Liver Digest

A weekly update of PLRC happenings

October 10, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Spotlight: Scott Morley, MBA

Coulter Program Director, Swanson School of Engineering

Entrepreneur in Residence, Innovation Institute

In this issue

Funding Opportunity

PLRC Pilot & Feasibility Awards (2020-2021 cycle)

Request for Applications is **available here.**

- LOIs are due October 15, 2019
- Applications are due December 2, 2019

Next Week's Seminars

PLRC Seminar Series - Dr. Josep Llovet

Tues., October 15, 2019

12:00 to 1:00 p.m.

S120 BST

Josep Llovet, MD

Professor of Medicine

Founder and Director of the Liver Cancer Program

Mount Sinai School of Medicine

Molecular Targeted Therapies in HCC

This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.

Pizza will be provided.

Liver Seminar - Dr. George Michalopoulos
Wed., October 16, 2019
12:00 to 1:00 p.m.
1104 Scaife

George K. Michalopoulos, M.D., Ph.D.
Professor and Chair
Department of Pathology
University of Pittsburgh

Liver Regeneration

Department of Pathology Seminar.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Wang P, Sachar M, Lu J, Shehu AI, Zhu J, Chen J, Liu K, Anderson KE, **Xie W**, Gonzalez FJ, Klaassen CD, **Ma X**. The essential role of the transporter ABCG2 in the pathophysiology of erythropoietic protoporphyria. Sci Adv. 2019 Sep 18;5(9):eaaw6127. doi: 10.1126/sciadv.aaw6127. eCollection 2019 Sep. PubMed PMID: 31555729; PubMed Central PMCID: PMC6750912.

ABSTRACT
Erythropoietic protoporphyria (EPP) is an inherited disease caused by loss-of-function mutations of ferrochelatase, an enzyme in the heme biosynthesis pathway that converts protoporphyrin IX (PPIX) into heme. PPIX accumulation in patients with EPP leads to phototoxicity and hepatotoxicity, and there is no cure. Here, we demonstrated that the PPIX efflux transporter ABCG2 (also called BCRP) determines EPP-associated phototoxicity and hepatotoxicity. We found that ABCG2 deficiency decreases PPIX distribution to the skin and therefore prevents EPP-associated phototoxicity. We also found that ABCG2 deficiency protects against EPP-associated hepatotoxicity by modulating PPIX

distribution, metabolism, and excretion. In summary, our work has uncovered an essential role of ABCG2 in the pathophysiology of EPP, which suggests the potential for novel strategies in the development of therapy for EPP.

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

Original Article:

Strauss KA, Ahlfors CE, Soltys K, Mazareigos GV, Young M, Bowser LE, Fox MD, **Squires JE, McKiernan P**, Brigatti KW, Puffenberger EG, Carson VJ, Vreman HJ. Crigler-Najjar syndrome type 1: pathophysiology, natural history, and therapeutic frontier. Hepatology. 2019 Sep 25. doi: 10.1002/hep.30959. PubMed PMID: 31553814.

ABSTRACT

We describe the pathophysiology, treatment, and outcome of Crigler-Najjar type 1 syndrome (CN1) in 28 UGT1A1 c.222C>A homozygotes followed for 520 aggregate patient-years. Unbound ('free') bilirubin (Bf) was measured in patient sera to characterize the binding of unconjugated bilirubin (BT) to albumin (A) and validate their molar concentration ratio (BT /A) as an index of neurological risk. Two custom phototherapy systems were constructed from affordable materials to provide high irradiance in the outpatient setting; light dose was titrated to keep BT /A at least 30% below intravascular BT binding capacity (i.e. BT /A=1.0). Categorical clinical outcomes were ascertained by chart review, and a novel measure was used to quantify liver fibrosis. Unbound bilirubin had a non-linear relationship to BT (R2 = 0.71) and BT /A (R2 = 0.76), and Bf as a percentage of BT correlated inversely to the bilirubin-albumin equilibrium association binding costant (R2 = 0.69), which varied 10-fold among individuals. In newborns with CN1, unconjugated bilirubin increased 4.3±1.1 mg/dL•day. Four (14%) neonates developed kernicterus between 14 and 45 days of age; peak BT ≥30 mg/dL and BT /A ≥1.0 mol:mol were equally predictive of perinatal brain injury (sensitivity 100%, specificity 93.3%, positive predictive value 88.0%), and starting phototherapy after age 13 days increased this risk 3.5-fold. Consistent phototherapy with 33-103 μW/cm2 •nm for 9.2 ± 1.1 hours/day kept BT and BT /A within safe limits throughout childhood, but BT increased 0.46 mg/dL per year to reach dangerous concentrations by age 18 years. Liver transplantation (n=17) normalized BT and eliminated phototherapy dependence. Liver explants showed fibrosis ranging from mild to severe. Seven decades after its discovery, CN1 remains a morbid and potentially fatal disorder.

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

Opinion Article:

Yarchoan M, Agarwal P, Villanueva A, Rao S, Dawson LA, Llovet JM, Finn RS, Groopman JD, El-Serag HB, **Monga SP**, Wang XW, Karin M, Schwartz RE, Tanabe KK, Roberts LR, Gunaratne PH, Tsung A, Brown KA, Lawrence TS, Salem R, Singal AG, Kim AK, Rabiee A, Resar L, Hoshida Y, He AR, Ghoshal K, Ryan PB, Jaffee EM, Guha C, Mishra L, Coleman CN, Ahmed MM. Recent Developments and Therapeutic Strategies against Hepatocellular Carcinoma. Cancer Res. 2019 Sep 1;79(17):4326-4330. doi: 10.1158/0008-5472.CAN-19-0803. PubMed PMID: 31481419.

ABSTRACT

Hepatocellular carcinoma (HCC) has emerged as a major cause of cancer deaths globally. The landscape of systemic therapy has recently changed, with six additional systemic agents either approved or awaiting approval for advanced stage HCC. While these agents have the potential to improve outcomes, a survival increase of 2-5 months remains poor and falls short of what has been achieved in many other solid tumor types. The roles of genomics, underlying cirrhosis, and optimal use of treatment strategies that include radiation, liver transplantation, and surgery remain unanswered. Here, we discuss new treatment opportunities, controversies, and future directions in managing HCC.

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

Original Article:

Lu Y, Meng R, Wang X, Xu Y, Tang Y, Wu J, Xue Q, Yu S, Duan M, Shan D, **Wang Q**, Wang H, **Billiar TR**, Xiao X, Chen F, Lu B. Caspase-11 signaling enhances graft-versus-host disease. Nat Commun. 2019 Sep 6;10(1):4044. doi: 10.1038/s41467-019-11895-2. PubMed PMID: 31492850; PubMed Central PMCID: PMC6731232.

ABSTRACT

Acute graft-versus-host disease (GVHD) remains a major obstacle for the wider usage of allogeneic hematopoietic stem cell transplantation (allo-HSCT), which is an effective therapy for hematopoietic malignancy. Here we show that caspase-11, the cytosolic receptor for bacterial endotoxin (lipopolysaccharide: LPS), enhances GVHD severity. Allo-HSCT markedly increases the LPS-caspase-11 interaction, leading to the cleavage of gasdermin D (GSDMD). Caspase-11 and GSDMD mediate the release of interleukin-1α (IL-1α)

in allo-HSCT. Deletion of Caspase-11 or Gsdmd, inhibition of LPS-caspase-11 interaction, or neutralizing IL-1α uniformly reduces intestinal inflammation, tissue damage, donor T cell expansion and mortality in allo-HSCT. Importantly, Caspase-11 deficiency does not decrease the graft-versus-leukemia (GVL) activity, which is essential to prevent cancer relapse. These findings have major implications for allo-HSCT, as pharmacological interference with the caspase-11 signaling might reduce GVHD while preserving GVL activity.

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

Original Article:

Haugen CE, McAdams-DeMarco M, Verna EC, Rahimi R, Kappus MR, **Dunn MA**, Volk ML, Gurakar A, **Duarte-Rojo A**, Ganger DR, O'Leary JG, Ladner D, Garonzik-Wang J, Segev DL, Lai JC. Association Between Liver Transplant Wait-list Mortality and Frailty Based on Body Mass Index. JAMA Surg. 2019 Sep 11. doi: 10.1001/jamasurg.2019.2845. PubMed PMID: 31509169; PubMed Central PMCID: PMC6739734.

ABSTRACT

IMPORTANCE: Among liver transplant candidates, obesity and frailty are associated with increased risk of death while they are on the wait-list. However, use of body mass index (BMI) may not detect candidates at a higher risk of death owing to the fact that ascites and muscle wasting are seen across transplant candidates of all BMI measurements.

OBJECTIVE: To evaluate whether the association between wait-list mortality and frailty varied by BMI of liver transplant candidates.

DESIGN, SETTING, AND PARTICIPANTS: A prospective cohort study was conducted at 9 liver transplant centers in the United States from March 1, 2012, to May 1, 2018, among 1108 adult liver transplant candidates without hepatocellular carcinoma.

EXPOSURES: At outpatient evaluation, the Liver Frailty Index score was calculated (grip strength, chair stands, and balance), with frailty defined as a Liver Frailty Index score of 4.5 or more. Candidates' BMI was categorized as nonobese (18.5-29.9), class 1 obesity (30.0-34.9), and class 2 or greater obesity (≥35.0).

MAIN OUTCOMES AND MEASURES: The risk of wait-list mortality was quantified using competing risks regression by candidate frailty, adjusting for age, sex, race/ethnicity, Model for End-stage Liver Disease Sodium score, cause of liver disease, and ascites, including an interaction with candidate BMI.

RESULTS: Of 1108 liver transplant candidates (474 women and 634 men; mean [SD] age, 55 [10] years), 290 (26.2%) were frail; 170 of 670 nonobese candidates (25.4%), 64 of 246 candidates with class 1 obesity (26.0%), and 56 of 192 candidates with class 2 or greater obesity (29.2%) were frail (P = .57). Frail nonobese candidates and frail candidates with class 1 obesity had a higher risk of wait-list mortality compared with their nonfrail counterparts (nonobese candidates: adjusted subhazard ratio, 1.54; 95% CI, 1.02-2.33; P = .04; and candidates with class 1 obesity: adjusted subhazard ratio, 1.72; 95% CI, 0.99-2.99; P = .06; P = .75 for interaction). However, frail candidates with class 2 or greater obesity had a 3.19-fold higher adjusted risk of wait-list mortality compared with nonfrail candidates with class 2 or greater obesity (95% CI, 1.75-5.82; P < .001; P = .047 for interaction).

CONCLUSIONS AND RELEVANCE: This study's finding suggest that among nonobese liver transplant candidates and candidates with class 1 obesity, frailty was associated with a 2-fold higher risk of wait-list mortality. However, the mortality risk associated with frailty differed for candidates with class 2 or greater obesity, with frail candidates having a more than 3-fold higher risk of wait-list mortality compared with nonfrail patients. Frailty assessments may help to identify vulnerable patients, particularly those with a BMI of 35.0 or more, in whom a clinician's visual evaluation may be less reliable to assess muscle mass and nutritional status.

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

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