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BLADDER

A multi-omic investigation of male lower urinary tract symptoms: potential role for JC virus

Samuel Thomas, Christopher D Dunn, Lewis J Campbell, **Douglas W Strand**, **Chad M Vezina**, **Dale E Bjorling**, **Kristina L Penniston**, Lingjun Li, **William A Ricke**, **Tony L Goldberg**

Male lower urinary tract symptoms (LUTS) comprise a common syndrome of aging that negatively impacts quality of life. The etiology of LUTS is multifactorial, involving benign prostatic hyperplasia, smooth muscle and neurologic dysfunction, inflammation, sexually transmitted infections, fibrosis, and potentially dysbiosis, but this aspect remains poorly explored. We investigated whether the presence of infectious agents in urine might be associated with LUTS by combining next-generation DNA sequencing for virus discovery, microbiome analysis for characterization of bacterial communities, and mass spectrometry-based metabolomics. In urine from 29 LUTS cases and 9 controls from Wisconsin, we found a statistically significant association between a diagnosis of LUTS and the presence of JC virus (JCV), a common neurotropic human polyomavirus (Polyomaviridae, Betapolyomavirus) linked to severe neurologic disease in rare cases. This association (based on metagenomics) was not borne out when specific polymerase chain reaction (PCR) testing was applied to this set of samples, likely due to the greater sensitivity of PCR. These data provide preliminary support the hypothesis that viruses such as JCV may play a role in the development or progression of LUTS, together with other infectious agents and host metabolic responses.

Benchmarking DNA isolation kits used in analyses of the urinary microbiome

Lisa Karstens, **Nazema Y Siddiqui**, Tamara Zaza, Alecsander Barstad, **Cindy L Amundsen**, **Tatyana A Sysoeva**

The urinary microbiome has been increasingly characterized using next-generation sequencing. However, many of the technical methods have not yet been specifically optimized for urine. We sought to compare the performance of several DNA isolation kits used in urinary microbiome studies. A total of 11 voided urine samples and one buffer control were divided into 5 equal aliquots and processed in parallel using five commercial DNA isolation kits. DNA was quantified and the V4 segment of the 16S rRNA gene was sequenced. Data were processed to identify the microbial composition and to assess alpha and beta diversity of the samples. Tested DNA isolation kits result in significantly different DNA yields from urine samples. DNA extracted with the Qiagen Biostic Bacteremia and DNeasy Blood & Tissue kits showed the fewest technical issues in downstream analyses, with the DNeasy Blood & Tissue kit also demonstrating the highest DNA yield. Nevertheless, all five kits provided good quality DNA for high throughput sequencing with non-significant differences in the number of reads recovered, alpha, or beta diversity.

Changes in patient reported outcome measures after treatment for female urethral stricture

Giulia I Lane, Alyssa Gracely, Pansy Uberoi, Una Lee, Ariana L Smith, Jennifer T Anger, Didi Theva, Jessica DeLong, Casey Kowalik, Priya Padmanabhan, Charles R Powell, Maude E Carmel, **J Quentin Clemens**, Anne P Cameron, Priyanka Gupta

There is a paucity of patient reported outcome measure (PROM) data for women with urethral strictures. To address this gap, we aim to evaluate change in PROM among women who underwent surgery for a stricture. Women with urethral strictures have severe lower urinary tract symptoms which improved after surgery. This study substantiates the claims that recognizing and treating women with urethral stricture disease greatly improves lower urinary tract symptoms and QOL.

Molecular mechanisms of voiding dysfunction in a novel mouse model of acute urinary retention

Xiang Xie, Huan Chen, Lanlan Zhang, Daniel Chan, **Warren G Hill**, **Mark L Zeidel**, **Weiqun Yu**

Acute urinary retention (AUR) is a common urological emergency and affects a significant patient population. The inability to eliminate urine may lead to permanent damage to the bladder's structure and functioning. To closely mirror the potential high pressures that patients with AUR could experience, we catheterized anesthetized female mice via the urethra and filled the bladder by pumping saline (25 µL/min) into the bladder lumen to 50 cm or 80 cm water pressure. A water column with designated height (50 or 80 cm) was then adjusted to maintain constant pressure in the bladder lumen for 30 minutes. Functional and morphological evaluations were performed from 0 to 24 hours after AUR treatment. Mice exhibited incontinence and overactivity with diminished voiding pressure. Bladder smooth muscle (BSM) from pressure-treated mice have significantly diminished contraction force, suggesting that bladder voiding dysfunction can be attributed to impaired BSM contractility. Finally, altered expression of β1-integrin and extracellular matrix mediated mechanotransduction pathways were detected, suggesting a profound remodeling process. These data demonstrated an easy to perform, quantifiable, and reproducible AUR mouse model, which mimics well the characteristics of human AUR patients, and our data generate new insights into the molecular mechanisms that occur following AUR.

Age-dependent decrease in TRPM4 channel expression but not trafficking alters urinary bladder smooth muscle contractility

Sarah E Maxwell, **M Dennis Leo**, **John Malysz**, **Georgi V Petkov**

Increasing evidence supports a novel role of transient receptor potential melastatin-4 (TRPM4) channels in UBSM physiology. However, it remains unknown whether the functional expression of these key regulatory channels fluctuates in UBSM over different life stages. Here, we examined TRPM4 channel protein expression (Western blot) and the effects of TRPM4 channel inhibitors, 9-phenanthrol and glibenclamide, on phasic contractions of UBSM isolated strips obtained from juvenile (UBSM-J, 5-9 weeks old) and adult (UBSM-A, 6-18 months old) male

guinea pigs. Compared to UBSM-J, UBSM-A displayed a 50-70% reduction in total TRPM4 protein expression, while the surface-to-intracellular expression ratio (channel trafficking) remained the same in both age groups. Consistent with the reduced total TRPM4 protein expression in UBSM-A, 9-phenanthrol showed lower potencies and/or maximum efficacies in UBSM-A than UBSM-J for inhibiting amplitude and muscle force of spontaneous and 20 mM KCl-induced phasic contractions. In both age groups, regardless of the overall reduced total TRPM4 protein expression in UBSM-A, cell surface TRPM4 protein expression (~80%) predominated over its intracellular fraction (~20%), revealing preserved channel trafficking mechanisms toward the cell membrane. Collectively, this study reports novel findings illuminating a fundamental physiological role for TRPM4 channels in UBSM function that fluctuates with age.

STONES

Dietary Oxalate Loading Impacts Monocyte Metabolism and Inflammatory Signaling in Humans

Parveen Kumar, Mikita Patel, **Robert A Oster**, Vidhush Yarlagadda, Adam Ambrosetti, **Dean G Assimos**, **Tanecia Mitchell**

Diet has been associated with several metabolic diseases and may impact immunity. Increased consumption of meals with high oxalate content may stimulate urinary calcium oxalate (CaOx) crystals, which are precursors to CaOx kidney stones. The purpose of this study was to investigate whether dietary oxalate loading impacts monocyte cellular bioenergetics, mitochondrial complex activity, and inflammatory signaling in humans. Healthy participants (n = 40; 31.1 ± 1.3 years) with a BMI of 24.9 ± 0.6 kg/m2 consumed a controlled low oxalate diet for 3 days before drinking a blended preparation of fruits and vegetables containing a large amount of oxalate. Blood and urine were collected before (pre-oxalate) and for 5 h after the oxalate load to assess urinary oxalate levels, monocyte cellular bioenergetics and mitochondrial complex activity, and plasma cytokine/chemokine levels. Urinary oxalate levels significantly increased in post-oxalate samples compared to pre-oxalate samples. Monocyte cellular bioenergetics, mitochondrial complex I activity, and plasma cytokine and chemokine levels were altered to varying degrees within the study cohort. We demonstrate for the first time that dietary oxalate loading may impact monocyte metabolism and immune response in a cohort of healthy adults, but these responses are variable.

PROSTATE

TNF Blockade Reduces Prostatic Hyperplasia and Inflammation while Limiting BPH Diagnosis in Patients with Autoimmune Disease

Renee E. Vickman, LaTayia Aaron-Brooks, Renyuan Zhang, **Nadia A. Lanman**, Brittany Lapin, Victoria Gil, Max Greenberg, Takeshi Sasaki, **Gregory M. Cresswell**, **Meaghan M. Broman**, Jacqueline Petkewicz, Pooja Talaty, Brian T. Helfand, Alexander P. Glaser, Chi-Hsiung Wang, **Omar E. Franco**, **Timothy L. Ratliff**, Kent L. Nastiuk, **Susan E. Crawford**, **Simon W. Hayward**

Benign prostatic hyperplasia (BPH) is ostensibly linked to autoimmune (AI) diseases, but whether the prostate is a target of systemic inflammation associated with AI conditions is unknown. This study was conducted to determine if AI disease correlates with BPH diagnosis and whether systemic targeting of an inflammatory mediator limits prostatic inflammation and hyperplasia. Patient medical records (n=112,152) were evaluated to determine BPH prevalence among different AI diseases. Inflammatory cells from human BPH tissues were analyzed by single-cell (sc)RNA-seq and the tumor necrosis factor (TNF)α-antagonist etanercept was tested in two murine models of prostatic enlargement. BPH prevalence was significantly higher among patients with AI disease compared to unaffected individuals. However, AI patients treated with TNFα-antagonists had a significantly reduced incidence of BPH. These studies are the first to show that patients with AI diseases have a heightened susceptibility to BPH and that the TNFα-signaling axis is important for BPH pathogenesis. Macrophage-secreted TNFα may mechanistically drive BPH via chronic activation of the signaling axis and NFκB. TNFα blockade appears to be a promising new pharmacological approach to target inflammation and suppress BPH.

- Jennifer Allmaras, MPH, 3/23/2021

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