Liver Digest

A weekly update of PLRC happenings

March 21, 2019

www.livercenter.pitt.edu

Featured Faculty - Dr. Alan Wells

In this issue

- Funding opportunities

Next Week's Seminar

PLRC Seminar Series - 2018 P&F Awardees

Tue, 03/26/2019

11:30 a.m. - 1:00 p.m.

1102 Scaife

Three of the 2018-19 Pilot and Feasibility Awardees will present their work at this seminar.

Juliane I. Beier, PhD

Assistant Professor of Medicine, Division of Gastroenterology, Hepatology, and Nutrition

"Epitranscriptomic changes in vinyl chloride-induced liver injury"

Tirthadipa Pradhan-Sundd, PhD

Research Instructor, Department of Pathology, Division of Experimental Pathology

"Molecular mechanisms of sickle cell hepatic crisis"

Dean Yimlamai, MD, PhD

Assistant Professor of Pediatrics, Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition

"The Prohibitins as Novel Regulators of Liver Hippo Signaling"

Pizza will be provided.

For a complete list of upcoming PLRC seminars, please visit our website: **http://www.livercenter.pitt.edu/events**

Liver-Themed Gut Club - May 2

Dr. Fasiha Kanwal, the division chief at Baylor, will speak at the May 2, 2019 Pittsburgh Gut Club accredited dinner/lecture series on "The Changing Epidemiology of Liver Cancer."

Liver-related clinical and research trainees are invited to attend the lecture with fee-waived registration. All faculty are invited to attend as well but are required to pay to attend. But, they welcome your trainees as fee-waived participants.

To register for this event, please complete the registration form found in the brochure available on the here (trainees mark "fee waived" in the payment section), and scan (joj2@pitt.edu) or fax (412-578-9537) it to Joy Merusi by April 15th.

Faculty Highlights

Original Article:

Bove KE, Thrasher AD, Anders R, Chung CT, Cummings OW, Finegold MJ, Finn L, **Ranganathan S**, Kim GE, Lovell M, Magid MS, Melin-Aldana H, Russo P, Shehata B, Wang L, White F, Chen Z, Spino C, Magee JC. Inflammation, Active Fibroplasia, and End-stage Fibrosis in 172 Biliary Atresia Remnants Correlate Poorly With Age at Kasai Portoenterostomy, Visceral Heterotaxy, and Outcome. Am J Surg Pathol. 2018 Dec;42(12):1625-1635. doi: 10.1097/PAS.0000000000001146. PubMed PMID: 30247160.

ABSTRACT

Published histologic studies of the hilar plate or entire biliary remnant at the time of Kasai portoenterostomy (KHPE) have not provided deep insight into the pathogenesis of biliary atresia, relation to age at surgery, prognosis or the basis for successful drainage. We report detailed histologic findings in 172 centrally reviewed biliary remnants with an average of 6 sections per subject. Active lesions were classified as either necroinflammatory (rare/clustered in a few subjects) or active concentric fibroplasia with or without inflammation (common). Inactive lesions showed bland replacement by collagen and fibrous cords with little or no inflammation. Heterogeneity was common within a given remnant; however, relatively homogenous histologic patterns, defined as 3 or more inactive or active levels in the hepatic ducts levels, characterized most remnants. Homogeneity did not correlate with age at KHPE, presence/absence of congenital anomalies at laparotomy indicative of heterotaxy and outcome. Remnants from youngest subjects were more likely than older subjects to be homogenously inactive suggesting significantly earlier onset in the youngest subset. Conversely remnants from the oldest subjects were often homogenously active suggesting later onset or slower progression. More data are needed in remnants from subjects <30 days old at KHPE and in those with visceral anomalies. Prevalence of partially preserved epithelium in active fibroplastic biliary atresia lesions at all ages suggests that epithelial regression or injury may not be a primary event or that reepithelialization is already underway at the time of KHPE. We hypothesize that outcome after KHPE results from competition between active fibroplasia and reepithelialization of retained, collapsed but not obliterated lumens. The driver of active fibroplasia is unknown.

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

Original Article:

Molina L, Yang H, Adebayo Michael AO, **Oertel M**, **Bell A**, Singh S, Chen X, Tao J, **Monga SP**. mTOR inhibition affects Yap1-β-catenin-induced hepatoblastoma growth and development. Oncotarget. 2019 Feb 19;10(15):1475-1490. doi: 10.18632/oncotarget.26668. eCollection 2019 Feb 19. PMID: 30863496.

ABSTRACT
Hepatoblastoma (HB) is the most common pediatric liver malignancy. Around 80% of HB demonstrate simultaneous activation of β-catenin and Yes-associated protein 1 (Yap1). The mechanism by which these signaling pathways contribute to HB pathogenesis remain obscure. Recently, mTORC1 activation was reported in human HB cells and in a murine HB model driven by β-catenin and Yap1. Here, we directly investigate the therapeutic impact of mTOR inhibition following HB development in the Yap1-β-catenin model. HB were established by hydrodynamic tail vein injection of Sleeping Beauty transposase and plasmids coding for ΔN90-β-catenin and S127A-Yap1. Five weeks after injection, when HB were evident, mice were randomized into Rapamycin diet-fed or basal-diet-fed groups for 5-weeks. Tumor growth was monitored via ultrasound imaging and mice in both groups were euthanized after 5-weeks for molecular analysis. Transcriptomic analysis showed a strong correlation in gene expression between HB in the Yap1-β-catenin model and HB patient cohorts. Rapamycin treatment decreased HB burden, almost normalizing liver weight to body weight ratio. Ultrasound imaging showed reduction in tumor growth over the duration of Rapamycin treatment as compared to controls. Majority of HB in the controls exhibited crowded fetal or embryonal histology, while remnant tumors in the experimental group showed well-differentiated fetal morphology. Immunohistochemistry confirmed inhibition of mTORC1 in the Rapamycin group. Thus, Rapamycin reduces HB in a clinically relevant model driven by β-catenin and Yap1, supporting use of mTORC1 inhibitors in their therapy. We also show the utility of standard and 3D ultrasound imaging for monitoring liver tumors in mice.

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

Original Article:

Kakar S, Dugum M, Cabello R, **Humar A**, Ahmad J, **Malik SM**. Incidence of Recurrent NASH-Related Allograft Cirrhosis. Dig Dis Sci. 2018 Dec 17. doi: 10.1007/s10620-018-5413-9. [Epub ahead of print] PubMed PMID: 30560336.

ABSTRACT
BACKGROUND: Cirrhosis secondary to nonalcoholic steatohepatitis (NASH) is projected to become the leading indication for liver transplantation (LT) in the USA in the next decade. The long-term implications of post-LT NASH, specifically on the development of allograft cirrhosis, are not well known.

METHODS: A retrospective cohort of patients at a single large center undergoing LT for NASH from 2000 to 2015 was identified using a prospectively collected database. A total of 226 patients undergoing LT for NASH were identified. Mean follow-up for the cohort

was 7 years. Seventy-five percent of patients underwent at least one liver biopsy post-LT.

RESULTS: Eighty-one patients (36%) developed recurrence of biopsy-proven NASH. Fifteen patients developed bridging fibrosis but only four patients (1.8%) progressed to recurrent NASH cirrhosis at a mean of 9 years post-LT. Body mass index at the time of LT was statistically higher in the NASH allograft cirrhosis group. Recurrent disease was less common and less severe in those transplanted with black donors. All four patients with recurrent NASH cirrhosis developed evidence of portal hypertension, but all remained alive at follow-up.

CONCLUSION: Although recurrent NASH following LT is common, the development of allograft cirrhosis is rare. These findings are useful when counseling patients and important to consider during their post-LT care.

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

Original Article:
Gong S, Yan Z, Liu Z, Niu M, Fang H, Li N, Huang C, Li L, Chen G, Luo H, Chen X, Zhou H, Hu J, Yang W, Huang Q, Schnabl B, Chang P, **Billiar TR**, Jiang Y, Chen P. Intestinal microbiota mediates the susceptibility to polymicrobial sepsis-induced liver injury by granisetron generation in mice. Hepatology. 2018 Dec 1. doi: 10.1002/hep.30361. [Epub ahead of print] PubMed PMID: 30506577.

ABSTRACT
Sepsis-induced liver injury is recognized as a key problem in intensive care units. The gut microbiota has been touted as an important mediator of liver disease development; however, the precise roles of gut microbiota in regulating sepsis-induced liver injury are unknown. Here, we aimed to investigate the role of the gut microbiota in sepsis-induced liver injury and the underlying mechanism. Cecal ligation and puncture (CLP) was used to induce polymicrobial sepsis and related liver injury. Fecal microbiota transplantation (FMT) was used to validate the roles of gut microbiota in these pathologies. Metabolomics analysis was performed to characterize the metabolic profile differences between sepsis-resistant (Res; survived to 7 days after CLP) and sepsis-sensitive (Sen; moribund before or approximately 24 hours after CLP) mice. Mice gavaged with feces from Sen mice displayed more-severe liver damage than did mice gavaged with feces from Res mice. The gut microbial metabolic profile between Sen and Res mice was different. In particular, the microbiota from Res mice generated more granisetron, a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, than the microbiota from Sen mice. Granisetron protected mice against CLP-induced death and liver injury. Moreover, proinflammatory cytokine expression by macrophages after lipopolysaccharide (LPS) challenge was markedly reduced in the presence of granisetron. Both treatment with granisetron and genetic knockdown of the 5-HT3A receptor in cells suppressed nuclear

factor kappa B (NF-κB) transactivation and phosphorylated p38 (p-p38) accumulation in macrophages. Gut microbial granisetron levels showed a significantly negative correlation with plasma alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels in septic patients. Conclusion:Our study indicated that gut microbiota plays a key role in the sensitization of sepsis-induced liver injury and associates granisetron as a hepatoprotective compound during sepsis development.

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

Funding Opportunities

Feasibility and Planning Studies for Development of Specialized Programs of Research Excellence (SPOREs) to Investigate Cancer Health Disparities (P20 Clinical Trial Optional)

(RFA-CA-19-034)

National Cancer Institute

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