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BLADDER

A constrained mixture-micturition-growth (CMMG) model of the urinary bladder: Application to partial bladder outlet obstruction (BOO)

Cheng F, Watton PN, Pederzani G, Kurobe M, Takaoka EI, Chapple C, **Birder L**, **Yoshimura N**, Robertson AM

We present a constrained mixture-micturition-growth (CMMG) model for the bladder. It simulates bladder mechanics, voiding function (micturition) and tissue adaptations in response to altered biomechanical conditions. The CMMG model is calibrated with both in vivo and in vitro data from healthy male rat urinary bladders (cystometry, bioimaging of wall structure, mechanical testing) and applied to simulate the growth and remodeling (G&R) response to partial bladder outlet obstruction (BOO). The bladder wall is represented as a multi-layered, anisotropic, nonlinear constrained mixture. A short time scale micturition component of the CMMG model accounts for the active and passive mechanics of voiding. Over a second, longer time scale, G&R algorithms for the evolution of both cellular and extracellular constituents act to maintain/restore bladder (homeostatic) functionality. The CMMG model is applied to a spherical membrane model of the BOO bladder utilizing temporal data from an experimental male rodent model to parameterize and then verify the model. Consistent with the experimental studies of BOO, the model predicts: an initial loss of voiding capacity followed by hypertrophy of SMC to restore voiding function; bladder enlargement; collagen remodeling to maintain its role as a protective sheath; and increased voiding duration with lower average flow rate. This CMMG model enables a mechanistic approach for investigating the bladder's structure-function relationship and its adaption in pathological conditions. While the approach is illustrated with a conceptual spherical bladder model, it provides the basis for application of the CMMG model to anatomical geometries. Such a mechanistic approach has promise as an in silico tool for the rational development of new surgical and pharmacological treatments for bladder diseases such as BOO.

Gardnerella Exposures Alter Bladder Gene Expression and Augment Uropathogenic Escherichia coli Urinary Tract Infection in Mice

Gilbert NM, O'Brien VP, Waller C, Batourina E, **Mendelsohn CL**, Lewis AL

The anaerobic actinobacterium Gardnerella was first isolated from the bladder by suprapubic aspiration more than 50 years ago. Since then, Gardnerella has been increasingly recognized as a common and often abundant member of the female urinary microbiome (urobiome). Some studies even suggest that the presence of Gardnerella is associated with urological disorders in women. We recently reported that inoculation of Gardnerella into the bladders of mice results in urothelial exfoliation. Here, we performed whole bladder RNA-seq in our mouse model to identify additional host pathways involved in the response to Gardnerella bladder exposure. The transcriptional response to Gardnerella reflected the urothelial turnover that is a consequence of exfoliation while also illustrating the activation of pathways involved in inflammation and immunity. Additional timed exposure experiments in mice provided further evidence of a potentially clinically relevant consequence of bladder exposure to Gardnerella-increased susceptibility to subsequent UTI caused by uropathogenic Escherichia coli. Together, these data provide a broader picture of the bladder's response to Gardnerella and lay the groundwork for future studies examining the impact of Gardnerella on bladder health.

Nanotechnology as a tool to advance research and treatment of non-oncologic urogenital diseases

Loloi J, Babar M, **Davies KP**, **Suadicani SO**

Nanotechnology represents an expanding area of research and innovation in almost every field of science, including Medicine, where nanomaterial-based products have been developed for diagnostic and therapeutic applications. Because of their small, nanoscale size, these materials exhibit unique physical and chemical properties that differ from those of each component when considered in bulk. In Nanomedicine, there is an increasing interest in harnessing these unique properties to engineer nanocarriers for the delivery of therapeutic agents. We provide an update on research that is paving the way for clinical translation of nanotechnology in the areas of erectile dysfunction (ED), overactive bladder (OAB), interstitial cystitis/bladder pain syndrome (IC/BPS), and catheter-associated urinary tract infections (CAUTIs). Overall, preclinical and clinical studies have proven the utility of nanomaterials both as vehicles for transdermal and intravesical delivery of therapeutic agents and for urinary catheter formulation with antimicrobial agents to treat non-oncologic urogenital diseases.

KIDNEY

Genome-wide polygenic score to predict chronic kidney disease across ancestries

Khan A, Turchin MC, Patki A, Srinivasasainagendra V, Shang N, Nadukuru R, Jones AC, Malolepsza E, Dikilitas O, Kullo IJ, Schaid DJ, Karlson E, Ge T, Meigs JB, Smoller JW, Lange C, Crosslin DR, Jarvik GP, Bhatraju PK, Hellwege JN, Chandler P, Torvik LR, Fedotov A, Liu C, Kachulis C, Lennon N, Abul-Husn NS, Cho JH, Ionita-Laza I, **Gharavi AG**, Chung WK, Hripcsak G, Weng C, Nadkarni G, Irvin MR, Tiwari HK, Kenny EE, Limdi NA, Kiryluk K.

Chronic kidney disease (CKD) is a common complex condition associated with high morbidity and mortality. Polygenic prediction could enhance CKD screening and prevention; however, this approach has not been optimized for ancestrally diverse populations. By combining APOL1 risk genotypes with genome-wide association studies (GWAS) of kidney function, we designed, optimized and validated a genome-wide polygenic score (GPS) for CKD. The new GPS was tested in 15 independent cohorts, including 3 cohorts of European

ancestry (n = 97,050), 6 cohorts of African ancestry (n = 14,544), 4 cohorts of Asian ancestry (n = 8,625) and 2 admixed Latinx cohorts (n = 3,625). We demonstrated score transferability with reproducible performance across all tested cohorts. The top 2% of the GPS was associated with nearly threefold increased risk of CKD across ancestries. In African ancestry cohorts, the APOL1 risk genotype and polygenic component of the GPS had additive effects on the risk of CKD.

PROSTATE

Glucocorticoids are induced while dihydrotestosterone levels are suppressed in 5-alpha reductase inhibitor treated human benign prostate hyperplasia patients

Jin R, Forbes C, Miller NL, **Strand D**, Case T, Cates JM, Kim HH, Wages P, Porter NA, Mantione KM, Burke S, Mohler JL, Matusik RJ

The development of benign prostatic hyperplasia (BPH) and medication-refractory lower urinary tract symptoms (LUTS) remain poorly understood. This study attempted to characterize the pathways associated with failure of medical therapy for BPH/LUTS. Transitional zone tissue levels of cholesterol and steroids were measured in patients who failed medical therapy for BPH/LUTS and controls. Prostatic gene expression was measured using qPCR and BPH cells were used in organoid culture to study prostatic branching. After failure of medical therapy for BPH/LUTS, 5ARI therapy continued to inhibit androgenesis but a 5ARI-induced pathway increased tissue levels of GC not seen in patients on α-blockers. GC stimulation of organoids indicated that the GC receptors are a trigger for controlling growth of prostate glands. A 5ARI-induced pathway revealed GC activation can serve as a master regulator of prostatic branching and growth.

T1 signal intensity ratio of the pancreas as an imaging biomarker for the staging of chronic pancreatitis

Tirkes T, Dasyam AK, Shah ZK, Fogel EL, Vege SS, Li L, Li S, Chang ST, Farinas CA, Grajo JR, Mawad K, Takahashi N, Venkatesh SK, Wachsman A, Fisher WE, Forsmark CE, Hart PA, Pandol SJ, Park WG, **Van Den Eeden SK**, Yang Y, Topazian M, Andersen DK, Serrano J, Conwell DL, Yadav D; Consortium for the Study of Chronic Pancreatitis, Diabetes, Pancreatic Cancer (CPDPC)

Our purpose was to validate the T1 SIR (T1 score) as an imaging biomarker for the staging of CP in a large, multi-institutional, prospective study. The prospective study population included 820 participants enrolled in the PROCEED study from nine clinical centers between June 2017 and December 2021. A radiologist at each institution used a standardized method to measure the T1 signal intensity of the pancreas and the reference organs (spleen, paraspinal muscle, liver), which was used to derive respective T1 scores. Participants were stratified according to the seven mechanistic stages of chronic pancreatitis (MSCP 0-6) based on their clinical history, MRCP, and CT findings. The T1 score calculated by SIR of the pancreas-to-spleen shows a negative linear correlation with the progression of chronic pancreatitis. It holds promise as a practical imaging biomarker in evaluating disease severity in clinical research and practice.

STONES

Automated Machine Learning Segmentation and Measurement of Urinary Stones on CT Scan

Babajide R, **Lembrikova K**, **Ziemba J**, Ding J, **Li Y**, Fermin AS, **Fan Y**, **Tasian GE**

The objective of this study is to evaluate the performance of an engineered machine learning algorithm to identify kidney stones and measure stone characteristics without the need for human input. We performed a cross-sectional study of 94 children and adults who had kidney stones identified on non-contrast CT. A previously developed deep learning algorithm was trained to segment renal anatomy and kidney stones and to measure stone features. The performance and speed of the algorithm to measure renal anatomy and kidney stone features were compared to the current gold standard of human measurement performed by three independent reviewers. The conclusion is that an engineered machine learning algorithm can identify and characterize stones more accurately and reliably than humans, which has the potential to improve the precision and efficiency of assessing kidney stone burden.

- Jennifer Allmaras, MPH and Muen Wang, 8/5/2022

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