Liver Digest

A weekly update of PLRC happenings

May 23, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

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Featured Faculty - Dr. Obaid Shaikh

In this issue

Upcoming Seminars

The PLRC's regular seminar series and SIG roundtables are on hiatus until the fall. We will continue to update you on liver-related seminars and events over the summer.

Starzl Transplant Institute Conference Series Internal Grand Rounds

Friday, May 24, 2019

8:00 – 9:00 a.m.

LHAS Auditorium, 7th Floor, Montefiore Hospital

Ali Al-Khafaji, MD, MPH, FCCM

Professor of Critical Care Medicine

Director, Transplant Intensive Care Unit

"Extracorporeal Liver Assist Device (ELAD) in Acute Alcoholic Hepatitis, An Update"

Sponsored by

Thomas E. Starzl Transplantation Institute

University of Pittsburgh School of Medicine

Department of Surgery, Division of Transplantation

Center for Continuing Education in the Health Sciences

Seminar: Postdoctoral candidate for Gavin Arteel's laboratory

Friday, May 24, 2019

Noon – 1:00 p.m.

S123 BST

Kelly Fader, PhD
Department of Chemistry and Molecular Biology
Michigan State University

"Persistent Aryl Hydrocarbon Receptor Activation Abolishes Circadian Regulation of Hepatic Metabolism in Mice"

Faculty Highlights

Original Article:

Xue-Ping Wang, Seohyun Janice Im, Deidra M. Balchak, Nicolas Montalbetti, Marcelo D. Carattino, Evan C. Ray, and **Ossama B. Kashlan**. Murine epithelial sodium (Na+) channel regulation by biliary factors. First Published on May 15, 2019. doi: 10.1074/jbc.RA119.007394 jbc.RA119.007394.

ABSTRACT
The epithelial sodium channel (ENaC) mediates Na+ transport in several epithelia, including the aldosterone-sensitive distal nephron, distal colon, and biliary epithelium. Numerous factors regulate ENaC activity, including extracellular ligands, post-translational modifications, and membrane-resident lipids. However, ENaC regulation by bile acids and conjugated bilirubin, metabolites that are abundant in the biliary tree and intestinal tract and are sometimes elevated in the urine of individuals with advanced liver disease, remains poorly understood. Here, using a Xenopus oocyte-based system to express and functionally study ENaC, we found that, depending on the bile acid used, bile acids both activate and inhibit mouse ENaC. Whether bile acids were activating or inhibiting was contingent on the position and orientation of specific bile-acid moieties. For example, a hydroxyl group at the 12-position and facing the hydrophilic side (12α-OH) was

activating. Taurine-conjugated bile acids, which have reduced membrane permeability, affected ENaC activity more strongly than did their more membrane permeant unconjugated counterparts, suggesting that bile acids regulate ENaC extracellularly. Bile acid-dependent activation was enhanced by amino acid substitutions in ENaC that depress open probability, and was precluded by proteolytic cleavage that increases open probability, consistent with an effect of bile acids on ENaC open probability. Bile acids also regulated ENaC in a cortical collecting duct cell line, mirroring the results in Xenopus oocytes. We also show that bilirubin conjugates activate ENaC. These results indicate that ENaC responds to compounds abundant in bile and that their ability to regulate this channel depends on the presence of specific functional groups.

For full text, please **click here**.

Original Article:
Patrick D. Wilkinson, Frances Alencastro, Evan R. Delgado, Madeleine P. Leek, Matthew P. Weirich, P. Anthony Otero, Nairita Roy, Whitney K. Brown, **Michael Oertel**, **Andrew W. Duncan**. Polyploid Hepatocytes Facilitate Adaptation and Regeneration to Chronic Liver Injury. The American Journal of Pathology. Volume 189, Issue 6, June 2019, Pages 1241-1255. https://doi.org/10.1016/j.ajpath.2019.02.008. PMID: 30928253.

ABSTRACT
The liver contains diploid and polyploid hepatocytes (tetraploid, octaploid, etc.), with polyploids comprising ≥90% of the hepatocyte population in adult mice. Polyploid hepatocytes form multipolar spindles in mitosis, which lead to chromosome gains/losses and random aneuploidy. The effect of aneuploidy on liver function is unclear, and the degree of liver aneuploidy is debated, with reports showing aneuploidy affects 5% to 60% of hepatocytes. To study relationships among liver polyploidy, aneuploidy, and adaptation, mice lacking E2f7 and E2f8 in the liver (LKO), which have a polyploidization defect, were used. Polyploids were reduced fourfold in LKO livers, and LKO

hepatocytes remained predominantly diploid after extensive proliferation. Moreover, nearly all LKO hepatocytes were euploid compared with control hepatocytes, suggesting polyploid hepatocytes are required for production of aneuploid progeny. To determine whether reduced polyploidy impairs adaptation, LKO mice were bred onto a tyrosinemia background, a disease model whereby the liver can develop disease-resistant, regenerative nodules. Although tyrosinemic LKO mice were more susceptible to morbidities and death associated with tyrosinemia-induced liver failure, they developed regenerating nodules similar to control mice. Analyses revealed that nodules in the tyrosinemic livers were generated by aneuploidy and inactivating mutations. In summary, we identified new roles for polyploid hepatocytes and demonstrated that they are required for the formation of aneuploid progeny and can facilitate adaptation to chronic liver disease.

For full text, please **click here**.

Original Article:
Kulkarni SS, Chen H, Josbeno DA, Schmotzer A, **Hughes C**, **Humar A**, Sood P, **Rachakonda V**, **Dunn MA**, Tevar AD. Gait Speed and Grip Strength Are Associated With Dropping Out of the Liver Transplant Waiting List. Transplant Proc. 2019 Jan 9. pii: S0041-1345(18)31029-7. doi: 10.1016/j.transproceed.2019.01.030. PubMed PMID: 30739717.

ABSTRACT
INTRODUCTION: Frailty measures can predict perioperative surgical risk in liver transplant patients. The 5-meter walk test (5MWT) and hand grip strength (HGS) are easy and reproducible frailty measures. We hypothesized that they could capture frailty in liver transplant listed patients and would be associated with dropping out of the waiting list.

METHODS: We conducted a retrospective analysis of patients undergoing

outpatient liver transplant listing at the University of Pittsburgh Medical Center from 2013 to 2016. We compared demographics, baseline laboratory markers, 5MWT, and HGS between patients who were dropped from the waiting list for medical reasons and those who remained or were successfully transplanted. Bivariate statistical analysis was performed using Fisher exact or $\chi 2$ tests.

RESULTS: We reviewed 197 patients listed for liver transplant. Average age was 57.1 years (range 20-74), and patients were predominantly white (90.4%). Patients' most common etiology of liver disease was hepatitis C (32.5%), 14 (7.1%) had a previous liver transplant, and average Model for End-Stage Liver Disease score upon listing was 16.0. Of the cohort, 38 (19.3%) were ultimately dropped from the waitlist due to non-hepatocellular carcinoma-related reasons. Patients dropped from the waiting list had weaker HGS (46.14 lb vs 59.6 lb; $P < .005$) and slower 5MWT speed (5MWT: 0.92 m/s vs 1.03 m/s; $P < .005$).

CONCLUSION: The 5MWT and HGS can easily measure frailty in patients being evaluated for liver transplant. These tests are associated with waiting list dropout, indicating that they can be valuable tools in the evaluation of these patients.

For full text, please **click here**.

Original Article:

Barritt AS 4th, Jiang Y, Schmidt M, Hayashi PH, **Bataller R**. Charges for Alcoholic Cirrhosis Exceed All Other Etiologies of Cirrhosis Combined: A National and State Inpatient Survey Analysis. Dig Dis Sci. 2019 Jan 23. doi: 10.1007/s10620-019-5471-7. PubMed PMID: 30673984.

ABSTRACT

BACKGROUND: Inpatient charges for patients with cirrhosis are substantial. We aimed to examine trends in inpatient charges among patients with cirrhosis to determine the drivers of healthcare

expenditures. We hypothesized that alcoholic cirrhosis (AC) was a significant contributor to overall expense.

METHODS: We performed a retrospective analysis of the Health Care Utilization Project Nationwide Inpatient Sample Database 2002-2014 (annual cross-sectional data) and New York and Florida State Inpatient Databases 2010-2012 (longitudinal data). Adult patients with cirrhosis of the liver were categorized as AC versus all other etiologies of cirrhosis combined. Patient characteristics were analyzed using ordinary least squares regression modeling. A random effects model was used to evaluate 30-day readmissions.

RESULTS: In total, 1,240,152 patients with cirrhosis were admitted between 2002 and 2014. Of these, 567,510 (45.8%) had a diagnosis of AC. Total charges for AC increased by 95.7% over the time period, accounting for 59.9% of all inpatient cirrhosis-related charges in 2014. Total aggregate charges for AC admissions were $28 billion and increased from $1.4B in 2002 to $2.8B by 2014. In the NIS and SID, patients with AC were younger, white and male. Readmission rates at 30, 60, and 90 days were all higher among AC patients.

CONCLUSIONS: Inpatient charges for cirrhosis care are high and increasing. Alcohol-related liver disease accounts for more than half of these charges and is driven by sheer volume of admissions and readmissions of the same patients. Effective alcohol addictions therapy may be the most cost-effective way to substantially reduce inpatient cirrhosis care expenditures.

For full text, please **click here**.

Original Article:

Berauer JP, Mezina AI, Okou DT, Sabo A, Muzny DM, Gibbs RA, Hegde MR, Chopra P, Cutler DJ, Perlmutter DH, Bull LN, Thompson RJ, Loomes KM, Spinner NB, Rajagopalan R, Guthery SL, Moore B, Yandell M, Harpavat S,

Magee JC, Kamath BM, Molleston JP, Bezerra JA, Murray KF, Alonso EM, Rosenthal P, **Squires RH**, Wang KS, Finegold MJ, Russo P, Sherker AH, Sokol RJ, Karpen SJ; Childhood Liver Disease Research Network (ChiLDReN). Identification of PKD1L1 Gene Variants in Children with the Biliary Atresia Splenic Malformation Syndrome. Hepatology. 2019 Jan 21. doi: 10.1002/hep.30515. [Epub ahead of print] PubMed PMID: 30664273.

ABSTRACT

Biliary atresia (BA) is the most common cause of end-stage liver disease in children and the primary indication for pediatric liver transplantation, yet underlying etiologies remain unknown. Approximately 10% of infants affected by BA exhibit various laterality defects (heterotaxy) including splenic abnormalities and complex cardiac malformations-a distinctive subgroup commonly referred to as the biliary atresia splenic malformation (BASM) syndrome. We hypothesized that genetic factors linking laterality features with the etiopathogenesis of BA in BASM patients could be identified through whole-exome sequencing (WES) of an affected cohort. DNA specimens from 67 BASM subjects, including 58 patient-parent trios, from the National Institute of Diabetes and Digestive and Kidney Diseases-supported Childhood Liver Disease Research Network (ChiLDReN) underwent WES. Candidate gene variants derived from a prespecified set of 2,016 genes associated with ciliary dysgenesis and/or dysfunction or cholestasis were prioritized according to pathogenicity, population frequency, and mode of inheritance. Five BASM subjects harbored rare and potentially deleterious biallelic variants in polycystic kidney disease 1 like 1 (PKD1L1), a gene associated with ciliary calcium signaling and embryonic laterality determination in fish, mice, and humans. Heterozygous PKD1L1 variants were found in 3 additional subjects. Immunohistochemical analysis of liver from the one BASM subject available revealed decreased PKD1L1 expression in bile duct epithelium when compared to normal livers and livers affected by other noncholestatic diseases. Conclusion: WES identified biallelic and heterozygous PKD1L1 variants of interest in 8 BASM subjects from the

ChiLDReN data set; the dual roles for PKD1L1 in laterality determination and ciliary function suggest that PKD1L1 is a biologically plausible, cholangiocyte-expressed candidate gene for the BASM syndrome.

For full text, please **click here**.

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