New CAIRIBU GU Basic Science, Clinical/Translational, and Population Health Research May 2022

BLADDER

PITing it forward: A new link in the journey of uropathogenic E. coli in the urothelium

Joshi CS, Cegelski L, **Mysorekar IU**

Urinary tract infections (UTIs) are a cause for alarm given the high rates of treatment failure. In a recent issue of Cell Reports, Pang et al. uncovered dueling molecular machinery at the host-pathogen interface in response to phosphate that points to new anti-infective strategies against UTIs.

Nerve growth factor-mediated Na + channel plasticity of bladder afferent neurons in mice with spinal cord injury

Ni J, Suzuki T, Karnup SV, Gu B, **Yoshimura N**

The aim of this study is to investigate the effect of nerve growth factor (NGF) neutralization on Na+ channel plasticity of bladder afferent neurons in mice with spinal cord injury (SCI). Female C57/BL6 mice were randomly divided into spinal intact (SI) group, SCI group and SCI + NGF-Ab group. SCI was induced by spinal cord transection at the Th8/9 level. In SCI + NGF-Ab group, anti-NGF antibodies (10 μg·kg-1 per hour) were continuously administered for 2 weeks using osmotic pumps. Bladder afferent neurons were labelled with Fluoro-gold (FG) injected into the bladder wall. L6-S1 dorsal root ganglion (DRG) neurons were dissociated and whole-cell patch clamp recordings were performed on FG-labelled neurons. Expression of Nav1.7 and Nav1.8 was examined by immunofluorescent staining. Whole-cell patch clamp recordings showed that TTX only partially inhibited action potentials (AP) and Na+ currents of bladder afferent neurons in SI mice, but it almost completely inhibited them in SCI mice. NGF mediates the Na+ channel plasticity with a shift from TTX-resistant Nav1.8 to TTX-sensitive Nav1.7 in bladder afferent neurons, which could be a possible underlying mechanism of bladder afferent hyperexcitability and detrusor overactivity after SCI.

Reduction of Bladder Capacity Under Anesthesia Following Multiple Recurrences and Repeated Surgeries of Hunner Lesions in Patients With Interstitial Cystitis

Furuta A, Suzuki Y, Igarashi T, Kimura T, Egawa S, **Yoshimura N**

The purpose of this study is to investigate the influence of multiple recurrences and repeated surgeries of Hunner lesions on bladder capacity under general anesthesia in patients with interstitial cystitis (IC). A total of 92 surgeries were performed in 47 HIC patients, 23 (49%) of whom required multiple procedures (range, 1-5 times). The mean recurrence-free time after the first surgery was 21.7 months. The recurrence-free rate was 53% at 24 months, and decreased to 32% at 48 months. There were no significant differences in age, sex, bladder capacity under anesthesia at the first surgery, duration from symptom onset to the first surgery, O'Leary-Sant questionnaire including symptom and problem indexes, visual analogue scale pain score, and the number of comorbidities between the cases with or without recurrence. Bladder capacity under anesthesia was gradually decreased as the number of surgeries was increased, and bladder capacity at the fourth procedure was significantly decreased to 80% of the capacity at the first surgery. These results suggest that multiple recurrences and repeated surgeries of Hunner lesions result in a reduction of bladder capacity under anesthesia in HIC patients although no predictive factors for recurrence of Hunner lesions were detected.

KIDNEY

Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

KDIGO Conference Participants, **Gharavi AG**

Numerous genes for monogenic kidney diseases with classical patterns of inheritance, as well as genes for complex kidney diseases that manifest in combination with environmental factors, have been discovered. Genetic findings are increasingly used to inform clinical management of nephropathies, and have led to improved diagnostics, disease surveillance, choice of therapy, and family counseling. All of these steps rely on accurate interpretation of genetic data, which can be outpaced by current rates of data collection. In March of 2021, Kidney Diseases: Improving Global Outcomes (KDIGO) held a Controversies Conference on "Genetics in Chronic Kidney Disease (CKD)" to review the current state of understanding of monogenic and complex (polygenic) kidney diseases, processes for applying genetic findings in clinical medicine, and use of genomics for defining and stratifying CKD. Given the important contribution of genetic variants to CKD, practitioners with CKD patients are advised to "think genetic," which specifically involves obtaining a family history, collecting detailed information on age of CKD onset, performing clinical examination for extrarenal symptoms, and considering genetic testing. To improve use of genetics in nephrology, meeting participants advise developing an advanced training or subspecialty track for nephrologists, crafting guidelines for testing and treatment, and educating patients, students, and practitioners. Key areas of future research, including clinical interpretation of genome variation, electronic phenotyping, global representation, kidney-specific molecular data, polygenic scores, translational epidemiology, and open data resources, were also identified.

PROSTATE

TNF is a potential therapeutic target to suppress prostatic inflammation and hyperplasia in autoimmune disease

Vickman RE, Aaron-Brooks L, Zhang R, Lanman NA, Lapin B, Gil V, Greenberg M, Sasaki T, **Cresswell GM**, Broman MM, Paez JS, Petkewicz J, Talaty P, Helfand BT, Glaser AP, Wang CH, **Franco OE**, **Ratliff TL**, Nastiuk KL, Crawford SE, **Hayward SW**

Autoimmune (AI) diseases can affect many organs; however, the prostate has not been considered to be a primary target of these systemic inflammatory

processes. Here, we utilize medical record data, patient samples, and in vivo models to evaluate the impact of inflammation, as seen in AI diseases, on prostate tissue. Human and mouse tissues are used to examine whether systemic targeting of inflammation limits prostatic inflammation and hyperplasia. Evaluation of 112,152 medical records indicates that benign prostatic hyperplasia (BPH) prevalence is significantly higher among patients with AI diseases. Furthermore, treating these patients with tumor necrosis factor (TNF)-antagonists significantly decreases BPH incidence. Single-cell RNA-seq and in vitro assays suggest that macrophage-derived TNF stimulates BPH-derived fibroblast proliferation. TNF blockade significantly reduces epithelial hyperplasia, NFκB activation, and macrophage-mediated inflammation within prostate tissues.

Together, these studies show that patients with AI diseases have a heightened susceptibility to BPH and that reducing inflammation with a therapeutic agent can suppress BPH.

STONES

Quality of life impact and recovery after ureteroscopy and stent insertion: insights from daily surveys in STENTS

Harper JD, Desai AC, Antonelli JA, **Tasian GE**, **Ziemba JB**, Al-Khalidi HR, Lai HH, **Maalouf NM**, Reese PP, Wessells HB, Kirkali Z, Scales CD Jr; NIDDK Urinary Stone Disease Research Network (USDRN)

Our objective was to describe day-to-day evolution and variations in patient-reported stent-associated symptoms (SAS) in the STudy to Enhance uNderstanding of sTent-associated Symptoms (STENTS), a prospective multicenter observational cohort study, using multiple instruments with conceptual overlap in various domains. In a nested cohort of the STENTS study, the initial 40 participants having unilateral ureteroscopy (URS) and stent placement underwent daily assessment of self-reported measures using the Brief Pain Inventory short form, Patient-Reported Outcome Measurement Information System measures for pain severity and pain interference, the Urinary Score of the Ureteral Stent Symptom Questionnaire, and Symptoms of Lower Urinary Tract Dysfunction Research Network Symptom Index.This first study investigating daily SAS allows for a more in-depth look at the lived experience after URS and the impact on quality of life. Different instruments measuring pain intensity, pain interference, and urinary symptoms produced consistent assessments of patients' experiences. The overall daily stability of pain and urinary symptoms after URS was also marked by high patient-level variation, suggesting an opportunity to identify characteristics associated with severe SAS after URS.

PATIENT-CENTERED RESEARCH

Comparative effectiveness of paediatric kidney stone surgery (the PKIDS trial): study protocol for a patient-centred pragmatic clinical trial

Ellison JS, Lorenzo M, Beck H, Beck R, Chu DI, Forrest C, Huang J, Kratchman A, Kurth A, Kurth L, Kurtz M, Lendvay T, Sturm R, **Tasian G**; Pediatric KIDney Stone Care Improvement Network

The strength of the evidence base for the comparative effectiveness of three common surgical modalities for paediatric nephrolithiasis (ureteroscopy, shockwave lithotripsy and percutaneous nephrolithotomy) and its relevance to patients and caregivers are insufficient. We describe the methods and rationale for the Pediatric KIDney Stone (PKIDS) Care Improvement Network Trial with the aim to compare effectiveness of surgical modalities in paediatric nephrolithiasis based on stone clearance and lived patient experiences. This protocol serves as a patient-centred alternative to randomised controlled trials for interventions where clinical equipoise is lacking. The primary study outcome is stone clearance, defined as absence of a residual calculus of >4 mm on postoperative ultrasound. Secondary outcomes include patient-reported physical, emotional and social health outcomes (primarily using the Patient-Reported Outcome Measurement Information System), analgesic use and healthcare resource use. Timing and content of secondary outcomes assessments were set based on feedback from patient partners. Heterogeneity of treatment effect for stone clearance and patient-reported outcomes by participant and stone characteristics will be assessed.

- Jennifer Allmaras, MPH & Muen Wang 4/26/2022

Email cairibu@urology.wisc.edu to feature your newly published research in next month's communique