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BLADDER

Continuous administration of mirabegron has advantages in inhibition of central sensitization compared with short-term treatment cessation in a mouse model of overactive bladder

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There is no clear pathophysiologic evidence determining how long overactive bladder (OAB) medication should be continued. We, therefore, investigated the effect of mirabegron using cessation (CES) or continuation (CON) treatment in an OAB animal model. Female C57BL/6 mice were divided into four groups (N = 8 each): Sham, OAB, CES, and CON groups. The OAB-like condition was induced by three times weekly intravesical instillations of KCl mixture with hyaluronidase. After the last intravesical instillation for inducing OAB, mirabegron (2 mg/kg/day) was administered in CES and CON groups for 10 and 20 days, respectively. Final experiments were carried out on0 days from the last intravesical instillation in all groups. After cystometry, mRNA levels of bladder muscarinic, β-adrenergic, and P2X purinergic receptors were measured to investigate bladder efferent and afferent activity. In addition, mRNA levels of CCL2 and CCR2 in L6-S1 dorsal root ganglia (DRG) were measured to assess afferent sensitization. Immunofluorescent staining of CX3CR1, GFAP, and CCR2 in the L6 spinal cord was also conducted to investigate glial activation and central sensitization. The conclusion showed continuous mirabegron treatment seems to prevent central sensitization and, thus, might be desirable for long-term disease control of OAB.

Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome

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This guideline provides direction to clinicians and patients regarding how to recognize interstitial cystitis/bladder pain syndrome (IC/BPS), conduct a valid diagnostic process, and approach treatment with the goals of maximizing symptom control and patient quality of life while minimizing adverse events and patient burden. In contrast to the prior versions, the 2022 updated Guideline no longer divides treatments into first-line through sixth-line tiers. Instead, treatment is categorized into behavioral/non-pharmacologic, oral medicines, bladder instillations, procedures, and major surgery. This approach reinforces that the clinical approach for IC/BPS needs to be individualized and based on the unique characteristics of each patient. In addition, new statements were written to provide guidance on cystoscopy for patients with Hunner lesions, shared decision-making, and potential adverse events from pentosan polysulfate. The supporting text on major surgery alsohas been completely revised. In conclusion, IC/BPS is a heterogeneous clinical syndrome. Even though patients present with similar symptoms of bladder/pelvic pain and pressure/discomfort associated with urinary frequency and strong urge to urinate, there are subgroups or phenotypes within IC/BPS. Except for patients with Hunner lesions, initial treatment should typically be nonsurgical. Concurrent, multi-modal therapies may be offered.

Development, regeneration and tumorigenesis of the urothelium

Gregory B Wiessner, Sakina A Plumber, Tina Xiang, **Cathy L Mendelsohn**

The urothelium of the bladder functions as a waterproof barrier between tissue and outflowing urine. Largely quiescent during homeostasis, this unique epithelium rapidly regenerates in response to bacterial or chemical injury. The specification of the proper cell types during development and injury repair is crucial for tissue function. This Review surveys the current understanding of urothelial progenitor populations in the contexts of organogenesis, regeneration and tumorigenesis. Furthermore, we discuss pathways and signaling mechanisms involved in urothelial differentiation, and consider the relevance of this knowledge to stem cell biology and tissue regeneration.

The Impact of Methenamine Hippurate Treatment on Urothelial Integrity and Bladder Inflammation in Aged Female Mice and Women With Urinary Tract Infections

Jessica L Sawhill, Amy Mora, Kendall McDaniel, Marianne M Ligon, **Jerry L Lowder**, **Indira U Mysorekar**, Christine M Chu

Antibiotics are commonly used to treat and prevent urinary tract infection (UTI), but resistance is growing. Nonantibiotic prophylaxis such as methenamine hippurate (MH) shows clinical promise, but its impact on bladder factors influencing recurrent UTIs (rUTIs) is not well described. The aim of the study was to examine the effect of MH on bladder inflammation and barrier function in aged mice and women with rUTI. This study included urine samples from an experimental study involving aged female mice with and without methenamine treatment as well as women with rUTI who received either no prophylaxis, MH alone, vaginal estrogen therapy and/or d-mannose alone, or MH in addition to vaginal estrogen therapy and/or d-mannose. In the aged mice model, there was a decreased urothelial permeability (as seen by retention of fluorescein isothiocyanate-conjugated-dextran fluorescence in superficial cells) and increased urinary IgA in mice treated with MH compared with controls. In human samples, there was significantly increased urinary IgA in those taking MH alone compared with no prophylaxis (830.1 vs 40.1 ng/mL, P = 0.04), but no significant difference in interleukin. Methenamine hippurate seems to enhance barrier function as evidenced by decreased urothelial permeability and increased urinary IgA levels, without worsening inflammation. This may reflect another beneficial mechanism by which MH helps prevent rUTI.

[Inhibition of hypoxia-inducible factor-prolyl hydroxylation protects from cyclophosphamide-induced bladder injury and urinary dysfunction]

Douglass B Clayton, Ching Man Carmen Tong, Belinda Li, Abby S Taylor, Shuvro De, Matthew D Mason, Anne G Dudley, Olena Davidoff, Hanako Kobayashi, Volker Hans Haase

Disruption of the blood-urine barrier can result in acute or chronic inflammatory bladder injury. Activation of the oxygen-regulated hypoxia-inducible factor (HIF) pathway has been shown to protect mucosal membranes by increasing the expression of cytoprotective genes and by suppressing inflammation. The activity of HIF is controlled by prolyl hydroxylase domain (PHD) dioxygenases, which have been exploited as therapeutic targets for the treatment of anemia of chronic kidney disease. Here we established a mouse model of acute cyclophosphamide (CYP)-induced blood-urine barrier disruption associated with inflammation and severe urinary dysfunction to investigate the HIF-PHD axis in inflammatory bladder injury. We found that systemic administration of dimethyloxalylglycine (DMOG) or molidustat, two small molecule inhibitors of HIF-prolyl hydroxylases (HIF-PHIs), profoundly mitigated CYP-induced bladder injury and inflammation as assessed by morphologic analysis of transmural edema and urothelial integrity and by measuring tissue cytokine expression. Void spot analysis to examine bladder function quantitatively demonstrated that HIF-PHI administration normalized micturition patterns and protected against CYP-induced alteration of urinary frequency and micturition patterns. Our studies highlight the therapeutic potential of HIF-activating small molecule compounds for the prevention or therapy of bladder injury and urinary dysfunction due to blood-urine barrier disruption.

[Longitudinal urinary microbiome characteristics in women with urgency urinary incontinence undergoing sacral neuromodulation]

Margaret G Mueller, Promi Das, Uduak Andy, Lisa Brennaman, Alexis A Dieter, Denicia Dwarica, Anna C Kirby, Jonathan P Shepherd, W Thomas Gregory, **Cindy L Amundsen**

The objective was to evaluate the stability of the urinary microbiome communities in women undergoing sacral neuromodulation (SNM) for urgency urinary incontinence (UUI). We hypothesized that clinical response to SNM therapy would be associated with changes in the urinary microbiome. Women completed the Overactive Bladder Questionnaire Short-Form, the International Consultation on Incontinence Questionnaire Short Form, and the Female Sexual Function Index at baseline and 3 months post-SNM implantation. Transurethral urinary specimens were obtained for microbiome analysis at baseline and 3 months postoperatively. Nineteen women who underwent SNM and provided both baseline and 3-month urine samples were included in this analysis. Women reported improvement in objective (number of UUI episodes) and subjective (symptom severity and health-related quality of life) measures. Ninety percent of the bacteria were classified as Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. No significant differences were observed in each subject's beta-diversity at 3 months compared with their baseline microbiome. The conclusion showed that our descriptive pilot study of a cohort of women who had achieved objective and subjective improvements in UUI following SNM therapy demonstrates that the urinary microbiome remains relatively stable, despite variability amongst the cohort.

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

Chetanchandra S Joshi, Lynette Cegelski, **Indira U Mysorekar**

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.

KIDNEY

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

Ali Gharavi, KDIGO Conference Participants

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 the use of genetics in nephrology, meeting participants advised 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.

Snapshots of nascent RNA reveal cell- and stimulus-specific responses to acute kidney injury

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The current strategy to detect acute injury of kidney tubular cells relies on changes in serum levels of creatinine. Yet serum creatinine (sCr) is a marker of both functional and pathological processes and does not adequately assay tubular injury. In addition, sCr may require days to reach diagnostic thresholds, yet tubular cells respond with programs of damage and repair within minutes or hours. To detect acute responses to clinically relevant stimuli, we created mice expressing Rosa26-floxed-stop uracil phosphoribosyltransferase (Uprt) and inoculated 4-thiouracil (4-TU) to tag nascent RNA at selected time points. Cre-driven 4-TU-tagged RNA was isolated from intact kidneys and demonstrated that volume depletion and ischemia induced different genetic programs in collecting ducts and intercalated cells. Even lineage-related cell types expressed different genes in response to the stressors. TU tagging also demonstrated the transient nature of the responses. Because we placed Uprt in the ubiquitously active Rosa26 locus, nascent RNAs from many cell types can be tagged in vivo and their roles interrogated under various conditions. In short, 4-TU labeling identifies stimulus-specific, cell-specific, and time-dependent acute responses that are otherwise difficult to detect with other technologies and are entirely obscured when sCr is the sole metric of kidney damage.

STONES

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

Jonathan S Ellison, Matthew Lorenzo, Hunter Beck, Ruth Beck, David I Chu, Christopher Forrest, Jing Huang, Amy Kratchman, Anna Kurth, Laura Kurth, Michael Kurtz, Thomas Lendvay, Renae Sturm, **Gregory Tasian**, 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 PKIDS is a collaborative learning organisation composed of 26 hospitals that is conducting a prospective pragmatic clinical trial comparing the effectiveness of ureteroscopy, shockwave lithotripsy and percutaneous nephrolithotomy for youth aged 8-21 years with kidney and/or ureteral stones. Embedded within clinical care, the PKIDS trial will collect granular patient-level, surgeon-level and institution-level data, with a goal enrolment of 1290 participants over a 21-month period. 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.

PATIENT-CENTERED RESEARCH

Quality of Life of Urolithiasis Patients During the COVID-19 Pandemic: A Multi-Institutional Cross-Sectional Study

Victor K F Wong, Naeem Bhojani, Vincent Bird, Necole Streeper, Stephen Y Nakada, **Kristina Penniston**, Ben H Chew

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented global event that has caused significant fear and anxiety across all populations. To date, there have been no studies on how major health crises have affected the stone-related quality of life (QOL) of urolithiasis patients. In this multi-institutional study, we investigated the association between fear of COVID-19 and the QOL of urolithiasis patients during the COVID-19 pandemic using the Fear of COVID-19 Scale (FCV-19S) and the Wisconsin Stone Quality of Life (WISQOL) questionnaires. Four hundred respondents participated in this study. Overall mean total standardized FCV-19S and WISQOL scores (both transformed to min-max 0-100) were4.3 and 70.3, respectively. A significant inverse correlation ($r = -0.265$, $p < 0.0001$) demonstrated that suggesting greater COVID-19 fear may result in lower stone-related QOL. A significant difference in fear and QOL scores was observed between the sexes, with women having more COVID-19 fear (35.8 vs8.6, $p < 0.01$) and lower stone-related QOL (64.2 vs 75.2, $p < 0.01$). Quartile ANOVA analysis revealed significant mean difference in WISQOL scores across all FCV-19S score quartiles ($p < 0.05$). Using two validated questionnaires (FCV-19S and WISQOL) and correlating patient-reported responses, we found that greater fear for COVID-19 was associated with lower stone-related QOL in urolithiasis patients.

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

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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. Pain intensity, pain interference, urinary symptoms, and bother were obtained preoperatively, daily until stent removal, and at postoperative day (POD) 30. 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.

- Jennifer Allmaras, MPH and Muen Wang 5/25/2022

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