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BLADDER

Temporal Relationships Between Pain, Mood and Urinary Symptoms in Urologic Chronic Pelvic Pain Syndrome (UCPPS): A MAPP Network Study

Bruce D Naliboff, Andrew D Schrepf, Alisa J Stephens-Shields, J Quentin Clemens, Michael A Pontari, Jennifer Labus, Bayley J Taple, Larissa V Rodriguez, Eric Strachan, James W Griffith

The purpose of the study was to determine the time-lagged, bidirectional relationships among clinical variables of pelvic pain, urinary symptoms, negative mood, non-pelvic pain and quality of life (QOL) in men and women with UCPPS, incorporating interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The results show clear evidence for a bidirectional positive relationship between changes in pelvic pain severity and urinary symptom severity. Increases in either variable predicted significant increases in the other two weeks later, beyond that explained by their concurrent relationship at each time point. Pelvic pain and to a lesser degree urinary frequency also showed similar bidirectional relationships with negative mood and decreased QOL. The feedforward aspects of these relationships can facilitate a downward spiral of increased symptoms and worsening psychosocial function, and suggest the need for multifaceted treatments and assessment to address this possibility in individual patients.

Copy Number Variant Analysis and Genome-wide Association Study Identify Loci with Large Effect for Vesicoureteral Reflux

Miguel Verbitsky et al., Jonathan Barasch, Simone Sanna-Cherchi, Cathy L Mendelsohn, Ali G Gharavi

Vesicoureteral reflux (VUR) is a common, familial genitourinary disorder, and a major cause of pediatric urinary tract infection (UTI) and kidney failure. The genetic basis of VUR is not well understood. A diagnostic analysis sought rare, pathogenic copy number variant (CNV) disorders among 1737 patients with VUR. A GWAS was performed in 1395 patients and 5366 controls, of European ancestry. Altogether, 3% of VUR patients harbored an undiagnosed rare CNV disorder, such as the 1q21.1, 16p11.2, 22q11.21, and triple X syndromes ((OR, 3.12; 95% CI, 2.10 to 4.54; P=6.35×10-8) The GWAS identified three study-wide significant and five suggestive loci with large effects (ORs, 1.41-6.9), containing canonical developmental genes expressed in the developing urinary tract (WDPCP, OTX1, BMP5, VANGL1, and WNT5A). These data demonstrate the genetic heterogeneity of VUR. Altogether, 6% of patients with VUR harbored a rare CNV or a common variant genotype conferring an OR >3. Identification of these genetic risk factors has multiple implications for clinical care and for analysis of outcomes in VUR.

Vaginal Estrogen Therapy Is Associated With Decreased Inflammatory Response in Postmenopausal Women With Recurrent Urinary Tract Infections

Melanie R Meister, Caihong Wang, Jerry L Lowder, Indira U Mysorekar

Vaginal estrogen therapy (VET) has been shown to decrease the risk of recurrent urinary tract infections (UTIs) in postmenopausal women, but the mechanism of action has not been fully described. Our objectives were to assess whether the postmenopausal urine inflammatory profile changes in response to VET. We prospectively enrolled postmenopausal patients into 3 groups: (1) currently using VET without a history of recurrent UTIs (rUTIs); (2) history of UTIs, currently using VET; and (3) history of rUTIs, not using VET but willing to start. We followed patients over 6 to 19 months and collected urine samples at 3 time points. We performed comprehensive cytopathologic analysis, quantitative urine inflammatory scoring, and enzyme-linked immunosorbent assay for interleukin 6. Postmenopausal women with rUTIs on VET demonstrate decreased cell shedding, reduced urine inflammatory scores, and decreased urine interleukin 6. Modulation of the genitourinary inflammatory profile may represent one mechanism through which VET helps prevent rUTIs in postmenopausal women.

STONES

The role of cavitation in energy delivery and stone damage during laser lithotripsy

Derek S Ho, Dominick Scialabba, Russell Stevens Terry, Xiaojian Ma, Junqin Chen, Georgy Sankin, Gaoming Xiang, Robert Qi, Glenn M Preminger, Michael Eric Lipkin, Pei Zhong

While cavitation during laser lithotripsy contributes to the Moses effect, the impact of cavitation on stone damage is less clear. The role of cavitation in laser energy delivery was characterized using photodetector measurements synced with high-speed imaging for laser pulses of varying durations. BegoStone samples were treated with the laser fiber oriented perpendicularly in contact with the stone in water or in air to assess the impact of cavitation on crater formation. Crater volume and geometry were quantified using optical coherence tomography. Furthermore, the role of cavitation in stone damage was elucidated by treatment in water with the fiber oriented parallel to the stone surface and by photoelastic imaging. The longer pulse mode produced smaller crater volume, suggesting additional processes secondary to photothermal ablation are involved in stone damage. Our critical observations of the difference in stone damage treated in water vs. in air, combined with the crater formation by parallel fiber suggest that cavitation is a contributor to stone damage during laser lithotripsy.

Effect of alanine supplementation on oxalate synthesis

Kyle D Wood, Brian L Freeman, Mary E Killian, Win Shun Lai, Dean Assimos, John Knight, Sonia Fargue

The Primary Hyperoxalurias (PH) are rare disorders of metabolism leading to excessive endogenous synthesis of oxalate and recurring calcium oxalate kidney stones. Alanine glyoxylate aminotransferase (AGT), deficient in PH type 1, is a key enzyme in limiting glyoxylate oxidation to oxalate. The affinity of AGT for its co-substrate, alanine, is low suggesting that its metabolic activity could be sub-optimal in vivo. To test this hypothesis, we examined the effect of L-alanine supplementation on oxalate synthesis in cell culture and in mouse models of

Primary Hyperoxaluria Type 1 (Agxt KO), Type 2 (Grhpr KO) and in wild-type mice. Our results demonstrated that increasing L-alanine in cells decreased synthesis of oxalate and increased viability of cells expressing GO and AGT when incubated with glycolate. In both wild type and Grhpr KO male and female mice, supplementation with 10% dietary L-alanine significantly decreased urinary oxalate excretion ~30% compared to baseline levels. This study demonstrates that increasing the availability of L-alanine can increase the metabolic efficiency of AGT and reduce oxalate synthesis.

PROSTATE

Progenitors in prostate development and disease

Diya B Joseph, Anne E Turco, Chad M Vezina, Douglas W Strand

The prostate develops by epithelial budding and branching processes that occur during fetal and postnatal stages. The adult prostate demonstrates remarkable regenerative capacity, with the ability to regrow to its original size over multiple cycles of castration and androgen administration. This capacity for controlled regeneration prompted the search for an androgen-independent epithelial progenitor in benign prostatic hyperplasia (BPH) and prostate cancer (PCa). BPH is hypothesized to be a reawakening of ductal branching, resulting in the formation of new proximal glands, all while androgen levels are decreasing in the aging male. Advanced prostate cancer can be slowed with androgen deprivation, but resistance eventually occurs, suggesting the existence of an androgen-independent progenitor. Recent studies indicate that there are multiple castration-insensitive epithelial cell types in the proximal area of the prostate, but not all act as progenitors during prostate development or regeneration. This review highlights how recent cellular and anatomical studies are changing our perspective on the identity of the prostate progenitor.

Abnormal expression of Rab27B in prostatic epithelial cells of benign prostatic hyperplasia alters intercellular communication

Yu Dai, Bo Ai, Ying Liu, Laura E Pascal, Zhou Wang, Rajiv Dhir, Xuegang Sun, Yu Jiang

Abnormal intraglandular stromal-epithelial interactions have been known as a main key contributing factor for development of Benign Prostatic Hyperplasia (BPH). In this study we compared the proteomic profiles of hyperplastic tissue with adjacent normal tissue of BPH and identified Rab27B small GTPase, a key regulator of exocytosis, as a protein that was overexpressed in the epithelium of BPH tissue. Overexpression of Rab27B in prostatic epithelial cells strongly increased the signaling activities of the PI3K/AKT and ERK1/2 pathways, whereas, downregulation of Rab27B expression in the epithelial cells of BPH reduced the signaling activities and decreased cell proliferation. The elevated Rab27B expression caused an overall increase in cell surface presentation of growth factor receptors without affecting their expression. However, the small GTPase also possesses an inhibitory activity against mTORC1 independent of its role in cell surface presentation of growth factor receptors. Our findings demonstrate a pivotal role of the small GTPase in autocrine and paracrine signaling and suggest that its abnormal expression underlies the dysregulated stromal-epithelial interactions in BPH.

- Jennifer Allmaras, MPH, 2/23/2021

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