Innovations in Nephrology

Rady Children's Hospital San Diego

Rady Children's - A comprehensive system focused solely on children.

PEOPLE

Dr. Ingulli finds success with transition program

Elizabeth Ingulli, M.D., medical director of the Kidney Transplant Program at Rady Children's Hospital-San Diego and a professor of pediatrics at UC San Diego School of Medicine, goes beyond focusing on patients' medical needs to help them achieve good long-term outcomes.

As teens comprise the majority of pediatric kidney transplant patients, Dr. Ingulli started a transition program about eight years ago to help them successfully transition to the adult world. To this end, she works with adult nephrologists in the community as well as social workers and a psychologist at Rady Children's. Financial counselors from the Hospital are also involved to help manage the healthcare costs.

During the medical visits, patients learn extensively about their disease, medications and laboratory tests. As noncompliance is high among the teenage population, the goal is for patients to fully understand every aspect of their post-transplant care and to be able to successfully navigate the adult healthcare environment. At their behavioral health visits, patients learn how to cope with their chronic illness, manage stress and self-advocate -- skills critical to functioning as an adult that many of these patients have not developed.

Transplant outcomes have improved as a result of the program, Dr. Ingulli notes, and she hopes to add psychiatry resources to further expand the behavioral health component.

PROGRAMS

Apheresis and dialysis programs provide expert care

The Nephrology division provides comprehensive dialysis and apheresis programs, including both outpatient and inpatient care, under the direction of Nadine Benador, M.D.

A clinical expert in dialysis and apheresis for neonates to young adults, as well as a clinical professor of pediatrics at UC San Diego School of Medicine, Dr. Benador participates in postgraduate apheresis education for adult and pediatric nephrologists at UC San Diego through seminars and an annual national conference. She has been providing dialysis and apheresis services to children for nearly 20 years.

In the outpatient dialysis center, a unit with five dialysis stations, patients can receive hemodialysis three to four times a week with highly skilled nurses, or families can learn to perform peritoneal dialysis at home. On average, about 25 patients receive dialysis each month until they can receive a kidney transplant.

The apheresis program offers plasmapheresis for renal indications such as focal and segmental glomerulosclerosis, transplant rejection or desensitization prior to transplant. Plasmapheresis is also provided to neurology patients with certain clinical indications and extremely sick patients with sepsis in the pediatric intensive care unit.

For patients with cancer and blood disorders, the program works with the Hematology/Oncology division to provide red cell exchange for sickle cell patients, leukapheresis for leukemia patients when they present with very high white blood cell counts and stem cell collection for patients who need bone marrow transplants.

In fiscal year 2016, 138 apheresis procedures were performed: 104 on an inpatient basis and 34 for outpatient care.

RESEARCH

The role of leptin in chronic kidney disease complications

Nephrology Division Chief Robert Mak, M.D., Ph.D., a professor of pediatrics at UC San Diego School of Medicine, studies the role of leptin in patients with chronic kidney disease (CKD)-associated cachexia. His research has found that inhibition of the leptin/melanocortin signal pathway may represent a novel approach to treat this complication. Dr. Mak recently extended

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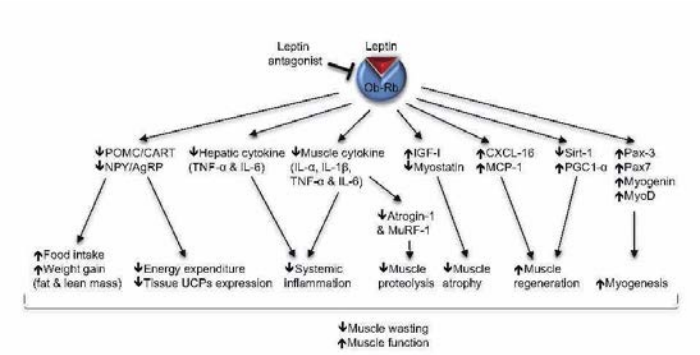
these findings to nephropathic cystinosis, a genetic disorder that presents with CKD and cachexia.

Increases in serum leptin levels have been associated with inflammation and muscle wasting in patients with chronic kidney disease (CKD)-associated cachexia. This anorexigenic hormone is mainly secreted by adipose tissues and modulates energy homeostasis through melanocortin signaling in the hypothalamus. Leptin signaling in the arcuate nuclei is enabled by stimulating pro-opiomelanocortin neurons, which in turn activates the release of a-melanocyte-stimulating hormone and stimulates the type 4 melanocortin receptor signaling (MC4R).

Click to enlarge.



Impact of PLA on energy homeostasis and muscle wasting in CKD

Dr. Mak and his colleagues have shown leptin/melanocortin signaling to be an important mechanism underlying CKD-associated cachexia. In their work with transgenic mice, the deletion of leptin receptor (db/db) and MC4-R knockout attenuated the aberrant metabolic effects of CKD-associated cachexia. Additionally, the administration of a synthetic MCR-4 peripheral antagonist normalized food intake, improved weight gain, improved lean mass content and normalized the basal metabolic rate in CKD mice relative to control mice.

The researchers also evaluated the effects of leptin receptor antagonism. The administration of pegylated leptin receptor antagonist (PLA) in CKD mice improved food intake, weight gain, lean mass and in vivo muscle function, as well as the basal metabolic rate. Moreover, it significantly decreased expression of uncoupling proteins, corrected an aberrant muscle mass signaling pathway and normalized muscle protein levels of IL-1a, IL-1ß, IL-6, and TNF-a.

Read the abstracts to learn more.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4864942

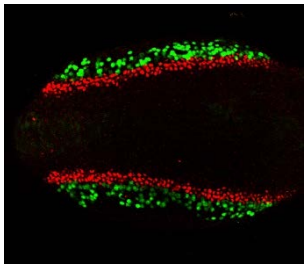
https://www.ncbi.nlm.nih.gov/pubmed/24115476

RESEARCH

Discovery of genetic network involved in kidney development

Elliot Perens, M.D., Ph.D., an assistant adjunct professor of pediatrics at UC San Diego School of Medicine, and his colleagues have identified a gene regulatory network important for kidney development. Long term, understanding the genetic regulation of kidney development should improve diagnostic, prognostic and therapeutic options for children with kidney birth defects. Such therapeutic options may include novel renal replacement therapies using stem cell and regenerative technologies.

The first step in kidney and urinary tract development is the formation of the intermediate mesoderm (IM). Because of the genetic connections between IM development, congenital renal anomalies and regenerative medicine, the researchers' goal was to elucidate the genetic networks that control IM specification and differentiation. To do so, they took advantage of the robust genetic, optical and experimental benefits of the zebrafish as a model organism. Importantly, like mammalian kidneys, zebrafish kidneys are derived from the IM. Work in multiple organisms, including zebrafish, has defined several conserved transcription factors and signaling pathways that promote IM formation. It is not yet understood, however, how the precise dimensions of the IM are determined or how the IM is distinguished from its neighboring territories.



Posterior of zebrafish embryos: Green = cells expressing Hand2; Red = kidney progenitor cells (intermediate mesoderm) expressing Pax2

Using zebrafish kidneys, Dr. Perens and his colleagues demonstrated that the transcription factor Hand2 limits IM dimensions by controlling cell fate decisions along the lateral border of the IM. More specifically, they showed that hand2 promotes venous progenitor development while inhibiting IM formation at this interface. Their studies also suggest that hand2 and osr1, a zinc-finger transcription factor gene previously implicated in promoting kidney formation, have functionally antagonistic roles during kidney development.

Together, this data sheds light on a previously unrecognized genetic network regulating IM dimensions and suggests a model in which hand2 functions in opposition to osr1 to coordinate the allocation of progenitor cells to kidney and vein lineages. Ongoing studies by the researchers are taking advantage of the unique advantages of the zebrafish model system to explore the lineage relationship between kidney and vasculature cells and to expand the understanding of the gene regulatory networks that regulate intermediate mesoderm development.

The findings were published in *Elife*.