Liver Digest

A weekly update of PLRC happenings

October 17, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featuring Coulter Program - Scott Morley, MBA

In this issue

Please check before Publishing or Presenting

Before you submit a paper or give a presentation, please remember to acknowledge all PLRC Cores used and PLRC Grant support (as appropriate) in your work. Suggested text: "This research was supported by the [ ] shared resource of the NIH/NIDDK P30DK120531."

The NIH Policy for Communicating and Acknowledging Federal Funding is available here: https://grants.nih.gov/grants/acknow.htm

---

PLRC at AASLD

PRESENTATIONS and POSTERS

Many of our members will be presenting their work at the AASLD Liver Meeting November 8-12, 2019, in Boston. We have compiled a list of those presentations, which is **available here**. If you are presenting or have a poster at the Meeting, and it is not on this list, please email Ann Vinski (**vinskiam@upmc.edu**) to have it added.

COCKTAIL RECEPTION

Please join UPMC Thomas E. Starzl Transplantation Institute, the UPMC Center for Liver Diseases, and the Pittsburgh Liver Research Center for cocktails and hors d'oeuvres while attending The Liver Meeting 2019. Invitation and link to RSVP are **available here**.

Next Week's Seminar

Liver Seminar
Wed, 10/23/2019
12:00 to 1:00 p.m.
1104 Scaife Hall

Alphonse E. Sirica, PhD
Professor of Pathology, Division of Cellular and Molecuar Pathogenesis
Virginia Commonwealth University School of Medicine

TGF-β Periostin, and Mesothelin in Intrahepatic Cholangiocarcinoma: Pathological Insights and Translational Implications

Pathology Department Seminar, co-sponsored by PLRC

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Honghai Liu, Cheng-Hai Zhang, Niyatie Ammanamanchi, Sangita Suresh, Christopher Lewarchik, Krithika Rao, Gerrida M. Uys, Lu Han, Maryline Abrial, **Dean Yimlamai**, Balakrishnan Ganapathy, Christelle Guillermier, Nathalie Chen, Mugdha Khaladkar6, Jennifer Spaethling, James H. Eberwine, Junhyong Kim, Stuart Walsh, Sangita Choudhury, Kathryn Little, Kimberly Francis, Mahesh Sharma, Melita Viegas, Abha Bais, Dennis Kostka, Jun Ding, Ziv Bar-Joseph, Yijen Wu, Vijay Yechoor, Mousumi Moulik, Jennifer Johnson, Jacqueline Weinberg, Miguel Reyes-Múgica, Matthew L. Steinhauser, Bernhard Kühn. Control of cytokinesis by beta-adrenergic receptors indicates an approach forregulating cardiomyocyte endowment. Science Translational Medicine 09 Oct 2019: Vol. 11, Issue 513, eaaw6419. DOI: 10.1126/scitranslmed.aaw6419.

ABSTRACT
One million patients with congenital heart disease (CHD) live in the United States. They have a lifelong risk of developing heart failure. Current concepts do not sufficiently address mechanisms of heart failure development specifically for these patients. Here, analysis of heart tissue from an infant with tetralogy of Fallot with pulmonary stenosis (ToF/PS) labeled with

isotope-tagged thymidine demonstrated that cardiomyocyte cytokinesis failure is increased in this common form of CHD. We used single-cell transcriptional profiling to discover that the underlying mechanism of cytokinesis failure is repression of the cytokinesis gene ECT2, downstream of beta-adrenergic receptors (beta-ARs). Inactivation of the beta-AR genes and administration of the beta-blocker propranolol increased cardiomyocyte division in neonatal mice, which increased the number of cardiomyocytes (endowment) and conferred benefit after myocardial infarction in adults. Propranolol enabled the division of ToF/PS cardiomyocytes in vitro. These results suggest that beta-blockers could be evaluated for increasing cardiomyocyte division in patients with ToF/PS and other types of CHD.

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

Original Article:

Squires JE, Ng VL, Hawthorne K, Henn L, Sorensen LG, Fredericks EM, Alonso EM, Murray KF, Loomes KM, Karpen SJ, Cavallo LA, Molleston JP, Bezerra JA, Rosenthal P, **Squires RH**, Wang KS, Schwarz KB, Arnon R, Magee JC, Sokol RJ; Childhood Liver Disease Research Network (ChiLDReN). Neurodevelopmental Outcomes in Pre-School and School Aged Children with Biliary Atresia and their Native, Liver. J Pediatr Gastroenterol Nutr. 2019 Sep 6. doi: 10.1097/MPG.0000000000002489. PubMed PMID: 31503218.

ABSTRACT

Objectives: To assess neurodevelopmental outcomes among children with biliary atresia (BA) surviving with their native liver at age 3-12 years and evaluate variables that associate with neurodevelopment.

Methods: Participants (age 3-12 years) in a prospective, longitudinal, multicenter study underwent neurodevelopmental testing with Weschler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III, age 3-5 yrs.) and Weschler Intelligence Scale for Children, 4th edition (WISC-IV, age 6-12 yrs.). Continuous scores were analyzed using Kolmogorov-Smironov tests compared to a normal distribution (mean = 100 ± 15). Effect of covariates on Full-Scale Intelligence Quotient (FSIQ) was analyzed using linear regression.

Results: Ninety-three participants completed 164 WPPSI-III (mean age 3.9) and 51 WISC-IV (mean age 6.9) tests. WPPSI-III FSIQ (104 ± 14, $P < 0.02$), Verbal IQ (106 ± 14, $P < 0.001$), and General Language Composite (107 ± 16, $P < 0.001$)

distributions were shifted higher compared to test norms. WISC-IV FSIQ (105 ± 12, P < 0.01), Perceptual Reasoning Index (107 ± 12, P < 0.01), and Processing Speed Index (105 ± 10, P < 0.02) also shifted upwards. In univariate and multivariable analysis, parent education (P < 0.01) was a significant predictor of FSIQ on WPPSI-III and positively associated with WISC-IV FSIQ. Male sex and higher total bilirubin and gamma glutamyl transferase (GGT) predicted lower WPPSI-III FSIQ. Portal hypertension was predictive of lower WISC-IV FSIQ.

Conclusion: This cohort of children with BA and native liver did not demonstrate higher prevalence of neurodevelopmental delays. Markers of advanced liver disease (higher total bilirubin and GGT for age ≤5 yrs; portal hypertension for age ≥6) correlate with lower FSIQ and may identify a vulnerable subset of patients who would benefit from intervention.

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

Review Article:

Wilson GC, **Geller DA**. Evolving Surgical Options for Hepatocellular Carcinoma. Surg Oncol Clin N Am. 2019 Oct;28(4):645-661. doi: 10.1016/j.soc.2019.06.006. Review. PubMed PMID: 31472911.

ABSTRACT

Surgical resection and liver transplant remain the cornerstones of curative treatment options for hepatocellular carcinoma. Determining the best treatment option for each patient is a complex decision based on degree of liver cirrhosis, extent of tumor, and overall patient performance status. A multidisciplinary approach is best. With widespread adoption, the role of laparoscopic liver resection for hepatocellular carcinoma continues to expand. Long-term oncologic outcomes are similar for laparoscopic and open resection, with improved short-term results, mainly blood loss and hospital length of stay. Liver transplant remains the ideal treatment of cirrhotic patients with signs of portal hypertension and hepatocellular carcinoma.

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

Original Article:

Jamie L. Young, Xiaofang Yan, Jianxiang Xu, Xinmin Yin, Xiang Zhang, **Gavin E. Arteel**, Gregory N. Barnes, J. Christopher States, Walter H. Watson, Maiying

Kong, Lu Cai, Jonathan H. Freedman. Cadmium and High-Fat Diet Disrupt Renal, Cardiac and Hepatic Essential Metals. Scientific Reports volume 9, Article number: 14675 (2019). Published: 11 October 2019.

ABSTRACT
Exposure to the environmental toxicant cadmium (Cd) contributes to the development of obesity-associated diseases. Obesity is a risk factor for a spectrum of unhealthy conditions including systemic metabolic dyshomeostasis. In the present study, the effects of whole-life exposure to environmentally-relevant concentrations of Cd on systemic essential metal distribution in adult mice fed a high-fat diet (HFD) were examined. For these studies, male and female mice were exposed to Cd-containing drinking water for >2 weeks before breeding. Pregnant mice and dams with offspring were exposed to Cd-containing drinking water. After weaning, offspring were continuously exposed to the same Cd concentration as their parents, and divided into HFD and normal (low) fat diet (LFD) groups. At 10 and 24 weeks, mice were sacrificed and blood, liver, kidney and heart harvested for metal analyses. There were significant concentration dependent increases in Cd levels in offspring with kidney > liver > heart. Sex significantly affected Cd levels in kidney and liver, with female animals accumulating more metal than males. Mice fed the HFD showed > 2-fold increase in Cd levels in the three organs compared to similarly treated LFD mice. Cadmium significantly affected essential metals levels in blood, kidney and liver. Additionally, HFD affected essential metal levels in these three organs. These findings suggest that Cd interacts with HFD to affect essential metal homeostasis, a phenomenon that may contribute to the underlying mechanism responsible for the development of obesity-associated pathologies.

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

Review Article:
Ochando J, Ordikhani F, Jordan S, Boros P, **Thomson AW**. Tolerogenic Dendritic Cells in Organ Transplantation. Transpl Int. 2019 Aug 31. doi: 10.1111/tri.13504. Review. PubMed PMID: 31472079.

ABSTRACT
Dendritic cells (DCs) are specialized cells of the innate immune system that are characterized by their ability to take up, process and present antigens (Ag) to effector T cells. They are derived from DC precursors produced in the

bone marrow. Different DC subsets have been described according to lineage-specific transcription factors required for their development and function. Functionally, DCs are responsible for inducing Ag-specific immune responses that mediate organ transplant rejection. Consequently, to prevent anti-donor immune responses, therapeutic strategies have been directed towards the inhibition of DC activation. In addition however, an extensive body of pre-clinical research, using transplant models in rodents and non-human primates, has established a central role of DCs in the negative regulation of alloimmune responses. As a result, DCs have been employed as cell-based immunotherapy in early phase I/II clinical trials in organ transplantation. Together with in vivo targeting through use of myeloid cell-specific nanobiologics, DC manipulation represents a promising approach for the induction of transplantation tolerance. In this review, we summarize fundamental characteristics of DCs and their roles in promotion of central and peripheral tolerance. We also discuss their clinical application to promote improved long-term outcomes in organ transplantation.

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

Funding Opportunities

Organotypic Culture Models developed from Experimental Animals for Chemical Toxicity Screening (R43/R44 Clinical Trial Not Allowed)

(RFA-ES-20-005)

National Institute of Environmental Health Sciences

ALF Research Awards Program

Liver Scholar Award

Postdoctoral Research Fellowship Award

Our mailing address is:
Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261