’s role in podocyte functioning could lead to potential targets for treating nephrotic syndrome, Sodi said that “stable,” but that the study period compared with endothelin/synaptopin or dynamin may result in possible therapeutic interventions, but one must be cognizant as not all mechanisms of nephrotic syndrome are identical,” Sodi said, concluding “further investigation and research will be required.”

Tolvaptan Trial Shows Benefit in Slowing Progression of Autosomal Dominant Polycystic Kidney Disease

A phase III clinical trial of tolvaptan for autosomal dominant polycystic kidney disease (ADPKD) demonstrated the drug slowed the rate of disease progression by almost half in the study period compared with placebo. While encouraging, the trial results presented at Kidney Week 2012 are investigational and have yet to be evaluated by the FDA. The 3-year multi-center, double-blind, placebo-controlled study (the TEMPO 3/4 Trial) found that patients with ADPKD who took tolvaptan experienced an average increase in total kidney volume of 2.8 percent per year compared with 5.51 percent for those in the placebo group (1). Given these results, how could this trial expand our understanding of ADPKD and change the investigatory approach to the fourth leading cause of ESRD?

Prior to this study, physicians caring for patients with ADPKD were limited “to treating its complications (strict blood pressure control, dietary protein restrictions, and, at some centers, use for cardiovascular effects), since no treatment capable of inhibiting the development and progression of the cysts has been available,” said Vicente Torres, MD, PhD, of the Mayo Clinic and first author of the TEMPO trial. “In many patients, the growth of numerous cysts within the kidneys is accompanied by painful complications (such as bleeding into cysts or into the urinary tract, cyst infections, and passage of kidney stones), hypertension, and kidney failure.”

Vasopressin has been a pathway of interest to investigators in the ADPKD community, and has included research into the therapeutic use of water intake as a method to reduce vasopressin levels (2). A vasopressin V2 receptor antagonist, tolvaptan is currently indicated for hypervolemic and euhydrualic hyponatremia. “Vasopressin causes production of the cyclic adenosine monophosphate (cAMP), which is thought to accelerate the progression of ADPKD by stimulating proliferation of the cells lining the cysts and fluid secretion into the cysts,” said Torres. “By blocking the production of cAMP, it would be expected that tolvaptan would slow the progression of ADPKD.”
Renal Replacement Therapy: Cautiously Expanding the Donor Pool and Disparities in Transplant Access for Children

Two studies presented at Kidney Week 2012 offer a cross-section of the state of renal replacement therapy in the United States. The first study demonstrated that living kidney donors with prediabetes did not experience an increased risk for developing diabetes over a mean follow-up of 10 years. It indicates that the living kidney donor pool may be cautiously expanded to include prediabetic individuals, which could contribute to a reduction in the duration patients spend waiting for kidney transplants. The second study confirmed that minority children with kidney disease face disparities in access to renal replacement therapy, especially preemptive transplantation, compared to whites. Although transplantation is the preferred treatment option for children with ESRD, white children were four times more likely to receive a transplant as their initial renal replacement treatment compared with black children. Both studies reflect the complex situation that patients with kidney disease encounter when selecting renal replacement options, and identify knowledge gaps for future research that could contribute to improved decision making and outcomes.

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References

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